

Section 2. Protocol

This section contains a complete reference copy of the MTN-003 protocol. As of the date of this section, the following documents reflect current protocol specifications:

- Protocol Version 1.0, dated 22 May 2008
- Letter of Amendment #01, dated 31 March 2009
- Clarification Memo #01, dated 27 May 2009
- Clarification Memo #02, dated 25 August 2009
- Letter of Amendment #2, dated 26 March 2010

To ensure that this manual continues to reflect current protocol specifications in the future:

- Upon receipt of any protocol clarification memos, add a copy of the memo to this section.
- Upon receipt of any additional letters of amendment, add a copy of the letter of amendment to this section.
- Upon receipt of any full protocol amendments, replace the contents of this section with the amended protocol.

Further information on the content and required handling of protocol clarification memos, letters of amendment, and full amendments is available in Section 9.2 of the MTN Manual of Operations.

**Microbicide Trials Network
CLARIFICATION MEMO #02 TO:**

**MTN-003
DAIDS Document ID #10622**

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

**Version 1.0 / 22 May 2008
IND #: 55,690**

Date of Clarification Memorandum: 25 August 2009

Section 1: Summary of Clarifications and Rationale

The items clarified in this Clarification Memorandum (CM) have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB/EC approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB/EC overseeing the study at their site for information. This CM is official MTN-003 documentation and is effective immediately. A copy of this CM must be retained in each study site's Essential Documents file for MTN-003. No change in informed consent is necessitated by or included in this CM.

This CM provides clarification on the following items:

- Updates to the Protocol Team Roster
 - Anticipated bleeding associated with speculum insertion and specimen collection
 - Product hold following positive HIV test results
 - Schedule of dipstick urinalysis testing
 - Product hold related to hypophosphatemia
 - Elimination of discrepancy between Appendix I: Schedule of Study Visits and Evaluations and the protocol
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Section 2: Implementation

With the exception of the modifications to the Protocol Team Roster, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

1. The Protocol Team Roster is updated to reflect updates to contact information.

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The following individuals have been removed from the Protocol Team Roster: Roshini Govinden and Missy Cianciola.

2. Section 5.3 of the protocol has been clarified to reflect the fact that cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the IoR/designee is not exclusionary.

Section 5.3, Exclusion Criteria, note to item 7:

*Note: Cervical ~~friability~~ **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.*

3. Section 6.6, Retrieval of Unused Study Products, Table 5: Retrieval of Temporarily Held or Permanently Discontinued Study Product, first row is updated to clarify product hold guidelines:

	Retrieve Oral Study Product	Retrieve Vaginal Study Product
Permanent discontinuation or temporary hold due to potential HIV seroconversion	Within 24 hours	Within 24 hours

4. Section 7.5, Follow-up Visits, third paragraph, second sentence is updated to clarify that dipstick urinalysis (UA) testing should be done at the participants' next visit in the event of a missed visit:

However, for participants who miss visits at which pelvic exams, complete blood counts, serum chemistries, **dipstick UA for protein and glucose**, and/or plasma archive are specified to take place, these procedures must be conducted at the participants' next visit.

5. Section 7.5.3, Laboratory Procedures, Dipstick urinalysis subsection is updated to clarify the dipstick UA schedule. Appendix I: Schedule of Study Visits and Evaluations is updated accordingly:

- Dipstick urinalysis for protein, **and glucose**, ~~nitrites, and/or leukocyte esterase~~:
 - Month 1
 - Quarterly
 - At PUEV
 - When clinically indicated
- **Dipstick urinalysis for nitrites and leukocyte esterase (LE):**
 - **When urine protein is 1+ or greater, or when otherwise clinically indicated**

Appendix I: Schedule of Study Visits and Evaluations:

UA (protein and glucose)	X	▲	+	■	X	X	X	X	▲
UA (nitrites and LE)	X	▲	+	▲	▲	▲	▲	▲	▲

6. Product hold rules are further clarified in Section 9.5.6, Hypophosphatemia, Grades 3 and 4 subsection, last sentence:

If improvement to \leq Grade 2 can not be documented within one week of the receipt of the **confirmed** Grade 3 or 4 result, study product must be permanently discontinued.

7. Appendix I: Schedule of Study Visits and Evaluations is updated to maintain consistency with the protocol.

Physical Exam		X		■	X	X	X	X	✕▲
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The above information will be incorporated into the next version of the protocol at a later time if it is amended.

**Microbicide Trials Network
CLARIFICATION MEMO #01 TO:**

**MTN-003
DAIDS Document ID #10622**

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

**Version 1.0 / 22 May 2008
IND #: 55,690**

Date of Clarification Memorandum: 27 May 2009

Section 1: Summary of Clarifications and Rationale

The items clarified in this Clarification Memorandum (CM) have been approved by the NIAID Medical Officer and are to be implemented immediately upon issuance. IRB/EC approval of this CM is not required by the sponsor; however, investigators may submit the CM to the IRB/EC overseeing the study at their site for information. This CM is official MTN-003 documentation and is effective immediately. A copy of this CM must be retained in each study site's Essential Documents file for MTN-003. No change in informed consent is necessitated by or included in this CM.

The primary goal for this CM is to update the Protocol Team Roster. A clarification to Section 8.2, Adverse Events Definitions and Reporting Requirements is also made in this CM.

Section 2: Implementation

With the exception of the modifications to the Protocol Team Roster, text to be deleted is noted by ~~strike through~~ and text to be added is noted below in **bold**.

1. The Protocol Team Roster is updated to reflect modifications to the Protocol Team and updates to contact information.

The following additions are made to the Protocol Team Roster:

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The following listings have updated contact information:

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2. A note is added to the end of the fifth paragraph, first bullet in Section 8.2, Adverse Events Definitions and Reporting Requirements, to clarify the grading for glycosuria.

Note: The severity of glycosuria will be graded using the same grading scale as for proteinuria.

DATE: March 31, 2009
FROM: Z. Mike Chirenje, MD, FRCOG and Jeanne Marrazzo, MD, MPH
TO: MTN-003 Clinical Research Sites
SUBJECT: MTN-003 Letter of Amendment #01, dated March 31, 2009

The information contained in the accompanying Letter of Amendment (LoA) impacts the MTN-003 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. Site IRBs/ECs are responsible for assessing whether and how the changes included in the LoA are communicated to study participants. All IRB/EC requirements must be followed. As this LoA does not impact the overall risk-to-benefit profile of study participation or the informed consent documents, re-consenting is unnecessary. This LoA and all associated IRB/EC correspondence should be filed in essential documents files for MTN-003.

One purpose of the LoA is to eliminate a discrepancy between the MTN-003 protocol Version 1.0 and the Sample Informed Consent Form (Enrollment) regarding PBMC extraction from blood samples. Although the protocol includes a laboratory procedure for PBMC extraction from blood, the consent does not include reference to this procedure; therefore, blood cannot be collected for PBMC extraction. PBMC extraction is being removed from the protocol through this LoA to eliminate this discrepancy. Even prior to IRB/EC approval of this LoA, it is important that you do not collect any blood for PBMC extraction because the participants will not have consented to this.

Another purpose of this LoA is to allow site discretion to defer the informed consent process for specimen storage and possible future research testing from the Enrollment Visit to a subsequent visit to reduce burden on participants. Version 1.0 of the protocol states that consent for specimen storage will be obtained at the Enrollment Visit. Until the LoA has been approved by your IRB/EC, if a participant appears to be too tired or is otherwise unable to complete the stored specimen consent process at her Enrollment Visit, please document that in her record and defer the process until her next visit.

The LoA also clarifies the product use and adherence assessments that can be discontinued during periods of time when the participant is on product hold or discontinuation. There will be a separate ACASI questionnaire that site staff can select for participants with a product hold/discontinuation of 4 weeks or more prior to the visit at which ACASI is administered. Appropriate adherence assessment is addressed by the current Case Report Forms and ACASI instruments. Therefore, no additional action is required on the part of site staff.

Another item being addressed in the LoA is the elimination of reporting of fetal losses as adverse events (AEs) and expedited adverse events (EAEs). Prior to IRB/EC approval of this LoA, fetal losses must be reported as AEs and EAEs per Version 1.0 of the protocol. After IRB/EC approval has been obtained, fetal losses will no longer be reportable as specified in this LoA.

The LoA also contains several minor clarifications and updates, including updates to the Protocol Team Roster.

Please contact the MTN CORE if you have any questions or concerns about the information contained in this memo or in the LoA.

LETTER OF AMENDMENT #01 TO:

**MTN-003
DAIDS Document ID 10622**

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

**Version 1.0/22 May 2008
IND # 55,690**

Letter of Amendment Date: March 31, 2009

Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-003 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. Site IRBs/ECs are responsible for assessing whether and how the changes included below are communicated to study participants. All IRB/EC requirements must be followed. As this LoA does not impact the overall risk-to-benefit profile of study participation or the informed consent documents, re-consenting is unnecessary. This LoA and all associated IRB/EC correspondence should be filed in essential documents files for MTN-003.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-003. This LoA provides clarification on the following items:

1. Modifications to the Protocol Team, affecting the Protocol Team Roster, and updates to Sections 1.2 and 1.3
2. Elimination of a discrepancy between the protocol and Sample Informed Consent Form (Enrollment) regarding acquisition of specimens for PBMC analysis
3. Allowance for site-specific approaches to the timing of the informed consent process for storage and future research testing of specimens, to decrease burden to participants
4. Procedures during product hold periods and following permanent discontinuation, to decrease burden to study participants
5. Safety reporting requirements, including omission of fetal losses as reportable adverse events
6. Other minor corrections and updates

Implementation

This LoA is official MTN-003 protocol documentation. Prior to implementing revisions listed here, study sites will submit the LoA to all relevant regulatory authorities and IRBs/ECs. The DAIDS Regulatory Affairs Branch will submit the LoA to the US Food and Drug Administration for inclusion in Investigational New Drug application # 55,690. Upon receipt of all required regulatory and IRB/EC approvals, the revisions listed below will be implemented. Except for modifications to the Protocol Team Roster, text to be deleted is noted by ~~strike through~~ and text to be added is noted in **bold**.

Detailed Listing of Revisions

1. The Protocol Team Roster, Section 1.2, and Section 1.3 are updated to reflect modifications to the Protocol Team and updates to contact information.

The following additions are made to the Protocol Team Roster:

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The following listings are deleted from the Protocol Team Roster: Salim Abdool Karim, Nomampondo Barnabas, Muzala Kapina, Corey Kelly, Ayesha Kharsany, and Alain Kouda.

The following listings have updated contact information:

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In Sections 1.2 and 1.3, the following modifications are made:

1.2 Sponsor and Monitor Identification

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1.3 Medical Officers

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2. For consistency with the Sample Informed Consent Form (Enrollment), the protocol is modified (PBMC archive is deleted) in Sections 7.5.3, 7.6.1, 7.11, and Appendix I.

In Section 7.5.3, Laboratory Procedures:

- ~~PBMC archive:~~
 - ~~If indicated (when blood is collected [each sample] for Sample 2 per Appendix III~~
 - ~~Additionally if required per Section 7.6.1~~

In Section 7.6.1, Participants Who Become Infected with HIV, sixth paragraph:

- ~~PBMC archive:~~
 - ~~Months 1, 3, 6 and every 6 months post-seroconversion~~

Plasma and ~~PBMC~~ collected at the above-listed time points, as well as when blood is collected for confirmatory HIV testing, will be shipped to the MTN NL and utilized for the following:

In Section 7.11, Laboratory Procedures, under Local, Regional, or Network Laboratory:

- ~~PBMC archive~~

In Appendix I, SCHEDULE OF STUDY VISITS AND EVALUATIONS, the following deletion is made to the second note under the first table and to procedures in the second table (SCHEDULE OF POST-HIV-1 SEROCONVERSION LABORATORY PROCEDURES):

Note: *If Sample 2 is drawn (per Appendix III), blood is also collected for the following analyses: Plasma archive, CD4+ T-cell count, and HIV-1 RNA PCR, and ~~PBMC archive.~~*

SCHEDULE OF POST-HIV-1 SEROCONVERSION LABORATORY PROCEDURES

PBMC Archive	X	X	X	X	
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3. In Section 7.4.2, a note is added under the first bullet to allow for site-specific approaches to timing the completion of the informed consent for specimen storage and possible future research testing. Appendix I is updated accordingly.

7.4.2 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for specimen storage and possible future research testing

Note: *may be deferred (no later than Month 3 follow-up visit) in accordance with site SOPs.*

In Appendix I, Schedule of Study Visits and Evaluations, the following note is added under the first table.

NOTE: *Informed consent for specimen storage and possible future research testing may be deferred (no later than Month 3 follow-up visit) in accordance with site SOPs*

4. In Section 7.6, Follow up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product, the following clarification is made at the end of the first paragraph:

When a temporary hold or permanent discontinuation of study product occurs, the following assessments will be performed as noted below, and then discontinued until study product use resumes (in the case of a temporary hold):

- **Adherence assessment will be performed:**
 - **at the next monthly visit (if product hold/discontinuation starts < 7 days prior to the visit)**
 - **at the next quarterly visit (if product hold/discontinuation starts < 4 weeks prior to the visit)**
- **Last dose recall will be performed at the next quarterly visit**
- **Study product sharing assessment and assessment of partner’s reaction to study product use will be performed at the next annual visit (if product hold/discontinuation starts < 4 weeks prior to the visit)**

5. Fetal losses are omitted as reportable AEs via edits to Section 8.2 and text regarding EAE reporting is updated in Section 8.3.

In Section 8.2, Adverse Events Definitions and Reporting Requirements, third paragraph, text is added:

Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Study staff also will report on CRFs the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs, **except fetal losses**
 - **Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs. However, untoward maternal conditions that either result in or result from fetal losses will be reported as reproductive system AEs**
- All fractures
- All AEs of severity Grade 2 or higher in the following categories: dizziness, headache, nausea, vomiting, diarrhea, abdominal pain, rash
- All AEs of severity Grade 3 or higher
- All serious AEs, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 8.3 below; **this includes all congenital anomalies identified in the fetuses and/or infants of study participants.**

In Section 8.2, fourth paragraph, the last sentence is deleted:

~~After the Termination Visit, only pregnancy outcomes that meet criteria for expedited adverse event (EAE) reporting (see Section 8.3 below) occurring among participants known to be pregnant at the Termination Visit will be reported.~~

In Section 8.2, fifth paragraph, first bullet, text is added, and grading criteria are modified:

- AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 and the Female Genital Grading Table for Use in Microbicide Studies (~~Appendix~~ **Addendum** 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004), except that asymptomatic BV will not be a reportable AE and **bleeding during pregnancy prior to the onset of labor (regardless of trimester) will be graded per the table below.** AEs not included in the Female Genital Grading Table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

PARAMETER	GRADE 0 NORMAL	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
COMPLICATIONS OF PREGNANCY					
Bleeding during pregnancy prior to the onset of labor	None	Spotting or bleeding less than menses	Bleeding like menses or heavier, no intervention indicated	Profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated	Potentially life-threatening profuse bleeding and/or shock

In Section 8.3, Expedited Adverse Event Reporting Requirements, two updates are made:

The EAE reporting requirements and definitions for this study and the methods for expedited reporting of AEs to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in the DAIDS EAE Manual, available on the RCC website: <http://rcc.tech-res-intl.com/>. **Sites using the DAERS internet-based reporting system for submission of EAEs to DAIDS will follow the DAERS processes as outlined in the DAERS training information. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESsupport@niaid.nih.gov or from within the DAERS application itself. If the site cannot use DAERS to report an AE on an expedited basis, the EAEs must be documented on the DAIDS EAE Reporting Form available on the RCC website: <http://rcc.tech-res-intl.com>. DAIDS EAE forms should be submitted to DAIDS through the RCC Safety Office (rccsafetyoffice@tech-res.com) or call 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710.**

EAE Reporting Requirements for this Study

EAE Reporting Level

This study uses the Standard Level of expedited AE reporting as defined in the DAIDS EAE Manual, **except that fetal losses will not be reported as EAEs. Although not reported as EAEs, all fetal losses will be documented on case report forms and routinely reviewed by the PSRT and DSMB, as described in Section 8.1. After the Termination Visit, only pregnancy outcomes that meet criteria for EAE reporting (e.g., congenital anomalies) occurring among participants known to be pregnant at the Termination Visit will be reported.**

- 6. Minor clarifications and updates are made to Sections 5.2 and 9.5.6.

In Section 5.2, Inclusion Criteria, text is edited as follows:

- 4) HIV-uninfected based on testing performed by study staff at screening and enrollment (per applicable algorithms in Appendixes II and III)

In Section 9.5.6, Hypophosphatemia, the following edits are made:

ORAL STUDY PRODUCT

Grades 1 and 2

The phosphate test should be repeated within 2 weeks of the receipt of the results. **Intake of Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution—should be advised. Oral phosphate supplementation may be implemented at the discretion of the site investigator. Other causes of low phosphate should be investigated.** Unless other temporary product hold requirements apply, study product need not be held.

Grades 3 and 4

The phosphate test should be repeated within 1 week of the receipt of the results. **Intake of Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution—should be advised. Oral phosphate supplementation may be implemented at the discretion of the site investigator.** Other causes of low phosphate should be investigated. During the time that supplemental phosphate is provided to the participant and the time that testing is repeated, sites should follow temporary product hold/permanent discontinuation guidelines described in Section 9.4. If improvement to \leq Grade 2 can not be documented within one week **of the receipt of the Grade 3 or 4 result**, study product must be permanently discontinued.

LETTER OF AMENDMENT #02 TO:

MTN-003

DAIDS Document ID 10622

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

Version 1.0/22 May 2008

IND # 55,690

Letter of Amendment Date: March 26, 2010

Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-003 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. Site IRBs/ECs are responsible for assessing whether and how the changes included below are communicated to study participants. All IRB/EC requirements must be followed. As this LoA does not impact the overall risk-to-benefit profile of study participation or the informed consent documents, re-consenting is unnecessary.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-003. This LoA provides clarification on the following items:

1. Protocol Team Roster, to reflect updates to the Protocol Team
 2. Study procedures, regarding results of assays from other MTN protocols for use in VOICE, to decrease participant and laboratory burden; and the frequency of the assessment of intravaginal practices, to resolve a discrepancy between the ACASI instrument and the protocol
 3. Adverse event reporting requirements, to reflect recent updates to requirements for Expedited Adverse Event Reporting to the US NIH Division of AIDS
 4. Product use management, to avoid unnecessary product hold
 5. Investigator guidance for clinical management of laboratory test results
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Implementation

This LoA is official MTN-003 protocol documentation. Prior to implementing revisions listed here, study sites will submit the LoA to all relevant regulatory authorities and IRB/ECs. The DAIDS Regulatory Affairs Branch will submit the LoA to the US Food and Drug Administration for inclusion in Investigational New Drug application # 55,690. Upon receiving final IRB/EC and any other applicable regulatory entity approval(s) for this LoA, sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Compliance Center (RCC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that the required LoA registration documents have been received and are complete. Sites will not be able to implement the changes related to EAE reporting requirements in this LoA until after they have received a LoA registration notification from the DAIDS PRO. All other sections of this LoA will be implemented immediately upon IRB/EC approval. A copy of the DAIDS PRO

LoA registration notification along with this LoA and any IRB/EC correspondence should be retained in the site's regulatory files. Except for modifications to the Protocol Team Roster, text to be deleted is noted by ~~strike through~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

1. The Protocol Team Roster is updated.

The following individuals have been added to the Protocol Team Roster:

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The following individuals are removed from the Protocol Team Roster: Anne Coletti, Nancy Connolly, Nicola Coumi, Nozizwe Dladla-Qwabe, Vijayanand Guddera, Laura McKinstry, Emilder Tazvinga-Chihota, Francis Martinson, Nancy Padian, and Morenike Ukpong.

2. In Section 7, STUDY PROCEDURES, two edits are made.

A sentence is added at the end of the first paragraph in Section 7 to allow results from certain assays performed on the same day for other MTN studies to be used for VOICE.

Results from HIV rapid tests performed on the same day for other MTN studies may also be utilized for VOICE, provided the test kit and laboratory approved by MTN NL are the same for both studies, and the site has documented permission for this substitution from MTN NL.

Additionally, the frequency of assessment of intravaginal practices is modified in Section 7.5.1 and in Appendix I:

- Intravaginal practices assessment:
 - ~~Quarterly~~**Annually**
 - At PUEV
 - At Termination Visit

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR 1	SCR 2	ENR	MLY	QRT	SEM	ANN	PUEV	TERM
Intravaginal Practices Assess.					✗	✗	X	X	X

3. In Section 8, ASSESSMENT OF SAFETY, and Section 9, CLINICAL MANAGEMENT, text is edited to reflect updates to adverse event reporting. Of note, as of May 3, 2010, EAE reporting will follow revised guidelines included in the Manual for Expedited Reporting of Adverse Events to DAIDS, dated January 2010. The revised manual reduces the categories for relatedness from five to two (related

and not related), and mandates reporting of all SAEs to DAIDS, regardless of relatedness.

In Section 8.2, fifth paragraph, second bullet:

- The relationship of all AEs reported on CRFs will be assessed based on the Manual for Expedited Reporting of Adverse Events to DAIDS, dated ~~May 6, 2004~~ **January 2010** (DAIDS EAE Manual), the product Package Inserts and Investigators Brochures, and the clinical judgment of the IoR/designee. The study products that must be considered when AE relationship **is assessed** are TDF tablet, FTC/TDF tablet, tenofovir 1% vaginal gel, and study gel applicator.

In Section 8.3, second paragraph:

EAE Reporting Level

This study uses **the All SAEs category of the Standard Level of expedited** AE reporting as defined in the DAIDS EAE Manual. ~~, except that fetal losses will not be reported as EAEs.~~ Although not reported as EAEs, all fetal losses will be documented on case report forms and routinely reviewed by the PSRT and DSMB, as described in Section 8.1. After the Termination Visit, only pregnancy outcomes that meet criteria for EAE reporting (e.g., congenital anomalies) occurring among participants known to be pregnant at the Termination Visit will be reported.

In Section 8.3, third paragraph:

Study Agents for Expedited Reporting to DAIDS

The study agents that must be considered ~~in determining relationships of AEs requiring for~~ expedited reporting to DAIDS are: TDF tablet, FTC/TDF tablet, tenofovir 1% vaginal gel, and study gel applicator.

In Section 9.4, second paragraph:

Grade 3

Participants who develop a Grade 3 AE that is not specifically addressed below and is judged by the IoR/designee to be ~~probably not or not related to study product~~ may continue product use.

In Section 9.4, fifth paragraph:

Grade 4

A participant who develops a Grade 4 AE that is not specifically addressed below (regardless of relationship to study product) should have the study product held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT. In general, product use will not be resumed if the Grade 4 AE is considered ~~probably not, possibly, probably, or definitely~~ related to product use. If, in consultation with the PSRT, product use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study product must then be permanently discontinued.

In Section 9.5.1, Nausea, Vomiting, and/or Diarrhea, under VAGINAL STUDY PRODUCT:

VAGINAL STUDY PRODUCT

Unless other temporary product hold requirements apply, vaginal study product need not be held unless the IoR/designee has compelling evidence that the toxicity is ~~probably or definitely~~ related to vaginal study product. In this case, the IoR/designee must consult the

PSRT for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

In Section 9.5.2, AST and/or ALT Elevations, under VAGINAL STUDY PRODUCT:

VAGINAL STUDY PRODUCT

Unless other temporary product hold requirements apply, vaginal study product need not be held unless the IoR/designee has compelling evidence that the toxicity is ~~probably or definitely~~ related to vaginal study product. In this case, the IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

4. New text is added to the beginning of Section 9.3 to clarify product hold guidelines.

In general, product hold is not triggered by an AE deemed already resolved at the time of participant report or site discovery, according to the judgment of the IoR/designee. However, such an AE may trigger permanent discontinuation, if it is an AE recurrence specified by criteria below to result in permanent discontinuation of study product.

5. Text is edited in Section 9, CLINICAL MANAGEMENT, to provide guidance for management of laboratory test results.

In Section 9.5.2, AST and/or ALT Elevations, text is added under ORAL STUDY PRODUCT, fifth paragraph, first sentence:

Grade 4

Study product should be permanently discontinued **and the PSRT will be consulted**. The IoR/designee must follow the participant's ALT and AST at least weekly until levels are Grade ≤ 1 .

In Section 9.5.3, Creatinine, text is added within ORAL STUDY PRODUCT:

ORAL STUDY PRODUCT

The IoR/designee should temporarily hold oral study product for any rise in creatinine greater than or equal to 1.5 x participant's baseline value (BL). The creatinine should be repeated as soon as possible (at most within 1 week). Product use may be resumed when the creatinine level improves to $\leq 1.3 \times \text{BL}$, **in consultation with the PSRT**. If product use is resumed and the creatinine level increases to $\geq 1.5 \times \text{BL}$, product use must be permanently discontinued.

In Section 9.5.6, Hypophosphatemia, text is edited within ORAL STUDY PRODUCT, Grades 3 and 4:

Grades 3 and 4

The phosphate test should be repeated within 1 week of the receipt of the results, **and should be accompanied by serum creatinine testing and urine dipstick for protein/glucose; study product use may continue in the interim. If the participant does not have repeat testing within the specified time frame, PSRT consultation is required**. Intake of phosphate-rich food or fluid should be advised. Oral phosphate supplementation may be implemented at the discretion of the site investigator. Other causes of low phosphate should be investigated. ~~During the time that supplemental phosphate is provided to the participant and the time that testing is repeated, sites should follow temporary product hold/permanent discontinuation guidelines described in Section~~

~~9.4. If improvement to \leq Grade 2 can not be documented within one week of the receipt of the confirmed Grade 3 or 4 result, study product must be permanently discontinued.~~

In interpreting the results of testing accompanying the repeat phosphate test, sites should follow these guidelines:

- Participants with proteinuria and/or glycosuria of $\geq 3+$ will have oral study product held and require consultation with the PSRT for further testing and management.
- Participants with creatinine ≥ 1.5 x BL and/or creatinine clearance ≤ 50 mL/min, will have oral study product held, and will follow all additional management guidelines specific to the applicable adverse event noted in Sections 9.5.3 and 9.5.4.

Participants who do not meet the above criteria may continue study product, with the following additional requirements:

- Urine dipstick results of 1+ will be managed according to guidance in Sections 9.6 (for proteinuria) and 9.7 (for glycosuria).
- Findings of proteinuria and/or glycosuria of 2+ require consultation with the PSRT for the participant's further testing and management.

For participants with a confirmed Grade 3 result, the following additional requirements apply:

- Phosphate levels will be retested approximately weekly until return to \leq Grade 2, unless other retesting schedule has been advised by the PSRT.
- The PSRT will be consulted for further testing and management if phosphate levels do not return to \leq Grade 2 within two weeks of the receipt of a confirmed Grade 3 result.

Grade 4

Study product will be held and the PSRT will be consulted. The phosphate test should be repeated within 1 week of the receipt of the results, and should be accompanied by serum creatinine testing and urine dipstick for protein/glucose. If the participant does not have repeat testing within the specified time frame, PSRT consultation is required. Intake of phosphate-rich food or fluid should be advised. Oral phosphate supplementation may be implemented at the discretion of the site investigator. Other causes of low phosphate should be investigated.

Participants will have phosphate levels retested approximately weekly until return to \leq Grade 2, in consultation with the PSRT. Participants may resume study product, provided that:

- Study product hold is not otherwise indicated (e.g., due to the results of creatinine, creatinine clearance, urine protein, and/or urine glucose)
- The phosphate level has returned to \leq Grade 2
- A request to resume study product is approved by the PSRT

MTN-003

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

Microbicide Trials Network

Sponsored by:

**Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
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MTN-003

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

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LIST OF ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ACASI	audio computer-assisted self interview
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
BV	bacterial vaginosis
CDC	Centers for Disease Control
cGMP	current good manufacturing practices
CFR	Code of Federal Regulations
CI	confidence intervals
CONRAD	Contraceptive Research and Development Organization
C _{max}	maximum serum concentration
C _{min}	minimum serum concentration
CORE	Coordinating and Operations Center
C-PMPA	radiolabeled tenofovir
CRF	case report form
CROI	Conference on Retroviruses and Opportunistic Infections
CRPMC	Clinical Research Products Management Center
CTA	clinical trial agreement
CWG	Community Working Group
d4T	stavudine
DAIDS	Division of AIDS
DXA	Dual energy X-ray absorptiometry
DMPA	depot medroxyprogesterone acetate
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EC	ethics committee
EC ₅₀	50% effective concentration
EFV	efavirenz
FDA	Food and Drug Administration
FHCRC	Fred Hutchison Cancer Research Center
FHI	Family Health International

LIST OF ABBREVIATIONS AND ACRONYMS (CONTINUED)

FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practices
GEE	generalized estimating equations
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HEC	hydroxyethylcellulose
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HR	hazard ratio
IC-EC	intracellular-extracellular
IC ₅₀	50% inhibitory concentration
IATA	International Air Transport Association
IFN- γ	interferon gamma
IgA	immunoglobulin A
IL-2	interleukin-2
IND	investigational new drug
IoR	Investigator of Record
LPV	lopinavir
IRB	Institutional Review Board
ITT	intention to treat
IUCD	intrauterine contraceptive device
KOH	potassium hydroxide
LDMS	Laboratory Data Management System
LLN	lower limit of normal
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Disease
NICHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
NIH	(United States) National Institutes of Health
NL	network laboratory
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHRP	Office of Human Research Protections
p-y	person-years
PCR	polymerase chain reaction
PD	pharmacodynamic
PID	pelvic inflammatory disease
PK	pharmacokinetic(s)
PMPA	9-R-2-phosphonomethoxypropyl adenine
PMPApp	tenofovir diphosphate
PoR	Pharmacist of Record

LIST OF ABBREVIATIONS AND ACRONYMS (CONTINUED)

PrEP	pre-exposure prophylaxis
PUEV	Product Use End Visit
PSRT	Protocol Safety Review Team
RCC	Regulatory Compliance Center
RNA	ribonucleic acid
RT	reverse transcriptase
RTI	reproductive tract infection
RTV	ritonavir
RT-PCR	real time polymerase chain reaction
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDA	strand displacement amplification
SDMC	Statistical Data Management Center
SHIV	simian/human immunodeficiency virus
SMC	Study Monitoring Committee
SOP	standard operating procedure
SQ	subcutaneous
SSP	study specific procedures
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
ULN	upper limits of normal
UNAIDS	Joint United Nations Program on HIV/AIDS
UTI	urinary tract infection
VOICE	Vaginal and Oral Interventions to Control the Epidemic
WB	Western blot
WHO	World Health Organization
ZDV	zidovudine

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Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

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MTN-003

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

INVESTIGATOR SIGNATURE FORM

**Version 1.0
May 22, 2008**

A Study of the Microbicide Trials Network

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute of Child Health and Human Development
US National Institute of Mental Health
US National Institutes of Health

Co-Sponsored by:

CONRAD
Gilead Sciences, Inc.

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for each of the three study products for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, NICHD, NIMH, CONRAD, and Gilead Sciences, Inc. for review prior to submission.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record

Signature of Investigator of Record

Date

MTN-003

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

PROTOCOL SUMMARY

Short Title:	Vaginal and Oral Interventions to Control the Epidemic (VOICE)
Clinical Phase:	2B
IND Sponsor:	Division of AIDS, NIAID, US NIH
Co-Chairs:	Zvavahera Mike Chirenje, MD, FCROG and Jeanne Marrazzo, MD, MPH
Sample Size:	Approximately 4200
Study Population:	Sexually active HIV-uninfected women, 18 – 40 years old
Study Sites:	Study sites will be located in sub-Saharan Africa.
Study Design:	Phase 2B, five-arm, double-blinded, placebo-controlled, multi-site, randomized, controlled trial
Study Duration:	<p>Approximately 35 months total. Accrual will require approximately 21 months and follow-up will continue until 217 incident HIV infections are observed in the study, which is expected to occur approximately 14 months after the end of the accrual period.</p> <p>Each participant is expected to have a minimum of 12 and a maximum of 33 months of study product use. Each participant will have an additional approximate 8 weeks of follow-up off study product to identify potential delayed seroconversions due to masked infections that are not detected during the product use period.</p>
Study Products:	<p><u>Oral</u></p> <ul style="list-style-type: none">• Tenofovir disoproxil fumarate (TDF) 300 mg tablet• TDF placebo tablet• Emtricitabine/Tenofovir disoproxil fumarate (FTC/TDF) 200 mg/300 mg tablet• FTC/TDF placebo tablet <p><u>Vaginal</u></p> <ul style="list-style-type: none">• Tenofovir 1% gel• Placebo gel

Study Regimen:

Because similarly-appearing oral study products are not available for TDF, FTC/TDF, and placebo, participants randomized to the oral study group will take two tablets daily.

Table 1: Study Regimen

Study Group	Regimen
Oral	Two tablets by mouth daily, in one of the following combinations: <ul style="list-style-type: none">• One TDF 300 mg tablet and one FTC/TDF placebo tablet (TDF Group)• One TDF placebo tablet and one FTC/TDF 200 mg/300 mg tablet (FTC/TDF Group)• One TDF placebo tablet and one FTC/TDF placebo tablet (Oral Placebo Group)
Vaginal	One pre-filled applicator vaginally daily, containing one of the following: <ul style="list-style-type: none">• Vaginal tenofovir 1% gel• Vaginal placebo gel

Primary Objectives:

- To estimate the effectiveness of daily tenofovir 1% gel compared to a vaginal placebo gel, and the effectiveness of oral TDF and oral FTC/TDF compared to an oral placebo in preventing HIV infection among women at risk for sexually transmitted infection (STI)
- To evaluate the extended safety of daily tenofovir 1% gel, oral TDF, and oral FTC/TDF in women at risk for sexually transmitted HIV infection

Primary Endpoints:

- **Effectiveness**
 - HIV infection as measured by seroconversion according to the algorithm in Appendix III at the end of the study product use period (i.e., at the start of the additional 8 weeks of follow-up off product)
- **Safety**
 - Grades 2, 3, and 4 clinical and laboratory adverse events (AEs)

Secondary Objectives:

- **Adherence/Behavioral**
 - To evaluate adherence to daily regimens of vaginal gel (tenofovir 1% gel and placebo) vs. oral tablets (TDF, FTC/TDF, and placebos) used to prevent HIV infection

- To evaluate whether sexual activity, condom use, and intravaginal practices change over time in women who use either daily vaginal gel (tenofovir 1% gel and placebo) or daily oral tablets (TDF, FTC/TDF, and placebos)
- **HIV-1 Drug Resistance**
 - To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using study product by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants
- **Pharmacokinetic (PK)**
 - To evaluate the pharmacodynamic (PD) relationship between plasma drug concentrations and study outcomes (HIV seroconversion, toxicity [report of AEs or evidence of cervicovaginal inflammation], viral resistance) using PK-PD models
- **Delayed Seroconversion**
 - To assess the incidence of HIV seroconversion in each study product group during the approximate 8 weeks of follow-up off study product between the Product Use End Visit (PUEV) and the Termination Visit

Secondary Endpoints

- **Adherence/Behavioral**
 - Self-reported use of study product, sexual activity, condom use, and intravaginal practices, study product counts
- **HIV-1 Drug Resistance**
 - HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by genotypic methods
- **Pharmacokinetic**
 - Area under the curve (AUC), maximum serum concentrations (C_{max}), and minimum serum concentrations (C_{min})
- **Delayed Seroconversion**
 - HIV infection as measured by seroconversion (according to the algorithm in Appendix III) during the approximate 8 weeks of follow-up off study product between the PUEV and the Termination Visit

Exploratory Objectives:

- **Vaginal Microenvironment**
 - To correlate quantitative measurement of candidate biomarkers in the cervicovaginal environment with HIV seroconversion, reported product adherence, stage of menstrual cycle, contraceptive use, intercurrent STI and reported AEs
 - To measure the association between abnormal vaginal flora and HIV seroincidence
- **Method of Contraception**
 - To explore the potential relationship between method of contraception and HIV seroconversion, reported product adherence, and reported AEs

Exploratory Endpoints:

- **Vaginal Microenvironment**
 - Candidate biomarkers including measures of intrinsic immunity (innate antimicrobial factors [defensins, lactoferrin, secretory leukocyte protease inhibitor]), and functional immunity against HIV/STI and cervicovaginal inflammation (cytokines, chemokines, leukocytes)
 - Abnormal vaginal flora as assessed by Gram stain and bacterium-specific polymerase chain reaction (PCR) applied to vaginal fluid
- **Method of Contraception**
 - Method(s) of contraception used by participants

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

Protocol Number: MTN-003

Short Title: VOICE

Date: 22 May 2008

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2 INTRODUCTION

2.1 Oral Pre-Exposure Prophylaxis and Microbicides in HIV/AIDS Prevention

Twenty five years into the HIV/AIDS epidemic, the search for safe and effective methods of HIV prevention continues. As HIV incidence continues to rise in many areas of the world, the overwhelming majority of new HIV infections are occurring among women in sub-Saharan Africa. Increasing availability of antiretroviral therapy (ART) for infected persons will not address this, because the pace of new infections exceeds that of treatment initiation by a ratio of 6:1, at best.¹ Although male circumcision appears to provide considerable protection against HIV infection in men,² and when adopted widely, should reduce risk of HIV transmission at the population level, a major benefit to vulnerable women will not begin to accrue for several years, even with widespread uptake of this procedure.³

A series of reports has recently emphasized the daunting challenge of preventing HIV acquisition in women at high risk for HIV acquisition. The cervical diaphragm was shown to be of no benefit in a large randomized controlled trial.⁴ A trial of cellulose sulfate, a candidate microbicide, was recently halted when the product failed to prevent HIV acquisition; a trend towards increased risk of HIV infection was seen among women who received the product.⁵ The STEP study, a trial of a promising HIV vaccine based on an adenovirus delivery system, was halted in 2007 after the first interim analysis met the futility criteria. Additionally, the interim analysis of the STEP trial indicated that the risk of HIV infection was higher in vaccine recipients, among the subset of participants with pre-existing high titers of antibodies to adenovirus type 5, particularly among men who were not circumcised.⁶ Lastly, a phase 3 trial of the candidate microbicide Carraguard[®] failed to demonstrate efficacy in preventing male-to-female HIV transmission although it was shown to be safe for vaginal use.⁷ For these reasons, the

need for new effective prevention strategies is particularly urgent for women at risk of acquiring HIV. Pre-exposure prophylaxis (PrEP) with agents targeting HIV has emerged as a highly viable approach.

Three promising candidates for chemoprophylaxis of HIV infection, oral tenofovir disoproxil fumarate (TDF), oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF), and vaginal tenofovir gel have been proposed as prophylactic agents. The rationale for and science underlying selection of each of these agents is detailed below. Mindful of the challenge of appropriate allocation of scarce resources for effectiveness trials, the MTN will evaluate these agents in a single trial, MTN-003, or VOICE. VOICE will assess simultaneously the safety and effectiveness in preventing HIV acquisition of daily use of oral and vaginal formulations of tenofovir and oral FTC/TDF as compared to a corresponding placebo. The design of VOICE also allows limited comparisons of effectiveness, safety, adherence, and associated frequency of viral resistance among seroconverters across oral versus topical formulations of tenofovir. As such, this study will contribute significantly to HIV prevention research and provide vital and currently unavailable information on the relative risk-benefit profile of each product formulation.

2.2 Tenofovir Disoproxil Fumarate

2.2.1 Description

TDF is approved under the trade name Viread[®] for treatment of HIV-1 infection in adults.⁸ TDF is the oral pro-drug of tenofovir, an acyclic nucleotide analogue (9-R-2-phosphonomethoxypropyl adenine, PMPA) with activity *in vitro* against retroviruses, including HIV-1 and HIV-2, as well as hepadnaviruses. Further information on TDF is available in the current version of the Viread[®] package insert.⁸

2.2.2 Mechanism of Action

Once absorbed, TDF is rapidly converted by diester hydrolysis to tenofovir.⁸ Tenofovir is then phosphorylated by cellular enzymes to tenofovir diphosphate (PMPApp), which is a competitive inhibitor of HIV-1 reverse transcriptase (RT) that terminates the growing deoxyribonucleic acid (DNA) chain. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

2.2.3 Strength of Study Product

The strength of the TDF tablets will be the dose approved by the FDA for the indication of treatment of HIV-1 infection in adults (300 mg). For the treatment of HIV infection, TDF is administered once daily as one 300 mg tablet and has excellent activity against wild type and many drug resistant viruses.⁸

2.3 Emtricitabine/Tenofovir Disoproxil Fumarate

2.3.1 Description

FTC is approved for treatment of HIV-1 infection in adults.⁹ FTC is administered once daily, either as a single drug formulation (Emtriva[®]) or in fixed dose combination with

TDF (as Truvada[®]).¹⁰ FTC/TDF is approved for treatment of HIV-1 infection in adults. FTC (5-fluoro-1-(2R, 5S)-[2-(hydroxymethyl)-1,3-oxathiolane-5-yl] cytosine) is a synthetic nucleoside analogue with activity against HIV-1 RT. FTC is the negative enantiomer of a thio analogue of cytidine, which differs from other cytidine analogues in that it has a fluorine in the 5-position. Further information on Emtriva[®] is available in the current package insert.⁹

2.3.2 Mechanism of Action

FTC is a synthetic nucleoside analogue of cytidine and is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate.⁹ Emtricitabine 5'-triphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into the viral DNA resulting in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerases α and β , and mitochondrial DNA polymerase γ .

2.3.3 Strength of Study Product

Coformulation of FTC and TDF has been approved by the FDA.¹⁰ This once daily film-coated tablet contains 200 mg of FTC and 300 mg of TDF, which is equivalent to 245 mg of tenofovir disoproxil, as active ingredients. During PK studies, one Truvada[®] tablet was bioequivalent to one Emtriva[®] capsule (200 mg) plus one Viread[®] tablet (300 mg) following single-dose administration to healthy participants (n = 39). Further information on Truvada[®] is available in the current package insert.¹⁰

2.4 Tenofovir 1% Gel

2.4.1 Description

Tenofovir 1% gel contains 1 gm/100 mL of PMPA (9-R-2-phosphonomethoxypropyl adenine monohydrate), an acyclic nucleotide analogue with activity *in vitro* against retroviruses, including HIV-1 and HIV-2, as well as hepadnaviruses.¹¹ Further information is available in the current version of the tenofovir gel investigator's brochure.

2.4.2 Mechanism of Action

Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate.¹¹ Tenofovir requires subsequent phosphorylations by cellular enzymes to form tenofovir diphosphate. Tenofovir diphosphate inhibits the activity of HIV-1 RT by competing with the natural substrate deoxyadenosine 5'-triphosphate and, after incorporation into DNA, by DNA chain termination. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases α , β , and mitochondrial DNA polymerase γ .

2.4.3 Strength of Study Product

The strength of the tenofovir gel will be the strength (1%) previously tested in HPTN 050 (IND 55,690), CONRAD A04-095 (IND 73,382) and A04-099 (IND 73,382), HPTN 059 (IND 55,690), MTN-001 (IND 55,690), and MTN-002 (IND 55,690). The 4 mL application in this study delivers 40 mg of tenofovir to the vaginal compartment.

2.5 Placebo Gel

2.5.1 Description

The placebo gel is a vaginal product which contains hydroxyethylcellulose (HEC) as the thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide.¹² HEC is used to approximate the viscosity of other microbicide gel candidates.

2.5.2 Mechanism of Action

The placebo gel is designed to be inactive in the vagina. The gel is isotonic and formulated at a pH of 4.4 to avoid disrupting the normal vaginal pH and has minimal buffering capacity to avoid the inactivation of sexually transmitted pathogens.

2.5.3 Strength of Study Product

Each pre-filled applicator delivers approximately 4 mL of placebo gel.

2.6 *In vitro* Studies

2.6.1 *In vitro* Studies of Tenofovir

Anti-HIV-1 Activity

The *in vitro* antiviral activity of tenofovir against laboratory and clinical isolates of HIV-1 was assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes.⁸ The EC₅₀ (50% effective concentration) values for tenofovir were in the range of 0.04 µM - 8.5 µM. In drug combination studies of tenofovir with NRTIs (abacavir, didanosine, lamivudine [3TC], d4T, zalcitabine, zidovudine [ZDV]), NNRTIs (delavirdine, efavirenz [EFV], nevirapine [NVP]) and protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir [RTV], saquinavir), additive synergistic effects were observed. Tenofovir displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, G, and O (EC₅₀ values 0.5 µM - 2.2 µM) and showed strain specific activity against HIV-2 (EC₅₀ values ranged from 1.6 to 4.9 µM).

Resistance

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*.⁸ These viruses expressed a K65R mutation in RT and showed a 2 – 4 fold reduction in susceptibility to tenofovir. Of note, this mutation also confers increased susceptibility to some other NRTIs, and is associated with approximately 50% reduction in the replicative capacity of HIV-1 (potentially resulting in a “less fit” virus).¹³ Tenofovir-resistant isolates of HIV-1 have been recovered from some patients treated with Viread[®] in combination with certain antiretroviral (ARV) agents. In treatment-naïve patients, 8/47 (17%) isolates from patients failing Viread[®] + 3TC + EFV through week 144 showed >1.4 fold (median 3.7) reduced susceptibility *in vitro* to tenofovir. In treatment-experienced patients, 14/304 (5%) isolates from patients failing Viread[®] through week 96 showed >1.4 fold (median 2.7) reduced susceptibility to tenofovir. Genotypic analysis of resistant isolates showed a mutation in the HIV-1 RT gene resulting in the K65R amino acid substitution. HIV-1 isolates from patients (n = 20) whose HIV-1 expressed a mean of 3 ZDV-associated RT amino acid substitutions (M41L, D67N,

K70R, L210W, T215Y/F, or K219Q/E/N) showed a 3.1-fold decrease in the susceptibility to tenofovir. Multinucleoside resistant HIV-1 with a T69S double insertion mutation in the RT showed reduced susceptibility to tenofovir.

Cross-resistance

Cross-resistance among certain NRTIs has been recognized.⁸ The M184V/I and/or K65R substitutions selected *in vitro* by the combination of FTC and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either 3TC or FTC, and either abacavir or didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.

2.6.2 *In vitro* Studies of Emtricitabine

Anti-HIV-1 Activity

The *in vitro* antiviral activity of FTC against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells.⁹ The EC₅₀ values for FTC were in the range of 0.0013-0.64 µM (0.0003 – 0.158 µg/mL). In drug combination studies of FTC with NRTIs (abacavir, 3TC, stavudine [d4T], zalcitabine, ZDV), NNRTIs (delavirdine, EFV, NVP) and protease inhibitors (amprenavir, nelfinavir, RTV, saquinavir), additive to synergistic effects were observed. FTC displayed antiviral activity *in vitro* against HIV-1 clades A, B, C, D, E, F, and G (EC₅₀ values ranged from 0.007 to 0.075 µM) and showed strain specific activity against HIV-2 (EC₅₀ values ranged from 0.007 to 1.5 µM).

Resistance

FTC-resistant isolates of HIV have been selected *in vitro*.⁹ Genotypic analysis of these isolates showed that the reduced susceptibility to FTC was associated with a mutation in the HIV RT gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I). FTC-resistant isolates of HIV have been recovered from some patients treated with FTC alone or in combination with other ARV agents. In a clinical study, viral isolates from 6/16 (37.5%) treatment-naïve patients with virologic failure showed >20-fold reduced susceptibility to FTC. Genotypic analysis of the isolates showed that resistance was due to M184V/I mutations in the HIV RT gene.

Cross-resistance

FTC-resistance isolates (M184V/I) were cross-resistant to 3TC and zalcitabine but retained susceptibility *in vitro* to didanosine, d4T, tenofovir, ZDV, and NNRTIs (delavirdine, EFV, and NVP).⁹ Isolates from heavily treatment-experienced patients containing the M184V/I amino acid substitution in the context of other NRTI resistance-associated substitutions may retain susceptibility to tenofovir. HIV-1 isolates containing the K65R substitution, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by FTC. Viruses harboring mutations conferring reduced susceptibility to d4T and ZDV (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to FTC. HIV-1 containing the K103N substitution associated with resistance to NNRTIs was susceptible to FTC.

2.6.3 *In vitro* Studies of FTC and TDF in Combination

Anti-HIV-1 Activity

In combination studies evaluating the *in vitro* antiviral activity of tenofovir and FTC together, synergistic antiviral effects were observed.¹⁰

Resistance

HIV-1 isolates with reduced susceptibility to the combination of emtricitabine and tenofovir have been selected in cell culture.¹⁰ Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT.

Mitochondrial Toxicity

In vitro studies were conducted to assess the potential of mitochondrial toxicity of tenofovir, 3TC, FTC, didanosine, d4T, abacavir, and ZDV, either alone or in specified dual and triple combinations.¹⁴ HepG2 cells were treated for up to 25 days with NRTI concentrations equal to 1 time to 10 times the maximal therapeutic levels. Tenofovir and FTC whether administered alone or in combination, demonstrate low potential for interfering with mitochondrial function.

2.6.4 Condom Compatibility Studies of Tenofovir 1% Gel

The compatibility of tenofovir 1% gel was also tested with three types of lubricated male latex condoms.¹¹ A matched placebo gel and HEC placebo gel (planned for this trial) were used as comparator gels. The condoms tested were representatives of leading brands on the US market (Trojan[®] and Durex[®]) with either silicone or aqueous lubricant. The airburst test was used to evaluate changes in film integrity (strength) and test specimens were measured before and after treatment with the gels to assess changes in strength properties following the application of the three gel preparations. All three gels were shown to be compatible with the above condoms. The compatibility of tenofovir 1% gel with Alatech[™] Healthcare male latex silicone lubricated condoms was also evaluated, with matched placebo gel was used as a comparator. The two application treatments of tenofovir 1% gel and matched placebo gel increased airburst volumes by 5 – 6 L compared with the baseline. With an increase in volumes there was a decrease in airburst pressures by 0.2kPa. This implies a physical change to a more elastic condom. This slight change in physical properties suggests an interaction of the tenofovir 1% gel with the silicone lubricant, but does not indicate that the condoms are unsuitable for use in clinical studies.

2.6.5 *In vitro* and Condom Compatibility Studies of Placebo Gel

Dilutions of the HEC gel in culture medium exhibited negligible toxicity to human vaginal epithelial cells (standard MTT assay), even at the lowest dilution tested (1:2).¹² Exposure of human vaginal epithelial cells to the HEC gel resulted in minimal IL-1 α induction, even at the lowest dilutions tested (lowest dilution, 1:2).

Analyses of pH (HEC gel mixed with human seminal plasma, 8.03 \pm 0.26) found that a HEC formulation did not show significant buffering capacity and could not acidify the alkaline pH of seminal plasma, a favorable property for a placebo formulation.²⁶ *In vitro*

assessments of spermicidal activity utilizing human semen from healthy donors showed that HEC gel had no significant deleterious effects on sperm motility, even after 60-minute incubation.

The effects of HEC-based placebo gel on three brands of condoms including Trojan Enz[®], Durex[®] and Trojan Supra[®] have been evaluated.¹¹ The physical properties of the three types were not significantly affected. Although there were slight increases in airburst volume for all types, and increase in pressure for synthetic condoms following gel exposure, this was considered normal and not statistically significant. Tensile testing of condoms is expected to be completed prior to activation of VOICE.

2.7 Animal Studies

2.7.1 Animal Studies of Tenofovir and Tenofovir Disoproxil Fumarate

Toxicology

Tenofovir and TDF administered orally in toxicology studies to rats, dogs, and monkeys at exposures (based on AUCs) ≥ 6 fold those observed in humans caused bone toxicity.⁸ In monkeys bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in some monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown.

Four gravid rhesus monkeys were administered tenofovir subcutaneously once daily from 20 to 150 days of gestation (30 mg/kg; term: 165 ± 10 days).¹⁵ Fetuses were monitored sonographically, and maternal and fetal blood and urine samples were collected to assess hematologic parameters, clinical chemistry, insulin-like growth factor (IGF) levels, and bone biomarkers. Fetuses were delivered by hysterotomy near term for necropsy and evaluation of bone-related mechanical properties. Results of these studies showed 1) normal fetal development, although overall body weights and crown-rump lengths were less than those for age-matched controls ($p \leq .03$); 2) a significant reduction in circulating IGF-I ($p < .001$); 3) a small reduction in fetal bone porosity ($p \leq .03$); and 4) transient alterations in maternal body weights and bone-related biomarkers during treatment. Results of these studies suggest that chronic fetal exposure to subcutaneous tenofovir at the maternal dose of 30 mg/kg throughout gestation can alter select fetal parameters and transiently affect maternal bone biomarkers.

Evidence of renal toxicity from oral TDF was noted in 4 animal species.⁸ Increases in serum creatinine, blood urea nitrogen, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term oral carcinogenicity studies of TDF in mice and rats were carried out at exposures up to approximately 16 times (mice) and 5 times (rats) those observed in

humans at the therapeutic dose for HIV infection.⁸ At the high dose in female mice, liver adenomas were increased at exposures 16 times that observed in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose. TDF was mutagenic in the *in vitro* mouse lymphoma assay, but negative in an *in vitro* bacterial mutagenicity test (Ames test). In an *in vivo* mouse micronucleus assay, TDF was negative when administered to male mice.

Reproductive Toxicity

There were no effects on fertility, mating performance or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating, and to female rats for 15 days prior to mating through day seven of gestation.⁸ There was, however, an alteration of the estrous cycle in female rats. Reproduction studies performed in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons revealed no evidence of impaired fertility or fetal harm due to tenofovir. Subcutaneous administration of TDF to pregnant rhesus macaques resulted in a fetal/maternal concentration of 60%, demonstrating that TDF does cross the placenta.¹⁶ Studies in rats have shown that tenofovir passes into breast milk.

Effectiveness

Adult male rhesus macaques were inoculated intra-rectally once weekly for 14 weeks (or until they became infected) with SHIV_{SF162P3} at 10 median tissue culture infective doses (3.8×10^5 virus particles) that were approximately five-fold higher than the HIV-1 RNA levels noted in human semen during acute infection.¹⁷ Of the 12 macaques studied, 4 received oral TDF daily, 4 received oral TDF once weekly, and 4 control animals received no TDF. The control animals became infected after receiving a median of 1.5 virus inoculations; macaques receiving TDF daily and those receiving TDF weekly became infected after a median duration of 6.0 and 7.0 weeks, respectively. The animals continued to receive TDF after infection. One macaque in the daily TDF group remained uninfected after 14 weekly inoculations of virus. The K65R mutation was not detected in viral sequences from the infected animals through 31 weeks of the study. Although infection was delayed in treated macaques, compared with control macaques, the differences were not statistically significant ($p = .315$); however, the study was limited by the small numbers of animals evaluated and the variability in blood TDF levels that resulted from oral dosing. These data demonstrate that treatment with oral TDF provided partial protection against SHIV infection but ultimately did not protect all TDF treated animals against multiple virus challenges.

2.7.2 Animal Studies of Emtricitabine

Toxicology

In long-term oral carcinogenicity studies of FTC, no drug-related increases in tumor incidence were found in mice or rats.⁹ FTC was not genotoxic in the reverse mutation bacterial test, mouse lymphoma or mouse micronucleus assays.⁹

Reproductive Toxicity

FTC did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures than in humans.⁹ Fertility was normal in the offspring of mice exposed daily from before birth (*in utero*) through sexual maturity at daily doses approximately 60-fold higher than human exposure at the recommended dose. Reproduction studies in rats and rabbits at doses up to 14 and 19 times the human dose based on body surface area comparisons revealed no evidence of impaired fertility or harm to the fetus due to FTC.¹⁸ The incidence of fetal variations and malformations was not increased in embryofetal toxicity studies performed with FTC in mice at exposures (AUC) approximately 60-fold higher and in rabbits at approximately 120-fold higher than human exposures at the recommended daily dose.

2.7.3 Animal Studies of Emtricitabine and Tenofovir in Combination

Toxicology

A 14-day oral gavage toxicity study comparing non-degraded and degraded FTC/TDF was conducted in rats.¹⁴ There were no treatment-related effects on body weight, food consumption, hematology, biochemistry, or urinalysis parameters. There were marginal increases in the weights of adrenal glands in most groups, although no gross or histological changes were identified that might account for this change in weight. No treatment-related gross changes were observed at necropsy. Hyperplasia of the anterior duodenal mucosa overlying Brunner's glands, which was considered treatment-related, was seen at the high-dose level in 7 of the 10 rats treated with non-degraded FTC/TDF and in 2 of the 10 rats receiving degraded FTC/TDF.

A 4-week toxicity study in male dogs showed TDF at 30 mg/kg or in combination with 20mg/kg FTC minimally increased activated partial thromboplastin time and creatinine.¹⁴ Minimal tubular epithelial necrosis and slight to moderate tubular epithelial regeneration were also seen in dogs given TDF at 30mg/kg or in combination with 20mg/kg FTC. Renal findings were reversible after a 4-week recovery period (examined for FTC/TDF only). The no-observed-adverse-effect level of FTC/TDF is 2/3 mg/kg/day in dogs.

A fixed combination (2:3 ratio) of FTC/TDF was negative for the *in vitro* bacterial assay (Ames assay).¹⁴ This combination was positive for inducing forward mutations in the *in vitro* mouse lymphoma cell assay in the presence or absence of S9 metabolic activation. Increases in mutant frequency occurred at concentrations similar to that observed in TDF alone.

Effectiveness

A study conducted by the U.S. Centers for Disease Control (CDC) involved 3 groups of primates that received either FTC alone or a combination of tenofovir (oral or subcutaneous PMPA) and FTC as PrEP.¹⁹ Three drug treatments with different antiviral activity were each given once daily to a group of six rhesus macaques. Group 1 was treated with a human equivalent dose of subcutaneous (SQ) FTC (20 mg/kg; see next paragraph). Group 2 received oral FTC and TDF (20 mg/kg and 22 mg/kg, respectively) at a dose equivalent to Truvada in humans. Group 3 received SQ FTC (20 mg/kg) and a higher dose of tenofovir (22 mg/kg). Based on approximately double the molecular

weight and a 25%–50% tenofovir bioavailability in macaques following oral TDF administration, this dose corresponds to about 66–88 mg/kg of TDF given orally, or 3- to 4-fold the human equivalent dosing. Intermittent PrEP was given to a fourth group of macaques who received SQ the FTC and high-dose tenofovir used in group 3 only 2 h before and 24 h after each weekly virus challenge. A total of 18 control macaques did not receive any drug treatment. Of these macaques, nine were part of this study and nine were historical controls from earlier Rhesus macaque studies done under identical conditions with the same virus stock, inoculum size, and inoculation protocol.

Macaques were exposed rectally once weekly up to 14 weeks with a low dose of simian/human immunodeficiency virus (SHIV)_{SF162p3} (10 TCID₅₀ or 7.5x10⁶ vRNA) that expresses an R5 tropic HIV-1 envelope resembling transmitted HIV-1. Exposures stopped when a macaque became infected. Infection was monitored by serology and PCR amplification of SHIV *gag* and *pol* sequences from plasma and peripheral blood lymphocytes, respectively. Of 18 control animals, 17 became infected after a median of two challenges (range one to twelve). In group 1 (SQ FTC only), four of six animals become infected after 5, 10, 12, and 13 exposures (exact log-rank $p = 0.004$, Cox proportional hazard ratio [HR] = 3.8 compared to controls), respectively. In group 2 (oral FTC/TDF), only 2 of 6 animals become infected after 9 and 12 exposures ($p = 0.0004$, HR = 7.8), respectively. In group 3 (SQ FTC/PMPA), all 6 macaques were protected after 14 challenges ($p = 0.00005$).

In summary, using a repeated exposure model that attempts to simulate human transmission, investigators found that FTC alone or in combination with 2 different doses of TDF provides protection against rectal infection. Data demonstrate that full protection is possible and show a correlation between the level of protection and ARV potency. The model suggests that chemoprophylaxis with potent combinations may be more effective than single drugs in preventing sexual HIV transmission in humans.

The six rhesus macaques infected rectally with (SHIV)_{SF162p3} during chemoprophylaxis with FTC ($n = 4$) or FTC/TDF ($n = 2$) underwent further investigation. Daily treatment with their assigned study product SQ injections with FTC (20 mg/kg) or an oral combination of FTC/TDF (20 mg/kg FTC and 22 mg/kg TDF) was continued for 30 weeks after infection. Viral load dynamics and immunologic responses were monitored in these macaques and were compared with those seen in 13 untreated controls. Drug resistance was monitored by sequencing of SIV RT and by a sensitive real-time polymerase chain reaction (RT-PCR) assay for M184V. Median peak viremia in treated macaques was 2.0 log₁₀ lower than in untreated controls (4.9±0.5 log₁₀ vs. 6.9±0.3 log₁₀) and remained low during a follow-up period of 9 to 28 weeks. All untreated controls had detectable viremia during a median follow-up of 7 weeks (range 5 to 36 weeks). In contrast, 2 FTC and 1 FTC/TDF failures had undetectable virus loads at weeks 3, 4, and 7, respectively. Breakthrough viruses were all wild type. The M184V mutation emerged in 1 FTC and 1 FTC/TDF failure at 3 and 8 weeks after seroconversion, respectively. These 2 animals had higher peak viremia (7.13 log₁₀ and 5.6 log₁₀ vRNA/mL, respectively) than the 4 macaques that did not select M184V (5.4, 4.7, 4.3,

and 3.5 log₁₀ vRNA/mL) during extended treatment (median, 23 weeks). The TDF-associated K65R mutation was not detected in the two FTC/TDF failures.

In summary, breakthrough infections with SHIV during FTC or FTC/TDF chemoprophylaxis were associated with wild type viruses and a substantial reduction in viremia. Emergence of drug resistance correlated with higher plasma viremia and was not observed in animals with substantially blunted viremia. The investigators concluded that reduced primary viremia during chemoprophylaxis failure may have important implications for diminished transmissibility and slower disease progression.

2.7.4 Animal Studies of Tenofovir 1% Gel

Pharmacokinetics

Single-dose PK of vaginally administered tenofovir gel in female rabbits has been previously examined (0.5 mL, 1% w/v tenofovir, 5 mg/animal, 50 µCi/kg).²⁰ Plasma radioactivity concentrations were highest at the first sample time point (0.5 hr) and below the level of quantification at 24 hours. PK parameters including the proportion of dose absorbed systemically could not be estimated, due to the very low plasma concentrations.

In a tissue distribution study using the same radiolabeled tenofovir 1% vaginal gel formulation, dose and strength as the above study, eighteen female rabbits were administered an intravaginal dose using a gavage needle.¹¹ An additional eighteen rabbits received an intravaginal dose of 3% w/v tenofovir (15 mg per animal). Analysis of vaginal tissue sections found no clear relationship between tissue concentration and dose, with no consistent pattern of distribution. Very little radioactivity was recovered in non-vaginal tissues. Concentrations in blood (0.002 to 0.047 µg-eq/g of tissue) exemplified the variability of distribution of the product although the effect of oral absorption due to grooming behaviors of the animals may have impacted these results.

The PK, excretion and tissue distribution of ¹⁴C-PMPA were evaluated in rats following intravaginal administration of an earlier formulation of tenofovir gel containing propylene glycol.²¹ Four female rats received a single intravaginal dose administered as an aqueous gel containing 20 mg tenofovir/g. Plasma concentrations of total radioactivity were highly variable; this was attributed to inconsistent retention of the formulation within the vagina, or possibly oral absorption related to grooming. The apparent C_{max} for tenofovir occurred at the earliest time point (15 minute), suggesting that absorption from the vagina was relatively rapid. Thereafter, plasma concentrations declined with an approximate half-life of 1.6 hours. The bioavailability of intravaginal tenofovir was estimated by comparison of the observed AUC₍₀₋₂₄₎ with historical AUC data for an intravenous dose of 10 mg/kg tenofovir in rats (9.71 µg h/mL). The observed systemic bioavailability of intravaginal tenofovir was 7.9%.

In the excretion and distribution study, two groups of four additional rats received a single intravaginal dose of ¹⁴C-PMPA (approximately 10 mg/kg, 100 µCi/kg) administered as aqueous gel containing 20 mg tenofovir/g. This study found that much

of the dose was lost from the vaginal orifice by leakage. Vaginal tissue contained 0.1% of the dose and less than 0.01% of the dose was recovered in the ovaries and uterus.

The PK of radiolabeled tenofovir gel was evaluated via plasma and vaginal biopsies collected from four rhesus monkeys following single-dose intravaginal tenofovir 1% vaginal gel.¹¹ Radioactivity was detected starting at 15 minutes post application, with peak concentration of tenofovir in vaginal tissue at 8 hours and remaining high at 12 hours. No significant radioactivity was detected in whole blood or plasma.

Toxicology

The preclinical toxicity of tenofovir gel has been evaluated in 14-day rat and 10-day rabbit vaginal irritation and toxicity studies.^{20,22} Daily intravaginal administration of tenofovir gel produced no vaginal irritation in rats ($\leq 10\%$ tenofovir) and minimal to mild vaginal irritation in rabbits (3% or 10% tenofovir).

14-Day Vaginal Irritation and Toxicity Study of Tenofovir Gel in Rats

Ten female Sprague Dawley rats/group received either 0% (vehicle control), 1%, 3%, or 10% tenofovir gel (2.5% HEC formulation) by intravaginal administration (0.5 mL/dose) once daily for 14 days. There were no mortalities, and no tenofovir-related clinical signs of toxicity or changes in body weight, food consumption, or absolute/relative kidney weights. Individual and mean vaginal (gross) irritation scores for all tenofovir-dosed animals sacrificed at Day 15 were graded as 0 (no erythema or edema); microscopic irritation scores for the vagina, cervix, ovaries, uterine horns, and vulva were graded as 0 (normal histology). No tenofovir-related histopathological effects on the vagina, cervix, ovaries, uterine horns, vulva, or kidneys were observed.

10-Day Vaginal Irritation Study of Tenofovir Gel in Rabbits

The potential irritant effects of tenofovir were evaluated in vaginal tissues of female New Zealand White rabbits using three different gel formulations (2.5% HEC or 1.0 – 2.0% Carbopol[®] 1342).²³ This study consisted of eleven treatment groups (five rabbits/group) that received either: a sham treatment or Conceptrol[®] (positive control); 0%, 0.3%, 1.0%, 3.0%, or 10.0% tenofovir formulated in the HEC gel preparation; or 0% or 3.0% tenofovir formulated in a 1.0% or 2.0% Carbopol[®] 1342 gel preparation. With the exception of the sham dose group, all rabbits received dose formulation (1.0 mL/dose) daily applied topically to the mucosal surface of the vaginal vault for 10 consecutive days. No mortalities and no tenofovir-related clinical signs of toxicity or body weight changes were observed in this study. Group composite vaginal irritation scores for the 10% tenofovir topical gel (HEC formulation), 0% tenofovir (1.0% Carbopol[®] 1342 formulation), and Conceptrol[®] (positive control) dose groups were each rated as “mild.” Composite vaginal irritation scores rated “minimal” were observed for all other tenofovir, vehicle or sham treatment groups, regardless of the formulation. No unacceptable level of mucosal irritation was observed in any treatment group based on the protocol-derived criteria for this animal model. Generalized erosion and/or ulceration were observed only in animals receiving Conceptrol[®] positive control (two of five) or the 10% tenofovir topical gel (two of five).

Effectiveness

Six independent non-human primate studies provided some degree of evidence for efficacy using 1% or 10% gel. Although these data are limited and a powered statistical determination as to the efficacy of tenofovir 1% gel versus 10% cannot be made, empirical examination of the efficacy data identifies tenofovir 1% gel as the lowest efficacious concentration tested when given within two hours of virus challenge. All studies used SIVmac251, a highly infectious SIV isolate, and Indian-origin rhesus macaques (with the exception of study 6). Study 1 demonstrated protection of all four macaques that received 10% tenofovir gel as compared to no protection in the 2 macaques that received placebo gel. Likewise in study 2, 11 of 15 macaques that received 1% or 10% tenofovir gel were protected as compared to no protection in the 5 untreated control macaques that received no gel product. In studies 3, 4, and 5, <100% of the untreated controls were infected making these data problematic to interpret.

Table 2: Use of Topical Tenofovir to Prevent Vaginal Transmission of SIV

Study*	Number of Exposures	Treatment	Time of Administration	Number Infected	Progesterone Pretreatment
1	2	1 mL vehicle	-24 h, 0 h, 24 h, 48 h	2 of 2	No
		10% tenofovir	-24 h, 0 h, 24 h, 48 h	0 of 4	
2	1	untreated control	N/A	5 of 5	No
		10% tenofovir	-24 h, -15 m, +24 h	1 of 5	
		1% tenofovir	-24 h, -15 m, +24 h	1 of 5	
		1% tenofovir	-15 m	2 of 5	
3	1	untreated control	N/A	2 of 5	No
		vehicle	-15 m	1 of 5	
		1% tenofovir	-15 m	1 of 5	
		1% tenofovir	-2 h	3 of 5	
		1% tenofovir	-8 h	1 of 5	
4	1	untreated control	N/A	4 of 5	No
		vehicle	-15 m	2 of 5	
		1 % tenofovir	-15 m	1 of 5	
		1 % tenofovir	-2 h	1 of 5	
		1 % tenofovir	-8 h	2 of 5	
5	1	untreated control	N/A	2 of 5	No
		vehicle	-2 h	2 of 5	
		1 % tenofovir	-2 h	0 of 5	
6	1	1 % tenofovir	-12 h	5 of 8	Yes
		vehicle	-12 h	8 of 8	
		1 % tenofovir	-24 h	8 of 8	
		vehicle	-24 h	8 of 8	
		untreated control	N/A	8 of 8	
		1 % tenofovir	-72 h, -48 h, -24 h	6 of 8	

* All studies were performed with the SIVmac251 isolate of SIV, and female rhesus macaques were inoculated intravaginally. Virus challenges were performed without progesterone pretreatment in Studies 1–5; macaques in Study 6 were pretreated with 30 mg Dep-Provera 30 days prior to viral challenge. The indicated studies were performed by 3 independent investigators with Studies 2, 3, 4, and 5 being performed by the same laboratory.

Study 6 was different from the first five studies in that Chinese-origin rhesus macaques were used and they were pretreated with progesterone before virus challenge to enhance susceptibility to infection and synchronize reproductive cycles. This study was designed to determine whether topical dosing of tenofovir gel could be disassociated from the coital act while remaining an effective microbicide, in a regimen consistent with

the long intracellular half-life of the active metabolite, tenofovir diphosphate. A total of 48 macaques, pretreated with a 30 mg dose of depomedroxyprogesterone acetate (DMPA) 30 days prior to viral challenge, were divided into 6 groups of 8 animals each. Group 1 received one topical vaginal dose of tenofovir 1% gel 12 hours prior to one intravaginal viral challenge with a dilution of SIVmac251 stock representing approximately 50 TCID₅₀. In parallel, Group 2 received matched placebo gel. Group 3 received a single dose of tenofovir 1% gel 24 hours prior to viral challenge. The matched placebo gel was administered to Group 4 24 hours prior to viral challenge. Group 5 was an untreated control group receiving only the viral challenge. A single dose of tenofovir 1% gel was administered topically to Group 6 animals at 72, 48, and 24 hours prior to viral challenge. Thus, Group 6 animals received 3 consecutive days of gel; Group 4 served as the placebo control for Group 6. Based on plasma viral load, all untreated control animals became infected as did all placebo gel-treated macaques. Three animals were protected from infection in Group 1 receiving a single dose of 1% tenofovir gel 12 hours prior to virus exposure. Although no macaques receiving a single dose of tenofovir 1% gel 24 hours prior to virus exposure were protected, two of eight animals in Group 6 receiving multiple doses of tenofovir 1% gel remained uninfected. Infection status was confirmed using virus co-culture, seroconversion and lymph node DNA PCR. These data show 24 of 24 placebo gel-treated or untreated macaques became infected with SIVmac251 while 5 of 24 macaques were protected from SIV infection by vaginally administered tenofovir 1% gel.

Progesterone pretreatment (30 mg DMPA) is used in macaque studies to increase susceptibility to infection by a mechanism thought to involve thinning of the vaginal epithelium. It is generally required to achieve 100% infection in untreated control animals challenged with less infectious SHIV chimeric viruses. Although animals were pretreated with DMPA in this study but not the previous studies (1–5), this pretreatment may not be required for such a highly infectious virus as SIVmac251. In view of the potent infectivity of this virus, the lack of an endpoint in the animal titration of this stock (personal communication), and increased susceptibility resulting from progesterone pretreatment, it is possible that the amount of virus used was too high, thereby masking any protective effect. Further studies are required to understand the factors that impact protection by intravaginal tenofovir gel in the macaque model.

2.7.5 Animal Studies of Hydroxyethylcellulose and Placebo Gel

HEC is the thickener in the placebo gel. The results of multiple animal studies have been consistent with the safety of this ingredient.

Hydroxyethylcellulose

Up to 55 intravenous injections of HEC were given to dogs (dose and number not specified) without causing injury other than that typical of the other water-soluble cellulose ethers.¹² Only transitory changes in the blood picture and the deposition of the material on the intima of the blood vessels were noted. Groups of rats maintained for two years on diets containing HEC (n not specified, up to 5%) did not exhibit any

adverse effects.¹² HEC has also been administered to rats in single oral doses as high as 23,000 mg/kg without observed toxic effects (n not specified).

Intraperitoneal administration of unformulated HEC to pregnant mice in a 1% and 4% concentration caused an increase in resorptions, but no detectable increase in birth defects.²⁴ While no epidemiological studies of congenital anomalies in infants born to women exposed to HEC during pregnancy have been reported, the Teratogen Information System (TERIS) considers the magnitude of teratogenic risk to a child born after exposure during gestation to be none.²⁵

Placebo Gel

CF-1 mice (n not specified) pretreated with medroxyprogesterone acetate were administered 0.02 mL of HEC gel vaginally, followed by a 0.01 mL inoculum of 10 intravaginal dose₅₀ units of HSV-2 0.3 minutes later.²⁶ On day 3, vaginal lavage was cultured on human foreskin fibroblasts, and mice were considered infected if a cytopathic effect was observed after 3 days of incubation. Control animals were treated similarly but were not administered the test article. Infection rate following pretreatment with HEC gel (90%) was not significantly different from pretreatment with PBS (80%) or from mice given no treatment (% not specified). HEC gel did not enhance susceptibility of mice to HSV-2 when administered 12 hours before vaginal challenge.¹²

A 10-day rabbit vaginal irritation study (10/arm, 2 arms, HEC gel vs. 0.9% saline control) found that the HEC gel was not irritating to the vaginal mucosa of rabbits when dosed daily for 10 days. One animal in the HEC gel group had an instance of vaginal redness (compared to four animals in the saline group), which did not persist and was not evident at the end of the study. Diarrhea, few feces, and soiling of the anogenital area were noted in that animal. Body weight changes were noted to be normal. In 9 of 10 animals, necropsy results were normal. Anogenital soiling was observed in the animal that exhibited erythema during the in-life phase of the study. Histopathological changes observed were similar to those seen in the control group and likely attributable to those that occur as a result of the repeated insertion of a catheter, rather than due to any effect of the test samples.

The effect of the placebo gel on vaginal transmission of SHIV_{162p3} (10^3 TCID₅₀) to rhesus monkeys (n = 5, n = 3, respectively) was determined in two separate studies.¹² Macaques pretreated with medroxyprogesterone acetate were vaginally administered 1 mL of the HEC gel formulation 15 minutes prior to challenge with 0.5 mL SHIV_{162p3}. Investigators monitored total RNA load in the animal plasma for a total of 8 weeks by means of a standard quantitative RT-PCR. The first study utilized the HEC gel formulation at pH 6.5; the second study utilized a formulation at pH 4.4. In both studies, all monkeys were infected, as determined by the presence of viral RNA in circulating blood, regardless of the pH of the formulation.

2.8 Clinical Studies

2.8.1 Clinical Studies of Tenofovir Disoproxil Fumarate 300 mg Tablet

Pharmacokinetics

TDF PK have been evaluated in healthy volunteers and HIV-1 infected individuals.⁸ Tenofovir PK are similar between these populations and between male and female patients. Oral bioavailability of tenofovir from TDF in fasted patients is approximately 25%. *In vitro* binding of tenofovir to human plasma proteins is <0.7% and is independent of concentration over a range of 0.01-25 µg/mL. Following oral administration of one dose of TDF 300 mg to HIV-1 infected patients in the fasted state, maximum serum concentrations are achieved in 1.0 ± 0.4 hrs. Maximum serum concentration and AUC values are 296 ± 90 ng/mL and 2287 ± 685 ng-hr/mL, respectively. Approximately 70-80% of the intravenous dose of tenofovir is recovered as unchanged drug in urine. Tenofovir is eliminated by glomerular filtration and active tubular secretion. Following a single oral dose of TDF 300 mg, the terminal elimination half-life of tenofovir is approximately 17 hours. The PK of individual doses of tenofovir are dose proportional over a TDF dose range of 75 to 600 mg and are not affected by repeated dosing.

Safety

Gilead Study 903, a randomized, double-blind trial conducted in the United States, Europe and South America, was designed to compare the efficacy and safety of a treatment regimen of TDF, 3TC and EFV to a regimen of d4T, 3TC and EFV in 600 ARV-naïve HIV-1 infected patients in a 144-week, double-blind phase. Patients who completed the 144-week double-blind phase on TDF were then eligible to roll over to the extension phase (weeks 144-480). In the double-blind phase, the most common (occurring in 2% or greater of tenofovir recipients) AEs emerging after treatment with TDF plus EFV and 3TC in HIV-infection treatment naïve adults included whole body (headache, pain, fever, abdominal pain, back pain, asthenia), gastrointestinal (diarrhea, nausea, dyspepsia, vomiting), musculoskeletal (arthralgia, myalgia), nervous system (depression, insomnia, dizziness, anxiety), respiratory (pneumonia), and skin rash. The most frequent laboratory abnormalities were elevations in fasting cholesterol, creatine kinase, amylase, AST or ALT, hematuria, and decreased absolute neutrophil count. The frequency of all these events and laboratory abnormalities was similar or lower in the tenofovir treated group compared to the d4T-treated group.

Follow-up data from an interim 288-week analysis of patients who enrolled in the extension phase of the study have recently been reported.²⁷ Eighty-six patients (62% male, 70% white) initially randomized to the TDF arm continued treatment with TDF. No patient discontinued TDF due to renal events. Mean limb fat increased from 8.0 kg at week 96 to 8.8 kg at week 288. Thus, sustained TDF therapy was not associated with renal AEs or limb fat loss. Tenofovir is eliminated by the renal route, including tubular secretion. Thus, dose-interval adjustments are necessary for TDF in patients with significant renal impairment. TDF-induced nephrotoxicity has been reported in some series,²⁸ especially in patients with other medical problems or pre-existing renal dysfunction, although observational prospective studies tend to accord with Gilead

Study 903 in a finding of absence or low frequency of significant renal dysfunction,²⁹ when renal dysfunction occurs, it is generally predictable based on identifiable risk criteria.³⁰ One study that followed 27 HIV-infected children treated with TDF for 96 weeks found no evidence of impaired glomerular or tubular renal function.³¹

In Gilead Study 903 through 144 weeks, decreases from baseline in bone mineral density (BMD) were seen at the lumbar spine and hip in both arms of the study. At Week 144, there was a significantly greater mean percentage decrease from baseline in BMD at the lumbar spine in patients receiving TDF + 3TC + EFV (-2.2% ± 3.9) compared with patients receiving d4T + 3TC + EFV (-1.0% ± 4.6). Changes in BMD at the hip were similar between the two treatment groups (-2.8% ± 3.5 in the TDF group vs. -2.4% ± 4.5 in the d4T group). In both groups, the majority of the reduction in BMD occurred in the first 24–48 weeks of the study and this reduction was sustained through Week 144. Twenty-eight percent of TDF-treated patients vs. 21% of d4T treated patients lost at least 5% of BMD at the spine or 7% of BMD at the hip. Clinically relevant fractures (excluding fingers and toes) were reported in four patients in the TDF group and six patients in the d4T group. In addition, there were significant alterations in biochemical markers of bone metabolism (serum bone specific alkaline phosphatase, serum osteocalcin, serum C-telopeptide, and urinary N-telopeptide) in the TDF group relative to the d4T group, suggesting increased bone turnover. Serum parathyroid hormone levels and 1.25 Vitamin D levels were also higher in the TDF group. Except for bone specific alkaline phosphatase, these changes resulted in values that remained within normal range. Importantly, changes in BMD at the lumbar spine and hip noted in the first 48 weeks of the study were non-progressive through 288 weeks in the extension phase. However, the effects of TDF-associated changes in BMD and biochemical markers on long-term (>144 weeks) bone health and the risk of future fracture are unknown.

Severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV and have discontinued TDF. Both TDF and FTC are highly active against hepatitis B virus (HBV) and are recommended as part of the ART regimens in HIV/HBV co-infected individuals.^{32,33} However, HBV exacerbations (defined as significant increase in hepatic transaminases) have been observed after stopping TDF, adefovir (a nucleotide similar to TDF) or 3TC (closely related to FTC) in approximately 20% of persons with chronic active hepatitis B.^{34,35} Flares have typically been self-limited, but more serious liver decompensation has been reported.³⁶ While the risk is thought to be greater among persons with clinically apparent liver disease, and may be even lower in HIV-uninfected persons, it has not been studied in detail. For this reason, it is recommended that hepatic function be monitored closely with both clinical and laboratory follow-up for at least several months in patients who are coinfecting with HIV and HBV and discontinue TDF for at least several months after TDF and/or FTC are discontinued.

Peterson, et al. evaluated the safety of TDF 300 mg daily versus placebo for prevention of HIV-1 infection in women in a Phase 2 double-blind study conducted at 3 sites in West Africa.³⁷ The study closed prematurely resulting in insufficient power to evaluate

efficacy. In the primary safety analysis, with 428 person-years (p-y) of follow up, there was no significant difference in the rate of safety endpoints (defined as grade 2 or higher serum creatinine, grade 3 or 4 transaminase elevation, or grade 3 or 4 phosphate abnormality). Among the 368 participants on TDF, none had grade 3 or 4 transaminase elevation or grade 2 or higher creatinine. One TDF recipient had self-limited grade 3 phosphate. Additional safety information from clinical studies on the TDF 300 mg tablet is available in the package insert at: http://www.gilead.com/pdf/viread_pi.pdf.

Pregnancy Outcomes

The Antiretroviral Pregnancy Registry is intended to provide an early signal of any major teratogenic effect associated with a prenatal exposure to the products monitored through the Registry. The Registry is a voluntary prospective, exposure-registration, observational study designed to collect and evaluate data on the outcomes of pregnancy exposures to ARV products. Data through 07/31/07 show 6 defects among 380 first trimester TDF exposures.³⁸ This rate (1.6%) is not elevated compared to 4/263 (1.5%) after second/third trimester exposure, the 2.67% background rate of defects reported by the Centers for Disease Control Metropolitan Atlanta Congenital Defect Program³⁹, or the generally accepted background rate for birth defects in the US population (approximately 3 – 4%).

Effectiveness as PrEP

In the Peterson study referenced above, HIV seroconversion was observed in 2/427 participants in the TDF group (0.86 per 100 p-y) and 6/432 participants in the placebo group (2.48 per 100 p-y), yielding a rate ratio of 0.35 (95% CI, 0.03-1.93). Because this study was closed prematurely, the number of observed HIV infections was lower than planned; the rates of HIV seroconversion in the two groups were not significantly different. Standard genotypic resistance testing of one of the two participants who seroconverted on TDF revealed no drug resistance mutations.³⁷

2.8.2 Clinical Studies of Emtricitabine

Pharmacokinetics

Following oral administration, FTC is rapidly absorbed with peak plasma concentrations occurring at 1-2 hours post-dose.⁹ *In vitro* binding of FTC to human plasma proteins is <4% and is independent of concentration over the range of 0.02-200 µg/mL. Following administration of radiolabeled FTC, approximately 86% is recovered in the urine and 13% is recovered as metabolites. The metabolites of FTC include 3'-sulfoxide diastereomers and their glucuronic acid conjugate. FTC is eliminated by a combination of glomerular filtration and active tubular secretion. Following a single oral dose of FTC, the plasma FTC half-life is approximately 10 hours. No PK differences due to race have been identified following the administration of FTC.

Safety

More than 2000 adults with HIV infection have been treated with FTC alone or in combination with other ARV agents for periods of 10 days to 200 weeks in Phase 1-3 clinical trials.⁹ Assessment of AEs is based on data from studies FTC-301A and

FTC-303 in which 571 treatment-naïve patients (FTC-301A) and 440 treatment-experienced patients (FTC-303) received FTC 200 mg (n = 580) or comparator drug (n = 431) for 48 weeks. The most common AEs that occurred in patients receiving FTC with other ARV agents in clinical trials were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity. Approximately 1% of patients discontinued participation in the clinical trials because of these events. All AEs were reported with similar frequency in FTC and control treatment groups with the exception of skin discoloration, which was reported with higher frequency in the FTC-treated group. Skin discoloration, manifested by hyperpigmentation on the palms and/or soles was generally mild and asymptomatic. The mechanism and clinical significance are unknown. Laboratory abnormalities in these studies occurred with similar frequency in the FTC and comparator groups.

A randomized, double-blind, double-dummy study, FTC301-A, was carried out in 101 research clinics in North America, Latin America, and Europe, and compared the efficacy and safety of FTC (200 mg once daily) with d4T when used with a background regimen of didanosine and EFV in 571 ARV-naïve persons aged 18 years or older with viral load levels greater than or equal to 5000 copies/mL.⁴⁰ Median follow-up was 60 weeks. Overall, subjects in the d4T group had a greater probability of an AE that led to study drug discontinuation than did those in the FTC group (15% vs. 7%, $p = 0.005$). Skin discoloration was observed in 10 subjects (3%) in the 286 subjects in the FTC group and one patient in the 285 subjects in the d4T group, and was manifested by hyperpigmentation on the palms and/or soles that was generally mild and asymptomatic. In no subject did hyperpigmentation prompt discontinuation of study drug. Importantly, the frequency of other rash events did not differ between the two treatment arms.

The FTC 303/350 study was a controlled, open label equivalence trial of 440 patients with suppressed HIV-1 infection who were randomized to continue their current treatment regimen or replace 3TC with FTC (200 mg daily).⁴¹ Skin discoloration occurred in only 1.7% of subjects in the FTC group and in 1.4% of the 3TC group (difference not significant), and again, generally manifested as increased pigmentation on the palms and/or soles that was mild and asymptomatic. None of these events prompted discontinuation of study drugs.

In summary, available data indicate that hyperpigmentation is a side effect of FTC use, and that the incidence, while likely variable, is low (3% or less). The mechanism and clinical significance of this finding are not known. Whether hyperpigmentation varies with skin color or is associated with other host factors is also not clear.

The safety of FTC in pregnant women and fetuses at doses used in humans is not known.⁹ However, FTC is closely related to 3TC, a drug that is considered to be one of the preferred agents for treatment of pregnant women, and a common agent in regimens used in prevention of maternal to child transmission of HIV.

Exacerbations of HBV have been reported in patients after discontinuation of FTC, as noted above. Patients, who are coinfecting with HBV and HIV, may have increased values on liver function tests and exacerbation of hepatitis symptoms when FTC is stopped. These findings are typically self-limiting; however, serious complications have been reported. The causal relationship to FTC discontinuation is unknown. It is recommended that persons coinfecting with HBV and HIV be closely monitored with both clinical and laboratory follow-up for several months after stopping FTC treatment.⁹

Pregnancy Outcomes

As of 7/31/07, 2 defects among 132 first trimester exposures to FTC and 1 defect among 78 exposures during pregnancy after the first trimester had been reported.³⁸ This rate is not elevated compared to the 2.67% background rate of defects reported by the Centers for Disease Control Metropolitan Atlanta Congenital Defect Program³⁹ or the generally accepted background rate for birth defects (approximately 3 - 4%).

2.8.3 Clinical Studies of Emtricitabine and Tenofovir Disoproxil Fumarate in Combination (Truvada[®])

Pharmacokinetics

A PK study was conducted to establish the bioequivalence of the FTC 200 mg/TDF 300 mg fixed-dose combination tablet relative to administration of FTC capsules and TDF tablets as their individual dosage forms.¹⁰ The steady state PK of FTC and tenofovir were unaffected when FTC and TDF were administered together versus each agent dosed alone. A single FTC/TDF combination tablet and the individual dosage forms were administered to 44 healthy volunteers in a fasted state on two occasions which were separated by a 1-week washout period. Plasma PK parameters at steady-state were assessed over 48 hours post dose using a non-compartmental analysis. Results based on 39 subjects who completed the study revealed that the FTC/TDF combination tablet is bioequivalent to administration of TDF and FTC as their individual dosage forms as 90% of the confidence intervals (CIs) of the geometric mean ratios for C_{max} and AUC were within 80% to 125%.

Truvada[®] may be administered with or without food.¹⁰ Administration of Truvada[®] following a high fat (784 kcal; 49 grams of fat) or a light meal (373 kcal; 8 grams of fat) delayed the time of tenofovir C_{max} by approximately 0.75 hour. Mean increases in tenofovir AUC and C_{max} were approximately 35% and 15%, respectively, when administered with a high fat or light meal, compared to administration in the fasted state. In previous safety and efficacy studies, TDF was taken under fed conditions. FTC systemic exposures (AUC and C_{max}) were unaffected when Truvada[®] was administered with either a high fat or a light meal. *In vitro* and clinical PK drug-drug interaction studies have shown the potential for CYP450 mediated interactions involving FTC and tenofovir with other medicinal products is low. FTC and tenofovir are primarily excreted renally by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of FTC/TDF with drugs eliminated by active tubular secretion may increase concentrations of FTC, tenofovir, and/or the coadministered drug. Drugs that decrease renal function may increase concentrations of FTC and/or tenofovir.

Safety and Efficacy of FTC with TDF

Several studies have assessed the safety and efficacy of FTC with TDF, albeit none using the fixed dose combination.¹⁰ Four hundred and forty-seven HIV-1 infected patients have received combination therapy with Emtriva[®] and Viread[®] with either a NNRTI or protease inhibitor for 48 weeks in clinical studies. AEs and laboratory abnormalities observed in clinical trials were generally consistent with those seen in other studies in treatment-experienced or treatment-naïve patients receiving Emtriva[®] and/or Viread[®].

Study M02-418 was a phase III, randomized, open-label, multicenter study designed to compare lopinavir (LPV) 800 mg/RTV 200 mg QD vs. LPV 400 mg/RTV 100 mg BID with the background regimen of FTC 200 mg QD and TDF 300 mg QD in ARV-naïve patients with HIV-1 RNA >1000 copies/mL.^{42, 43, 44} A total of 190 patients between the ages of 19-75 years were enrolled; 115 to the QD arm and 75 to the BID arm. At week 48, based on the intention to treat (ITT) (NC=F) analysis, 70% of participants in the QD regimen demonstrated HIV-1 RNA <50 copies/mL compared with 64% of those in the BID group (95% CI: -7%; 20%). Gastrointestinal AEs were the most common cause for discontinuation. Overall, the most common AEs (>3%) reported were diarrhea, nausea, and vomiting, with diarrhea being reported significantly higher in the QD group (16% vs. 5%; $p = 0.04$). The most common Grade 3/4 laboratory abnormalities (>3%) reported were increased ALT (>5 x upper limit of normal [ULN]), AST (> 5 x ULN), triglyceride (>750 mg/dL), and amylase (>2 x ULN) levels; no significant differences between the two groups were observed.⁴⁴

Gilead Study 934 is a phase III, randomized, open-label, noninferiority, multicenter study designed to compare a regimen of TDF 300 mg + FTC 200 mg + EFV QD with a regimen of ZDV 300 mg/3TC 150 mg BID (as FD Combivir[®]) + EFV QD in ARV-naïve, HIV-1-infected participants.⁴⁵ The 48-week data demonstrated that using the time to loss of virologic response as the primary analysis (where missing, switch, or early termination is counted as a failure), the proportion of participants with plasma HIV-1 RNA levels < 400 copies/mL in an ITT population (n = 487) was 84% in the TDF + FTC group compared with 73% in the ZDV/3TC group ($p = 0.002$). The proportion of participants with plasma HIV-1 RNA levels < 50 copies/mL was 80% in the TDF+FTC group versus 70% in the ZDV/3TC group ($p = 0.020$). Significant differences were also seen between the TDF+FTC and the ZDV/3TC groups in the proportion of participants with increases in CD4+ cell counts (190 and 150 cells/mm³, respectively; $p = 0.002$). Safety analysis, based on 511 participants who received any study medication, showed that discontinuation due to AEs occurred more frequently in the ZDV/3TC group (9%) than in the TDF + FTC group (4%) ($p = 0.02$). The most common AE resulting in discontinuation related to study drug was anemia for the ZDV/3TC group (14/254) and NNRTI-associated rash (2/257) for the TDF+FTC group. Renal safety was similar in the two groups, and no participant discontinued study medication because of renal events. A significantly ($p < 0.001$) greater percentage of participants in the TDF+FTC arm had a lower mean increase from baseline in fasting total cholesterol levels (21 mg/dL) compared with participants in the ZDV/3TC arm (35 mg/dL). At week 48, total limb fat

was significantly less in a subset of participants receiving ZDV/3TC (mean of 6.9 kg or 15.2 pounds; n = 49) compared with a subset of participants receiving TDF+FTC (mean 8.9 kg or 19.6 pounds; n = 51; $p = 0.03$). All participants with confirmed >400 copies/mL of HIV-1 RNA at week 48 or early discontinuation were analyzed for genotypic resistance. Genotype data were limited to 23 participants on ZDV/3TC and 12 participants on TDF+FTC and showed mostly M184V/I (3% in ZDV/3TC participants vs. 1% in TDF + FTC participants) and/or EFV-resistance mutations (7% in ZDV/3TC vs. 4% in TDF + FTC participants), with no participants developing the K65R mutation.

Exacerbations of HBV have been reported after discontinuation of TDF and FTC, as noted above. HIV-infected persons coinfecting with HBV may have increased values on liver function tests and exacerbation of hepatitis symptoms when TDF or FTC is stopped.¹⁰ Usually symptoms are self-limiting; however, serious complications have been reported. Causal relationship to TDF or FTC discontinuation is unknown. Participants coinfecting with hepatitis B (HBV) and HIV should be closely monitored with clinical and laboratory follow-up for several months after stopping Truvada[®]. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of nucleoside analogues alone or in combination, including FTC, TDF, and other ARVs.

FTC/TDF is designated as FDA use-in-pregnancy Category B. Additional general information about FTC/TDF can be found in the most recent Truvada[®] package insert.¹⁰

2.8.4 Clinical Studies of Tenofovir 1% Gel

Pharmacokinetics

A Phase 1 Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel, also known as HPTN 050, is a recently completed study of tenofovir vaginal gel with published data.⁷² Eighty-four (60 HIV negative and 24 HIV positive) women applied either 0.3% or 1% tenofovir gel once or twice daily for 14 days. Systemic absorption was limited (maximum serum levels 3.1-25.8 ng/mL).

Safety

In HPTN 050, the tenofovir 1% gel formulation was well tolerated in both HIV uninfected and infected women.⁷² Ninety-two percent reported at least one AE. The majority of these events were mild (87%) and limited to the genitourinary tract (77%). The five most reported mild genital AEs were pruritus (n = 18), erythema (n = 14), petechial/ecchymosis (n = 14), vaginal discharge (n = 13), and burning (n = 10). Four severe AEs were reported, but only one (lower abdominal pain) was thought to be product-related. Product concentration, sexual activity and HIV status were not associated with a specific AE pattern. No clinically significant systemic toxicity was observed. No serious adverse events (SAEs) were reported.

Of 76 participants in the HPTN 050 study who had bacterial vaginosis (BV) evaluation (by using Nugent's score criteria) at both enrollment and Day 14, 30 women had asymptomatic BV at baseline and 15 of them became BV negative after 14 days of tenofovir gel use, while one out of 46 women without BV at baseline had BV detected at

14 days. Overall, 40% of the women had asymptomatic BV at baseline compared to 21% of the women after fourteen days of tenofovir gel use ($p = 0.0005$), suggesting that the gel did not increase women's risk of developing BV.

In a male tolerance study (CONRAD A04-099/IND 73,382), tenofovir 1% gel was well tolerated in men following seven days of once daily penile exposure. There were few genital findings observed after product use and all findings were classified as mild, small in size and requiring no treatment. Reported symptoms were mild, of short duration and resolved by the final visit. There were no noticeable differences between signs and symptoms of genital irritation in the circumcised compared to uncircumcised group.⁴⁶

A Phase 2 study of tenofovir 1% gel (HPTN 059) has completed follow up. This study assessed safety and acceptability of, and adherence to a regimen of tenofovir gel for vaginal use in HIV-uninfected women versus a placebo gel. Exploratory objectives included measurement of vaginal flora characteristics, assessment of the effects of gel on genital cytokine and chemokine expression, and the evaluation of cytokine and chemokine expression to correlate expression with evidence of inflammation, epithelial disruption and genital symptoms. The study was a Phase 2 four arm, three site, randomized, controlled trial comparing gel used once daily and gel used prior to intercourse, to placebo gel, with 6 months gel exposure and follow-up. The study was conducted among 200 women in Pune, India; Birmingham, Alabama, USA; and New York, New York, USA. Participants were sexually active, HIV-uninfected women between ages 18 and 50, but not menopausal or post menopausal. Participants had six months of study gel exposure and six months of follow-up. They were randomized to either once daily or coitally dependent group, and received either tenofovir or placebo gel. Participants received single use unit dose tubes and single use applicators.

No statistically significant differences were seen between those receiving active and placebo gels in complete blood count, liver function tests, or renal function tests. Among those using a study gel daily, no participants had pelvic exam findings involving generalized erythema or severe edema or deep epithelial disruption at any follow-up visit during the study. At the Week 24 Visit, no participants had exam findings suggestive of vaginitis, cervicitis, superficial disruption, disrupted blood vessels, or intermenstrual bleeding. Adherence to study gel was high, and was supported by PK data. 79% of women reporting gel use in past 12 hours had low but detectable plasma tenofovir supporting self-reported adherence data. Daily and coital use was highly acceptable to women. These data suggest a favorable safety and acceptability profile of tenofovir gel, and support routine monitoring for genital findings among women without genital symptoms at six month intervals.⁴⁷

Resistance

In HPTN 050, no new resistance mutations evolved in plasma or cervicovaginal lavage after 14 days of tenofovir gel use, but 3 women had plasma mutations associated with low level tenofovir resistance identified at both Days 0 and 14 (M41L, L210M, ±T215I/Y).

2.8.5 Clinical Studies of Placebo Gel

Unformulated HEC is known to be a non-irritating substance in humans (skin sensitization is unusual), with doses less than 2 gm/kg by ingestion not expected to be toxic.⁴⁸ No inhalation studies have been conducted, but exposure of humans to the dust in manufacturing operations over many years has not led to any known AEs. The HEC placebo formulation was developed and adopted for use in HPTN 035 (IND 62,366), the Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides Buffer Gel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women.

A randomized, closed label, Phase 1 study of daily vaginal HEC gel exposure was conducted in 2003.⁴⁹ Thirty women were randomized to twice-daily vaginal applications of 3.5 mL of HEC gel or polystyrene sulfonate (PSS) vehicle. The primary objective of this study was to assess and compare the gels' effects on symptoms and signs of irritation of the external genitalia, cervix, and vagina as seen on naked eye exam after 7 and 14 days of use including disruption as seen on colposcopy after 14 days of use. Both gels appeared safe for use twice a day for 14 days in sexually abstinent women. Two out of 14 women (14.3%) randomized to the PSS placebo gel reported at least one symptom of mild genital irritation, which included genital burning, soreness and pelvic pain. A lower proportion of women in the HEC group experienced any evidence (signs and/or symptoms) of genital irritation. Three out of 14 women (21.4%) had colposcopic findings that included erythema, petechiae and peeling.⁴⁹ No deep genital disruption was observed in either product group. Minimal changes in wet mounts, pH, Nugent scores, neutrophils, and vaginal flora were observed in both product groups.

A pilot study to optimize trial procedures for a proposed Microbicides Development Programme placebo-controlled trial utilized the same Universal Placebo gel as the study gel; no serious adverse product related events reported.¹²

2.9 Other Clinical Studies of Tenofovir for HIV Prevention

Several other studies of the safety and/or effectiveness of tenofovir as an HIV prevention strategy are ongoing or in development. These include studies in Table 3.

Table 3: Studies of Tenofovir 1% Gel Underway or in Development

Location	Sponsor	Population	Design
USA, Dominican Republic	CONRAD A04-095/IND 73,382	Sexually abstinent women	PK study; single dose and 14-day once or twice-daily.
South Africa	CAPRISA	Sexually active women	Phase 2B, two-arm, randomized placebo controlled, coitally dependent
South Africa, Uganda, USA	DAIDS/MTN-001/IND 55,690	Sexually active women	Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir
USA	DAIDS/MTN-002/IND 55,690	Healthy term gravidas	Phase 1 Study of Maternal Single-Dose Pharmacokinetics and Placental Transfer
USA	DAIDS/MTN-007/IND TBD	Sexually abstinent women and men	Phase 1 Rectal Safety

Studies examining the safety and/or effectiveness of oral formulations of tenofovir as a prevention strategy are summarized in Table 2 below.

Table 4: PrEP Studies

Location	Sponsor	Population	PrEP Strategy
Phase II			
West Africa (Ghana, Nigeria, Cameroon)	Family Health International	936 high-risk women	TDF
United States	CDC	400 men who have sex with men	TDF
Phase III			
Thailand	CDC	2000 injection drug users (~20% women)	TDF
Botswana	CDC	1200 men and women	FTC/TDF
Peru, Ecuador, Brazil, Thailand, South Africa, United States	NIH (iPrEx Study, IND 71,859)	1400 men who have sex with men (potential expanded sample size of 3500)	FTC/TDF
Africa	Family Health International	3800 high-risk women	FTC/TDF
Africa	University of Washington, Gates Foundation	3900 HIV-1 seronegative partners within HIV-1 discordant couples	FTC/TDF TDF

The VOICE Protocol Team will employ several mechanisms to ensure that results from ongoing studies will be carefully monitored and any implications for conduct of the VOICE study considered. These include the following: (1) The MTN Executive Committee (EC), chaired by Dr. Sharon Hillier, conducts monthly conference calls and meets in person biannually at a minimum, and reviews the status of large microbicide and oral PrEP studies carefully. This forum is a regular means for consistent and thorough communication regarding other study results. (2) Many investigators involved in the VOICE study are also closely involved in HPTN 035. When results from this study are available, the MTN EC will discuss them and consider any necessary modifications to the protocol. (3) Several VOICE investigators participate in a recently convened oral PrEP Principal Investigator forum, facilitated by Dr. Willard Gates at Family Health International. The purpose of this group is to discuss methodology, barriers, and problem-solving in the conduct of oral PrEP studies.

2.10 Study Hypotheses and Rationale for Study Design

2.10.1 Study Hypotheses

Safety Profile

VOICE hypothesizes that all three active study products will be safe, well-tolerated and acceptable for once daily use among healthy sexually active women. Therefore the null hypothesis is that there will be no difference in the safety profile between daily regimens of active products and placebo.

Effectiveness

The null hypothesis is that there will be an effectiveness of the active product of no more than 25%. That is, the trial is powered to detect 55% effectiveness in preventing acquisition of HIV-1 relative to placebo, and to rule out a lower effectiveness of 25%.

2.10.2 Rationale for Study Design

VOICE will be pivotal for the chemoprevention field; it is the first study to provide parallel comparison of two oral chemoprophylactic regimens and vaginal tenofovir relative to a corresponding oral or topical placebo, and will also provide power to explore the differences in adherence, safety, and effectiveness for oral vs. topical use. VOICE will also be the first study to evaluate the effectiveness of daily, non-coitally dependent use of an ARV-based microbicide for prevention of HIV. The study design includes both oral and vaginal agents because each approach carries specific theoretical and operational advantages. Vaginal use may confer less systemic drug levels and risk of resistance; oral use may be associated with higher rates of adherence and less variability in use with regular vs. casual partners than a vaginal product, and can be administered without knowledge of a partner. Therefore theoretical reasons may impact significantly the efficacy level and/or likelihood of selection of resistance, and only a trial comparing these approaches will begin to address these questions. Although not an equivalence study, VOICE is well powered to rule out low effectiveness of each intervention arm compared to its corresponding placebo. VOICE will also have power to compare adherence to study products with respect to use with different sexual partner types and behaviors, as well incidence of AEs by arm. Critically, VOICE will provide data on potential selection of HIV-1 drug resistance associated with each regimen.

The five-arm design has other distinct advantages. It will be extremely important to carefully assess the acceptability of route of delivery to participants in all PrEP trials, as reflected not only by qualitative assessments but by participants' reported adherence to study product. Only a study that randomizes women to either vaginal or oral product(s) will permit direct comparisons of the acceptability and adherence of these two routes of PrEP administration in a group of women who are not self-selected for product type as defined by pre-randomization status. Moreover, it will be critical to monitor other types of behavior that may differ by type of study product use, including sexual disinhibition and condom use. In contrast, women who choose to enroll in a study including only oral PrEP cannot accurately be compared to those who choose to enroll in a study of only vaginal PrEP; while measurable characteristics, such as demographics, can be compared, more subtle features that define participants' product preferences are likely not measurable. If PrEP is effective, strategies to implement regimens will need to carefully consider such data to prioritize the type of product and route that women at risk will be most likely to use.

Safety

Careful assessments of safety, including systemic safety, will be undertaken in VOICE, with special consideration for issues related to pregnancy, systemic toxicity, HIV-1 infection, hepatitis B infection, and bone mineral density (BMD). The study products which will be evaluated in this trial all have potential adverse effects, and tolerance to

tenofovir may vary depending on formulation and route of administration. The design of VOICE will allow safety comparisons of each product to its corresponding placebo, and may provide some data suggesting relative safety among active products. Most importantly, VOICE will undertake these research questions while protecting the safety of study participants.

Safety in Pregnancy

Oral TDF and oral FTC/TDF are both classified by the FDA as pregnancy category B. For both products, animal studies have failed to demonstrate risk to the fetus, but there are no adequate and well-controlled studies in pregnant women completed to date.

The VOICE study aims to minimize potential risk to pregnant women and their infants in several ways throughout study participation. The informed consent form for screening includes information regarding the prohibition of pregnancy during the trial, and the importance of avoiding study product exposure to a breastfeeding infant. During the eligibility assessment at screening and enrollment visits, women who are pregnant or who report the intention to become pregnant in the next 24 months are ineligible for further study participation. As part of the screening procedures, women are tested for pregnancy and assessed for their current contraceptive method, if any. Study sites will provide effective methods of contraception to participants if needed. Although women who are currently breastfeeding will not be eligible for the study, women will not be asked or encouraged to stop breastfeeding at screening, or at any time during study participation; all messages to participants related to breastfeeding will be consistent with WHO guidelines.

The informed consent process at the Enrollment Visit will also require discussion of pregnancy and breastfeeding, including the prohibition of pregnancy, as well as a discussion of the potential product-related risks to the fetus and breastfeeding infant. Eligibility criteria include a requirement for contraception use at Enrollment, and women who are currently pregnant or anticipating pregnancy in the next two years will not be eligible for enrollment. Women currently breastfeeding will also be ineligible for enrollment, as there are currently insufficient data on tenofovir levels in human breast milk. As part of study procedures, study sites will provide non-spermicide condoms and contraceptive services and related counseling to participants at Enrollment and during study follow-up.

During participant follow-up, routine monitoring for pregnancy will occur at least monthly. Urine pregnancy tests will be performed at all scheduled visits. Participants who become pregnant during their follow-up period will have their study product held, but may resume product use after giving birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff, provided they are not breastfeeding. All pregnancy outcomes will be captured on case report forms (CRFs) for that purpose. If breastfeeding, the participant may resume product use when she reports complete cessation of breastfeeding.

Participants with any documented exposure to study product during pregnancy may be offered participation in a pregnancy registry study proposed by the MTN. This study will evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy. Participants who are pregnant at the Termination Visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the Protocol Safety Review Team (PSRT), until it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant CRFs; outcomes meeting criteria for EAE reporting also will be reported on EAE forms.

Systemic Toxicity

The oral and vaginal study medications have been extensively studied in animals and humans as described above. The risk of significant systemic toxicity, while present, is relatively low and toxicity will be routinely monitored. Participants will be required to have good general health and essentially normal renal, hepatic and hematologic parameters at screening. Participants will undergo routine clinical and laboratory monitoring throughout the study. Signs and symptoms will be assessed at monthly visits and laboratory testing will be done at Month 1 and quarterly. Safety reports will be reviewed at least monthly by the Protocol Safety Review Team (PSRT).

AEs will be managed according to the guidelines in the Clinical Management section below (Section 9). Participants with AEs possibly, probably or definitely associated with the study medication will have study medications temporarily held or permanently discontinued according to Section 9 and in consultation with the PSRT.

HIV-1 Infection

The VOICE study is designed to minimize potential risks to women who are or may become infected with HIV, with particular attention to minimizing potential exposure to HIV monotherapy, with routine monthly testing for HIV. The informed consent process will include a thorough discussion of potential risks of study product exposure in HIV-infected participants, including the potential for selection of drug-resistant virus. Eligibility criteria for VOICE exclude women with known HIV-1 infection. Women who report non-therapeutic injection drug use in the 12 months prior to Screening Part 1 will not be enrolled. Thorough pre- and post-test counseling as well as HIV prevention counseling will be provided to all participants. Routine monitoring for HIV-1 infection will take place at monthly visits to minimize the potential for HIV-infected women to continue taking study products.

Adjustment in study procedures for participants who seroconvert during the study is outlined in Section 7. VOICE will provide services to seroconverters as outlined in Section 13.11.2, including comprehensive and “active management” of referral, whereby study staff will follow-up on referrals to outside services to determine the outcome of such referrals, and assist participants with maintenance of appropriate clinical follow-up according to site-specific policies. Participants who become infected with HIV during study participation will also have the opportunity to enroll in MTN-015, the MTN Seroconverter Study (www.mtnstopshiv.org). Finally, delayed seroconversion will be ascertained by HIV testing approximately 8 weeks after the PUEV.

Hepatitis B Infection

VOICE will be carried out in countries with high endemic rates of hepatitis B virus (HBV) infection. While TDF has potent activity against HBV, severe acute exacerbations of hepatitis B have been reported in patients who are coinfecting with HBV and HIV and have discontinued TDF. Although transaminitis associated with ongoing TDF use is uncommon, it has been reported. For these reasons, several mechanisms for protecting participants against AEs associated with TDF use, particularly in the setting of pre-existing or newly acquired HBV infection, are planned for the VOICE study.

First, all participants will undergo screening for HBV with assessment of hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) at the first screening visit. Those with active HBV infection as evidenced by detection of HBsAg will receive standardized counseling relevant to natural history and transmission risks of HBV, and will be excluded from enrollment. Those who test positive for HBsAb and thus have pre-existing immunity to HBV (either due to resolved natural infection or prior immunization) will be eligible for enrollment. Those who test negative for both HBsAg and HBsAb will be offered immunization against HBV and considered eligible for enrollment. Participants who decline HBV immunization will still be eligible for enrollment but will receive more intensive monitoring for incident HBV acquisition over the course of the study.

Participants who decline immunization for HBV, and thus will remain vulnerable to HBV infection over the course of the trial, will be monitored annually for HBV seroconversion with serologic testing if they are randomized to any of the study's oral arms. All participants, regardless of randomization to oral vs. vaginal study arms, will also have quarterly transaminase levels assessed as part of routine systemic safety monitoring. The management of persons in whom seroconversion is detected during follow-up will depend on their serologic profile at detection. Those with newly detected HBsAb (but not HBsAg) will be assumed to have experienced incident HBV infection with resolution, and thus will continue as assigned to their originally randomized product without cessation (and with ongoing routine quarterly transaminase measurement). Those with newly detected HBsAg will have study product discontinued, and will be followed monthly for an additional six months with transaminases to ensure that post-cessation hepatitis flares are diagnosed and managed appropriately.

Bone Mineral Density

VOICE will monitor indicators of bone health among all study participants. While clinically significant bone toxicity has not been observed in human trials of tenofovir performed to date, the effects of this drug on bone health in young, pre-menopausal women has not been studied. TDF and intravenous tenofovir both caused bone toxicity when administered in toxicology studies at high doses (6 – 12 times greater than the area under the curve for human administration). Reassuring data are available from Gilead Study 903, which continues to follow men and women receiving tenofovir as part of an ARV regimen, and has reported on bone monitoring for up to six years in this cohort. Although observed decreases in spine and hip bone mineral density were

statistically significant, they appear not to be clinically relevant, as evidenced by the absence of any fractures deemed related to this drug.

Using data from the Petitti et al. study of steroidal hormonal contraception and BMD, which included the UZ-UCSF site that will participate in the VOICE study, we may reasonably assume that the baseline BMD of VOICE study participants will be normal, if not higher than average.⁵⁰ The possible contributory effects of two other modifiers with potential effect on BMD also require attention. First, some data indicate potential risks to BMD related to use of DMPA. Based on baseline data from HPTN 035, we expect approximately 48% of VOICE study participants to use DMPA. Second, given the high frequency of breastfeeding among sub-Saharan African women, the VOICE study participants might also be at relatively increased risk for BMD loss relative to women who do not practice breastfeeding. However, there are data to indicate that the impact of both DMPA and breastfeeding on bone density, though measurable, is likely to be small and probably reversible, particularly in women with good baseline bone density, and may not increase the rate of cumulative lifetime risk of BMD loss.

The VOICE study will undertake standardized clinical monitoring related to clinical impact of tenofovir on bone, including annual height measurement and active surveillance for fractures in all participants. Additionally, to supplement data on the effect of tenofovir on BMD in women, we will conduct a substudy of bone density (concurrently with VOICE) among participants at selected sites with capacity for evaluation of bone density.

Effectiveness

Most consideration for potential PrEP strategies has been based on the nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs). NRTIs target HIV-1 early in its life cycle and achieve high levels in genital secretions,⁵¹ where HIV-1 exposure and transmission most often occurs. In comparison, other classes of HIV-1 medications have disadvantages for use as PrEP. NNRTIs have been associated with high toxicity in HIV-1 negative persons (e.g., lactic acidosis and severe hepatotoxicity with NVP used as post exposure prophylaxis) and high frequency of resistance and cross-class resistance. Protease inhibitors act late in the HIV-1 life cycle, have significant side effects, and are costly.

The macaque studies described above demonstrated partial protection when TDF alone was administered as PrEP. Subsequent macaque studies using the combination of FTC/TDF have demonstrated higher rates of protection as well as a suggestion of reduction in set-point viremia in breakthrough infections that did occur. Although these studies are relatively small, the data suggest that FTC/TDF may provide better PrEP protection than TDF alone. Moreover, the precise relevance of the differential effectiveness of TDF vs. FTC/TDF PrEP noted in the macaque models for sexual HIV-1 transmission in humans is not known. Numerous cofactors strongly modify the risk of HIV-1 acquisition in women, making the human model of transmission considerably more complex than animal models that involve infection of healthy animals with calibrated quantities of viral inoculum. For these reasons, clinical trials are needed to

provide an accurate estimate of the efficacy, safety, resistance in seroconverters and costs of TDF versus FTC/TDF PrEP relative to placebo in critical populations at high risk for acquiring HIV-1.

Adherence/Behavioral

Accurate adherence data are critical for the interpretation of results from randomized controlled prevention trials where distinguishing poor adherence (a behavioral measure) from method efficacy is essential. These data may be particularly useful when an effectiveness trial yields a null result and examining the levels of product use reported by participants in each arm could aid in interpretation of study findings. Therefore, patterns of product use, including missed doses will be monitored through monthly behavioral assessments. This regular monitoring of adherence also will permit tailored adherence counseling to study participants. In addition to the adherence measures, VOICE will evaluate sexual activity, condom use, and intravaginal practices, which are potential confounders or effect modifiers and, as such, could affect the interpretation of the intention to treat analysis. In addition, data on these factors can be used in other analyses, such as those using marginal structural models, which attempt to assess the direct effect of the product while maintaining random assignment, controlling for factors such as condom use patterns. These data, particularly those on condom use, could be monitored prospectively to provide evidence of unblinding and/or changes in condom use that could confound efficacy interpretations.

To contribute to understanding levels of product adherence during trial participation, and to determine whether they differ between women in the vaginal gel and oral tablet arms, individual and community factors that might be associated with product adherence will be assessed in a planned substudy, to be conducted concurrently with VOICE. Specifically, these will focus on sexual behavior practices, partnership characteristics, and community perceptions of microbicide trials, in addition to sociodemographic characteristics.

The challenges of accurate measurement of self-reported sensitive behaviors in STI/HIV prevention research have been highlighted by much epidemiologic research as well as several recently completed Phase 3 HIV prevention trials whose null findings underscored the urgent need to improve the measurement of adherence.⁵² Though imperfect ways to assess the accuracy of self-reported behaviors, including adherence, exist, increasing the privacy of the interview mode through audio computer-assisted self-interviewing (ACASI) has been found to reduce social desirability bias in reporting of sensitive behaviors.^{53, 54, 55, 56}

Although modeling studies have been conducted^{57,58} there is a shortage of empirical evidence, particularly in African female populations, regarding condom substitution and behavioral disinhibition associated with the introduction of new prevention intervention. However, based on the few HIV prevention trials completed to date or ongoing, we have some indications that use of vaginal products (gel, diaphragm, or both) may not be independent from condom use. In the MIRA trial, women in the intervention arm (diaphragm/gel/condoms) were less likely to use condoms than those in the control

(condom only) arm.⁴ In an ongoing microbicide trial, and a recently completed diaphragm, microbicide, and safety trial, consistent condom use was correlated with product use, suggesting that women who are able to negotiate use of one method may be more adept at negotiating a second method (A. Coletti, personal communication, 2007).⁵⁹

Other literature documenting the increase of unsafe sex practices among MSM in the United States due to the availability of HAART may add to our concern of potential behavioral disinhibition in the context of pre-exposure prophylaxis.^{60,61,62,63} Although in VOICE, test products will be administered non-coitally, women will be unblinded to the mode of product administration (i.e., orally and vaginally). Thus, both the potential for “prevention” misconception as well as differential condom use between routes of product administration is real.

With the condom use data collected in VOICE, we will have the opportunity to evaluate condom use through the following types of assessments:

- a. Estimation of four measures of condom use over time:
 - i. Use at last sex
 - ii. Proportion of protected acts
 - iii. Number of unprotected acts
 - iv. Proportion of protected acts
- b. The testing of differences in condom use between the active product and its corresponding placebo for each of the three active products
- c. The testing of differences in condom use between the vaginal and oral products
- d. The testing of changes in condom use over time
- e. The examination of the relationship between condom use and product adherence
- f. The examination of the relationship between condom use and HIV infection

Resistance

Evaluation of the effect of topical microbicides or oral chemoprophylaxis use on the natural history of HIV-1 infection, particularly the development of viral resistance, is essential for the development of guidance for the use of such products in populations at risk of HIV-1 infection. At this time, no data are available to predict the likelihood of either risk or benefit among microbicide study participants who become HIV-infected during product use. Careful monitoring of topical microbicide and oral chemoprophylaxis study participants who acquire HIV-1 infection during product usage will provide critical knowledge to inform the field. This study will routinely collect and monitor laboratory and clinical data from women who become HIV-1 infected during the trial. To provide adequate comparison group(s) for specific analyses of interest, all participants who seroconvert during study participation will be followed with resistance testing, regardless of the specific product or placebo or the route of administration.

Some data on HIV-1 resistance also support the need to study both TDF and FTC/TDF in a clinical trial. Mutations at M184V confer resistance to FTC and to the related drug, 3TC. The M184V mutation significantly reduces HIV-1 replication capacity and restores

susceptibility to TDF in viruses with prior resistance to this drug. This observation suggests that FTC/TDF may have a higher barrier to development of resistance to TDF alone. In one study, two macaques administered FTC/TDF PrEP developed breakthrough infection; one developed the M184V mutation, but neither developed K65R (the defining mutation for TDF resistance). The selection of such mutations in persons who acquire HIV-1 while taking PrEP is a critical outcome for this and other PrEP studies, and needs to be assessed in a trial that directly compares TDF alone with FTC/TDF.

Recent data have demonstrated the inadequacy of the standard genotype for detecting low-frequency drug resistance mutations.⁶⁴ Single genome sequencing has greater sensitivity and can identify linked mutations that confer high-level drug resistance not detected by standard genotype analysis. Approximately 500-1000 copies/mL are required to perform standard resistance assays that can detect drug-resistant variants that comprises >25% of the virus population present in the sample. More sensitive assays (which will also be used in VOICE), e.g., Single Genome Sequencing and Allele-specific PCR, require ~5,000 HIV-1 RNA copies/mL and can detect drug-resistant variants that comprise only 1-2% of the virus population in the sample.^{65, 66}

Pharmacokinetics

Although a great deal of tenofovir efficacy and safety has been established in the treatment setting, little is known about the drug concentration-response relationship for efficacy and safety. There are currently no published data relating concentration (or any other drug exposure variable) of tenofovir, either parent drug or phosphorylated forms, in any body compartment, including blood or PBMCs, with efficacy or safety in an antiviral treatment setting. In prevention, whether through PrEP or microbicides, there are even less data about active drug concentrations in the relevant site of action, namely, the susceptible CD4 bearing cells near the sexual mucosal surfaces in the female genital tract and the rectum. Less still is known about the tissue and intracellular levels of FTC. The picture is complicated by the fact that both tenofovir and FTC are prodrugs, which are phosphorylated within cells to the active forms, PMPApp and emtricitabine-triphosphate, respectively. It is most likely the level of exposure to intracellular PMPApp that best predicts antiviral efficacy and AEs. Accordingly, there is clearly a need to understand the intracellular-extracellular (IC-EC) relationships of tenofovir to more completely understand the relationship of drug dose to efficacy and safety outcomes.

Several clinical studies (CDC Botswana, CONRAD AO4-095, MTN-001) will provide much more data than currently exist to establish the relationship between concentrations of drug in the blood plasma, blood mononuclear cells, tissue, tissue mononuclear cells, and the lumen of receptive sexual organs. If there is a systematic relationship between these sites (blood, tissue, lumen), and within these sites (plasma/interstitium and cells), these ongoing studies are well positioned to provide this data through building PK models. Based on these models, it may be possible to use a sparse sampling approach to the analysis of tenofovir concentrations in VOICE to explore the relationship between drug exposure and seroconversions outcomes.

For example, a few samples of tenofovir levels in the blood plasma and the vaginal lumen, along with accurate time of dosing data, may be used to reconstruct patient specific concentration–time curves in the plasma and vagina. From these extrapolations, one may be able to impute intracellular values depending on the quality of the IC-EC models derived from more intensively sampled studies. These intracellular imputations based on patient-specific sparse sampling and population-based models may then be used to explore the relationship between active phosphorylated drug levels in the cells of interest in tissue adjacent to sexual mucosal surfaces and seroconversions events. Further, these models could be used to explore outcomes like drug toxicity and viral resistance. Imputed intracellular drug concentrations could also be used as a quantitative measure of adherence. Since observation times for blood levels are infrequent relative to the total number of daily doses taken, any of these potential uses of the blood and vaginal levels will depend greatly on (1) the accuracy of the population-based models, (2) the accuracy of time-of-dosing data from participants, and (3) the assumption of consistency of adherence and PK throughout the study.

Vaginal Microenvironment

Abnormal vaginal flora has been associated with a significant (approximately 2-fold) increase in the prospective likelihood of sexual HIV acquisition in several studies undertaken in sub-Saharan Africa.^{67,68,69} However, none of these studies have characterized vaginal flora in these women beyond clinical signs of BV,⁶⁷ morphological description by Gram stain (Nugent score)⁶⁹ or by culture of hydrogen peroxide-producing vaginal *Lactobacillus* species.⁶⁸ Bacteria associated with BV have recently been identified by cultivation-independent methods, including broad-range and (subsequently) bacterium-specific PCR assays applied to vaginal swabs and resulting in definition of several previously undescribed species in the *Clostridiales* order that are highly specific (>97%) for BV (BVAB1-3).⁷⁰ The collection of swabs for cervicovaginal biomarkers will permit future analyses of the potential association of these organisms with HIV seroconversion.

2.11 Potential for Development of Resistance in HIV-infected Individuals

The risk of development of HIV-1 drug resistance mutations and the impact of such mutations on subsequent combination ART (in women who become infected with HIV-1 while receiving any of the active study products) is not known and requires careful study. The potential to understand differential resistance patterns among PrEP strategies is an important and unique part of the VOICE study.

Several factors may contribute to the development of resistant virus in an HIV-infected individual. These include the following:

- Inadequate inhibitory potency of the ART regimen (e.g., single/dual NRTI);
- Incomplete adherence;
- Unfavorable PK (or antagonism); and
- The presence of resistant virus (*de novo* or transmitted).

In an infected individual, these factors may contribute to incomplete inhibition of viral replication, subsequent selection of pre-existing mutant strains, and the evolution of new mutants. In a clinical context, a primary concern becomes the reduction in drug susceptibility and a limited arsenal of current and possible future treatment options.

Although use of single or dual NRTI in an individual with chronic HIV-1 infection would be expected to result in the selection of drug resistant HIV, the impact of oral PrEP on resistance in the setting of seroconversion is not known. In the recent macaque study described above initial breakthrough infection of SHIV during TDF chemoprophylaxis was wildtype virus, suggesting that infection occurred in unprotected cells. At the current time human data are limited to the single participant in the West African TDF safety study by Peterson, et al.³⁷ Additionally, a mathematical model of oral TDF PrEP in Botswana predicted that of 600 persons receiving oral TDF, with 45 seroconversions, less than one participant would acquire or develop a drug resistant strain of HIV.⁷¹

Human data on the risk of selection of drug resistant mutations with vaginal tenofovir are limited. In HPTN 050, no new reverse transcriptase mutations were detected after two weeks of twice daily use of tenofovir 1% gel.⁷² It is postulated that topical administration of tenofovir will be less likely to select resistance than oral use; however, no data are available to confirm this theory.

VOICE is designed to minimize the potential for study drug exposure in HIV-infected individuals. All potential participants will be screened for HIV infection prior to the Enrollment Visit. After enrollment, study participants will be tested monthly for HIV antibody, allowing rapid identification of HIV infection and temporary product hold. Study products will be dispensed monthly only after results of the HIV testing are known. With these procedures in place, and in accord with current understanding of the generation and persistence of viral resistance, the likelihood that HIV-infected individuals would be exposed during this study to ARV drug product at a dose and duration sufficient to cause concern for the development of resistant virus will be minimized.

2.12 Justification of Dosing

TDF 300 mg Tablets

The ease of administration of one pill, once daily, of a safe and highly active ARV agent, makes oral prophylaxis against HIV infection an attractive option for persons at high risk for acquisition of HIV infection. For these reasons, TDF is an excellent candidate for study as an oral prophylactic agent for prevention of transmission of HIV.

Choice of the 300 mg strength of the TDF tablet is based upon practical and scientific considerations. The TDF 300 mg tablet, or Viread[®], is a medication US FDA approved for the indication of treatment of HIV-1 infection. More than 12,000 people have been treated with TDF alone or in combination with other ARV medications for periods of 28 days to 215 weeks in Phase 1–3 clinical trials and expanded access studies. A total of 1,544 patients have received TDF 300 mg once daily in Phase 1–3 clinical trials; over 11,000 people have received TDF in expanded access studies.⁸ A significant body of

safety data has been accumulated for daily use of the TDF 300 mg tablet. In addition, data on tenofovir PK and anti-viral activity in humans suggest a reasonable expectation of effectiveness as a prevention strategy.

FTC/TDF Tablets

Choice of the FTC/TDF tablet strength is based on the available strength of Truvada[®], a medication US FDA approved for the indication of treatment of HIV-1 infection. This once daily film-coated tablet contains 200 mg of FTC and 300 mg of TDF, which is equivalent to 245 mg of tenofovir disoproxil, as active ingredients.

Tenofovir 1% Gel

Choice of the tenofovir 1% gel concentration for VOICE is based on both animal and clinical evidence suggesting an appropriate safety profile and potency. Animal and human studies have demonstrated minimal vaginal irritation at this concentration. A rabbit vaginal irritation test identified tenofovir 1% gel as being histopathologically identical to placebo or control treatment, while on a qualitative basis 3% gel was more irritating to vaginal epithelia.¹¹ The tolerability of the 1% gel was confirmed in the HPTN 050 study, the Phase 1 dose ranging study of tenofovir gel (0.3% once daily, then 1.0% once daily, then 0.3% twice daily followed by 1% twice daily).¹¹ In this study, of the two doses and frequencies studied in the dose finding cohort, the 1% gel applied intravaginally twice daily for 14 days was well tolerated and was identified as the highest practical dose and frequency for further study in subsequent cohorts.

The second line of evidence is from vaginal transmission inhibition studies performed in non-human primates.¹¹ Six separate studies provided evidence for efficacy of the gel over a range of tenofovir concentrations (0.3% to 10%). Although the total data are limited and a powered statistical determination as to the efficacy of tenofovir 1% gel versus 0.3% and 10% cannot be made, empirical examination of the efficacy data identified tenofovir 1% gel as the lowest efficacious concentration tested when given within two hours of infection.

Finally, limited vaginal PK tenofovir data in primates suggest that tenofovir gel is broadly distributed in vaginal tissues following vaginal application and can penetrate epithelial tissues.⁷³ The amount of tenofovir administered by intravaginal application of 4 grams of a 1% dose (40 mg) is highly active against HIV and results in a reduction of plasma HIV ribonucleic acid (RNA) of 1.5 log₁₀ copies/mL after daily administration for 21 days. Comparison of the predicted cervicovaginal concentrations of tenofovir gel delivered to those achieved systemically at the standard treatment dose of 300 mg TDF, and tenofovir's characteristic prolonged intracellular half-life (diphosphate form, nine to 50 hours depending upon cell type), suggest that an initial and potentially durational barrier to HIV transmission may be possible. In terms of weighing potential risks and benefits, the tenofovir 1% gel minimizes the potential risks of vaginal epithelial toxicity while providing the potential benefit of delivering sufficient tenofovir to achieve an initial and possibly durational barrier to infection.

3 OBJECTIVES

3.1 Primary Objectives

- To estimate the effectiveness of daily tenofovir 1% gel compared to a vaginal placebo gel, and the effectiveness of oral TDF and oral FTC/TDF compared to an oral placebo in preventing HIV infection among women at risk for STI.
- To evaluate the extended safety of daily tenofovir 1% gel, oral TDF, and oral FTC/TDF in women at risk for sexually transmitted HIV infection.

3.2 Secondary Objectives

- **Adherence/Behavioral**

- To evaluate adherence to daily regimens of vaginal gel (tenofovir 1% gel and placebo) vs. oral tablets (TDF, FTC/TDF, and placebo) used to prevent HIV infection.
- To evaluate whether sexual activity, condom use, and intravaginal practices change over time in women who use either daily vaginal gel (tenofovir 1% gel and placebo) or daily oral tablets (TDF, FTC/TDF, and placebos).

- **HIV-1 Drug Resistance**

- To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using study product by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants.

- **Pharmacokinetic**

- To evaluate the PD relationship between plasma drug concentrations and study outcomes (HIV seroconversion, toxicity (report of AEs or evidence of cervicovaginal inflammation, viral resistance) using PK-PD models.

- **Delayed Seroconversion**

- To assess the incidence of HIV seroconversion in each study product group during the approximate 8 weeks of follow-up off study product between the PUEV and the Termination Visit.

3.3 Exploratory Objectives

- **Vaginal Microenvironment**

- To correlate quantitative measurement of candidate biomarkers in the cervicovaginal environment with HIV seroconversion, reported product

- adherence, stage of menstrual cycle, contraceptive use, intercurrent STI and reported AEs.
- To measure the association between abnormal vaginal flora and HIV seroconversion.
 - **Method of Contraception**
 - To explore the potential relationship between method of contraception and HIV seroconversion, reported product adherence, and reported AEs.

4 STUDY DESIGN

4.1 Identification of Study Design

VOICE is a Phase 2B, five-arm, multi-site, randomized, placebo-controlled trial. The study is double-blinded within each of mode of administration, but is open-label with respect to the mode of administration (vaginal or oral) assigned. Approximately 4200 participants will be randomized to the five study arms in a 1:1:1:1:1 ratio.

While investigators and participants will be aware of randomization to either the oral or vaginal administration of study product, they will not be aware of the specific study product assigned to each participant. All participants will complete monthly follow-up visits for a period of 12 – 33 months and will receive ongoing HIV risk reduction counseling, condoms, and diagnosis and treatment of STIs throughout the course of study participation. Participants will also complete a Termination Visit approximately 8 weeks following the end of their scheduled end of study product use.

4.2 Summary of Major Endpoints

- **Effectiveness**
 - HIV infection as measured by seroconversion according to the algorithm in Appendix III at the end of the study product use period (i.e., at the start of the additional 8 weeks of follow-up off product)
- **Safety**
 - Grades 2, 3, and 4 clinical and laboratory AEs

4.3 Description of Study Population

The study population will be sexually active HIV-uninfected women who meet criteria outlined in Section 5.

4.4 Time to Complete Accrual

Accrual is expected to be completed in approximately 21 months.

4.5 Study Groups

The five study groups are as follows:

- TDF group (TDF 300 mg and FTC/TDF placebo)
- FTC/TDF group (TDF placebo and FTC/TDF 200 mg/300 mg)
- Oral placebo group (TDF placebo and FTC/TDF placebo)
- Vaginal tenofovir 1% gel group
- Vaginal placebo gel group

4.6 Expected Duration of Participation

Each participant is expected to complete a minimum of 12 months and a maximum of 33 months of study product use. Each participant will complete approximately 8 additional weeks of follow-up off study product to assess for potential delayed seroconversions due to masked infections that are not detected during the product use period. In total, each participant will complete a minimum of 14 months and a maximum of 35 months of study follow-up. Based on projected rates of participant accrual, retention, and HIV seroincidence, the average duration of study product use across participants is expected to be 22.5 months.

4.7 Sites

Study sites will be located in sub-Saharan Africa.

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be utilized to ensure the appropriate selection of study participants

5.1.1 Recruitment

Participants will be recruited from a variety of sources across sites, including STD clinics, family planning clinics, and post-natal clinics, as well as community-based locations. Participants also will be referred to the study from other local research projects and other health and social service providers serving the target study population. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review.

5.1.2 Retention

Once a participant is enrolled/randomized in VOICE, the study site will make every effort to retain her in follow-up to minimize possible bias associated with loss-to-follow-up. Each study site will establish and follow standard operating procedures (SOPs) for participant retention to target loss-to-follow-up rates that do not exceed the incidence

rate of the primary study endpoint. As such, an average annual retention rate of 95 percent is targeted across sites. All study sites are responsible for developing and implementing local SOPs to achieve this. Components of such procedures include the following:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, and re-emphasis at each study visit. Also as part of the informed consent process, encouragement of participants to discuss potential study participation with their husbands/partners and other influential family members.
- Thorough explanation of the importance of all five study groups to the overall success of the study.
- Collection of detailed locator information at the study screening visits, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained outreach workers to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness of HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.

Study sites will use a participant tracking database to facilitate visit scheduling and timely identification and follow-up on missed visits. The MTN SDMC will generate monthly reports on the number and percentage of participants completing follow-up visits throughout the course of the study. The protocol team as well as the MTN Study Monitoring Committee (SMC) track retention rates closely and work with study sites as needed to take any required action to address below-target retention rates.

5.2 Inclusion Criteria

Women must meet all of the following criteria to be eligible for inclusion in the study:

- 1) Age 18 through 40 years (inclusive) at screening, verified per site SOPs; within this range sites may restrict the upper age limit per site SOPs, to target women at high risk of HIV infection
- 2) Able and willing to provide written informed consent to be screened for and to take part in the study.
- 3) Able and willing to provide adequate locator information, as defined in site SOPs
- 4) HIV-uninfected based on testing performed by study staff at screening and enrollment (per applicable algorithms in Appendices II and III)

- 5) Per participant report, sexually active, defined as having vaginal intercourse at least once in the 3 months prior to Screening Part 1
- 6) Per participant report, using an effective method of contraception at enrollment, and intending to use an effective method for the next 24 months; effective methods include hormonal methods; intrauterine contraceptive device (IUCD); and sterilization (of participant or her sexual partner or partners as applicable and with verification as defined in site SOPs)
- 7) At screening and enrollment, agrees not to participate in other research studies involving drugs, medical devices, or vaginal products for the next 24 months

5.3 Exclusion Criteria

Women who meet any of the following criteria will be excluded from the study:

- 1) Participant reported any of the following:
 - a) Known adverse reaction to any of the study products (ever)
 - b) Known adverse reaction to latex (ever)
 - c) Pathologic bone fracture not related to trauma (ever)
 - d) Non-therapeutic injection drug use in the 12 months prior to Screening Part 1
 - e) Post-exposure prophylaxis (PEP) for HIV infection within 6 months prior to enrollment
 - f) Last pregnancy outcome 42 days or less prior to enrollment
 - g) Gynecologic or genital procedure (e.g., biopsy, tubal ligation, dilation and curettage, piercing) 42 days or less prior to enrollment
 - h) Participation in any other research study involving drugs, medical devices, or vaginal products 30 days or less prior to enrollment
 - i) Currently breastfeeding
 - j) Currently using spermicide; interferon or interleukin therapy; medication(s) with significant nephrotoxic potential, including but not limited to amphotericin B, aminoglycosides, cidovir, foscarnet and systemic chemotherapy; medication(s) that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid)
 - k) As determined by the IoR/designee, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis
- 2) Has any of the following laboratory abnormalities:
 - a) AST or ALT greater than 1.5 x site laboratory ULN
 - b) Calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula where creatinine clearance (female) in mL/min = $(140 - \text{age in years}) \times (\text{weight in kg}) \times 0.85/72 \times (\text{serum creatinine in mg/dL})$

- c) serum creatinine greater than the site laboratory ULN for women
- d) hemoglobin less than 10.0 g/dl
- e) platelet count less than 100,000/mm³
- f) serum phosphate level below site laboratory LLN (lower limit of normal)
- g) positive for HBsAg test result
- h) Grade 2 or higher Pap result (at sites with capacity, where standard of care)
- i) Dipstick urinalysis results for protein
 - i) Any result of 2+ or greater at a single visit
 - ii) At least two results of 1+ or greater at separate visits
- j) Dipstick urinalysis results for glucose
 - i) Any single result of 2+ or greater at a single visit
 - ii) At least two results of 1+ or greater at separate visits

Note: Otherwise eligible participants with an exclusionary test result other than urine dipstick results may be re-tested during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 56 days of providing informed consent for screening, the participant may be enrolled.

Note: Women with a documented normal result within the 12 months prior to enrollment need not have Pap smear during the screening period. Women with abnormal Pap smears can be enrolled upon completion of the initial phase of evaluation if no current treatment is indicated (based on local standard of care for management of abnormal cervical cytology). Need for a repeat Pap within 6 months does not preclude enrollment prior to that result becoming available.

3) Is pregnant

Note: Self-reported pregnancy is adequate for exclusion from the study. A documented negative pregnancy test performed by study staff is required for inclusion.

4) Per participant report at Screening Part 1:

- a) Intends to become pregnant in the next 24 months
- b) Plans to relocate away from the study site in the next 24 months
- c) Plans to travel away from the study site for more than 8 consecutive weeks during the next 24 months

5) Diagnosed with urinary tract infection (UTI)

Note: Otherwise eligible participants diagnosed with UTI during screening will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 56 days of obtaining informed consent for screening, the participant may be enrolled.

6) Diagnosed with pelvic inflammatory disease, an STI or reproductive tract infection (RTI) requiring treatment per current WHO guidelines

Note: Otherwise eligible participants diagnosed during screening with pelvic inflammatory disease or STI/RTI requiring treatment per WHO guidelines — other than asymptomatic BV and asymptomatic candidiasis — will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 56 days of obtaining informed consent for screening, the participant may be enrolled. Genital warts requiring

treatment also must be treated prior to enrollment. Genital warts requiring therapy are defined as those that cause undue burden of discomfort to the participant, including bulky size, unacceptable appearance, or physical discomfort.

- 7) Has a clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff)

Note: Cervical friability judged to be within the range of normal according to the clinical judgment of the IoR/designee is not exclusionary.

Note: Otherwise eligible participants with exclusionary pelvic exam findings may be enrolled/randomized after the findings have improved to a non-exclusionary severity grading or resolved. If improvement to a non-exclusionary grade or resolution is documented within 56 days of providing informed consent for screening, the participant may be enrolled.

- 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

5.4 Co-enrollment Guidelines

As indicated in Section 5.2, participants should not take part in other research studies involving drugs, medical devices, or vaginal products while taking part in VOICE. Participants will be discouraged from taking part in non-investigational studies, except for the following:

- Participants may take part in ancillary studies approved by VOICE Protocol Chairs
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-infected persons

Should any participant report concurrent participation in contraindicated studies after enrolling in VOICE, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

Each participant will be randomized to one of the following regimens:

- One TDF 300 mg tablet by mouth (PO) every day and one FTC/TDF placebo tablet PO every day
- One TDF placebo tablet PO every day and one FTC/TDF 200 mg/300 mg tablet PO every day
- One TDF placebo tablet PO every day and one FTC/TDF placebo tablet PO every day

- One applicatorful of tenofovir 1% gel vaginally every day
- One applicatorful of placebo gel vaginally every day

6.2 Administration

Study staff will instruct participants in proper methods of administering and storing their study product(s).

For both oral and vaginal products, if a daily dose is missed, the participant will be instructed to administer the missed dose as soon as possible, unless the next dose is due within 6 hours. If the next dose is due within 6 hours, the missed dose will be skipped and the next dose will be administered as originally scheduled.

6.2.1 Oral Study Product

Study participants will be instructed to take the two tablets (one TDF [or placebo] and one FTC/TDF [or placebo]), by mouth, once each day without regard to meals. They will be instructed to take their tablets as close to the same time each day as possible.

6.2.2 Vaginal Study Product

Study participants will be instructed to insert one dose (the entire contents of one applicator) of product into the vagina once each day. They will be instructed to insert their gel as close to the same time each day as possible.

6.3 Study Product Formulation

Tenofovir Disoproxil Fumarate (TDF) 300 mg Tablet

Tenofovir disoproxil fumarate (Viread[®]) oral tablets contain a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir. Each film-coated tablet contains 300 mg of TDF. Tenofovir disoproxil fumarate tablets should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

TDF Placebo Tablet

TDF placebo tablets are film-coated and contain denatonium benzoate, a bittering agent, in addition to other inactive ingredients. TDF placebo tablets should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF) 200mg/300mg Tablet

Emtricitabine/tenofovir disoproxil fumarate (Truvada[®]) is a fixed dose combination tablet containing FTC and TDF. FTC is a synthetic nucleoside analogue of cytidine. One FTC/TDF tablet contains 200 mg FTC plus 300 mg of TDF. FTC/TDF should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

FTC/TDF Placebo Tablet

FTC/TDF placebo tablets are film-coated and contain denatonium benzoate, a bittering agent, in addition to other inactive ingredients. FTC/TDF placebo tablets should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

Tenofovir 1% Gel

Tenofovir 1% gel is a gel formulation of tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate), formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, HEC, and pH adjusted to 4-5. Tenofovir 1% gel is a transparent, viscous gel that will be supplied in pre-filled, single-use applicators. Each pre-filled applicator will deliver a dose of approximately 4 grams of gel containing approximately 40 mg of tenofovir. Tenofovir 1% gel should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

Placebo Gel

Placebo gel is an inert vaginal product which contains HEC as the gel thickener, purified water, sodium chloride, sorbic acid and sodium hydroxide. The gel is isotonic and formulated at a pH of 4.4 with minimal buffering capacity. HEC, the gelling agent, is used to approximate the viscosity of other microbicide gel candidates. Each pre-filled applicator will deliver approximately 4 mL of placebo gel. Placebo gel should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

6.4 Study Product Supply and Accountability

All study products will be available through the DAIDS Clinical Research Products Management Center (CRPMC). The Clinical Research Site (CRS) Pharmacist of Record (PoR) can obtain the study products for this protocol by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*. All study products must be stored in the pharmacy.

6.4.1 Study Product Supply

Oral Tablets

TDF tablets, TDF placebo tablets, FTC/TDF tablets, and FTC/TDF placebo tablets will be supplied by Gilead Sciences, Inc. (Foster City, CA, USA).

Vaginal Gels

Tenofovir 1% vaginal gel and placebo gel will be supplied by CONRAD (Arlington, VA, USA).

6.4.2 Study Product Accountability

The CRS PoR is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. All unused study products must be returned to the NIAID CRPMC after the study is completed or terminated unless otherwise instructed by the DAIDS Protocol Pharmacist. The procedures to be followed are provided in the manual, *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

6.5 Study Product Dispensing

Study products will be dispensed only to enrolled participants, upon receipt of a written prescription signed by an authorized prescriber. Products will be dispensed in

quantities sufficient to last until the next scheduled study visit. Dispensing will take place on the day of enrollment and at each scheduled follow-up visit, except at the PUEV and the Termination Visit. Allowances will be made for up to a 60-day supply of study product(s) to be dispensed to participants under exceptional circumstances (e.g., when they will not be able to attend a scheduled visit).

If a participant will miss two or more consecutive visits (requires more than a 60-day supply of study product), approval from a DAIDS Medical Officer must be obtained prior to dispensing any study product(s). All such circumstances must be documented fully by the IoR/designee as described in the MTN-003 SSP Manual.

6.6 Retrieval of Unused Study Products

As per Section 9, study product use for a participant may be temporarily held or permanently discontinued. Oral and vaginal study products must be retrieved (optimally within 24 hours) and returned to the study site pharmacy when study product use is permanently discontinued for HIV seroconversion (see Table 5). Oral study product also must be retrieved within 24 hours when product use is permanently discontinued due to Grade 3 or higher renal or hepatic toxicity as described in Sections 9.4 and 9.5. Refer to Table 5 for additional study product retrieval specifications in response to holds and discontinuations for other reasons. Study product retrieval may occur either by the participant returning the product to study staff within the specified timeframe or by study staff conducting outreach to retrieve the product from the participant (e.g., at her home).

Table 5: Retrieval of Temporarily Held or Permanently Discontinued Study Product

	Retrieve Oral Study Product	Retrieve Vaginal Study Product
Permanent discontinuation due to HIV seroconversion	Within 24 hours	Within 24 hours
Permanent discontinuation due to severe (Grade 3 or higher) renal or hepatic toxicity	Within 24 hours	Within 5 working days
Permanent discontinuation for any other reason	Within 5 working days	Within 5 working days
Temporary hold due to pregnancy	Within 5 working days	Within 5 working days
Temporary hold for reasons other than pregnancy with expected duration of at least 7 days	Within 7 working days	Within 7 working days

In addition to the specifications of Table 5, under any circumstances, if an oral or vaginal product hold extends for 7 days or more, and product has not been retrieved as of the seventh day, study staff members must make every effort to retrieve all unused study product within 7 additional working days.

It is not necessary to retrieve study products from participants for whom study product use is being temporarily held for less than 7 days. However, study products may be retrieved from such participants, to protect their safety, if there is concern that the participant may not comply with clinic staff instructions to refrain from study product use for the duration of the temporary hold. For all study product holds requiring retrieval of

unused product(s), if the study product(s) are not retrieved within time frame stated in Table 5 above, the MTN-003 PSRT must be informed.

For each participant, all other supplies remaining in the participant's possession should be retrieved at the PUEV. If the participant does not bring her remaining supplies to the PUEV, study staff must arrange to retrieve the supplies within 2 business days. If the study product(s) are not retrieved within that time frame, the MTN-003 PSRT must be informed.

The PoR will document all product returns and store returned study products in designated areas within the study pharmacy.

6.7 Study Product Adherence Assessment and Counseling

Study product use data will be collected via study product counts and standardized questions developed by the Protocol Team in conjunction with study site staff and community representatives, to maximize the accuracy of self-reported data.

Study product adherence counseling will be provided to all study participants upon enrollment into the study, and at every visit thereafter until the PUEV to help ensure high rates of study product use. Counseling will be provided in accordance with standard study methods that will address such topics as participant-centered strategies to remember to use the study product daily and to ensure the availability of the study product both in the home and away from home. Counseling also will include reminders to contact study staff with questions about study product use and requests for additional supplies. For participants who have adherence problems, every effort will be made to identify adherence strategies to increase their rates of study product use throughout the course of the study. All participants will be counseled to avoid contraindicated intravaginal practices, not to use other participants' study products, and not to distribute their study products to other people. Participants assigned to a study gel also will be counseled to only use the study gel vaginally.

6.8 Concomitant Medications

With the exception of medications listed below as prohibited, enrolled study participants may use concomitant medications during study participation. All concomitant medications, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations reported throughout the course of the study, beginning at Screening Part 2, will be recorded on CRFs designated for that purpose.

Prohibited Medications and Procedures

The following medications are prohibited in VOICE:

- interferon therapy
- interleukin therapy
- medications with significant nephrotoxic potential, including but not limited to the following:
 - amphotericin B

- aminoglycosides
- cidovir
- foscarnet
- systemic chemotherapy
- medications that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid).

Should a participant report use of any of these medications, the IoR/designee will institute a temporary product hold, for as long as the participant is taking the contraindicated medication.

Study product also will be held for participants who report taking PEP for HIV infection. Study product use may resume when such participants report completion of PEP and they are confirmed HIV negative based on testing performed at the study site per the algorithm in Appendix III.

All participants will be counseled to avoid the use of spermicide and other non-study vaginal products (other than tampons during menstruation and female condoms). Participants who report use of these products will be counseled regarding the use of alternative methods, but reported use of these products does not require any change in use of study products. Condoms provided by study staff will not be coated with any type of spermicide.

Participants are not expected to require gynecologic surgical procedures during follow-up; however, should such a procedure be required, the IoR/designee will consult the PSRT regarding ongoing product use by the participant.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-003 SSP Manual available at www.mtnstopshiv.org. Unless otherwise specified, the laboratory procedures listed in this section are performed at the local study site laboratories.

7.1 Pre-Screening

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants either on-site or at off-site locations. During these interactions, study staff may explain the study to participants and ascertain elements of presumptive eligibility, to be confirmed at an on-site screening visit. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants, provided the information is collected in such a

manner that it cannot be linked to participant identifiers. At each site, procedures and documentation will comply with local IRB/EC requirements.

7.2 Screening Part 1

Screening Part 1 may take place up to 56 days prior to Enrollment. Multiple visits may be conducted to complete all required procedures if necessary. If more than one visit is needed to complete all required procedures, procedures not completed at the first visit may be performed on the same day as Screening Part 2 (see Section 7.3). Written informed consent for screening will be obtained before any screening procedures are initiated. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

7.2.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for screening
- Demographic information
- Behavioral eligibility information
- Locator information
- HIV pre- and post-test counseling
- HIV/STI risk reduction counseling
- Offer HIV counseling and testing for partner(s)
- Provision of condoms
- Reimbursement
- Schedule next visit (if applicable)

7.2.2 Clinical Procedures

- Medical eligibility information (including exclusionary medical conditions and medications)
- Weight
- Urine collection
- Blood collection
- Disclosure of available test results
- Treatment for STI and/or UTI, if clinically indicated
- Offer of STI testing and treatment for partner(s) if indicated
- Ascertainment of current contraceptive method (if any) and contraceptive counseling
- Provision of contraception if indicated per site SOP

Note: Pelvic exams may be performed at Screening Part 1 Visits at study sites where local standards of care require an exam to guide treatment of STI symptoms. Such exams will not substitute for the pelvic exams required at Screening Part 2 Visits for all participants (see Section 7.3.2).

7.2.3 Laboratory Procedures

- Urine pregnancy test
- Urine strand displacement amplification (SDA) for chlamydia and gonorrhea
- Dipstick urinalysis for protein, glucose, nitrites, and leukocyte esterase
- HIV serology
- Syphilis serology
- Complete blood count with differential and platelets
- Serum chemistries
- HBsAg test
- HBsAb test

Note: An algorithm for management of hepatitis B serologic assays assessed at screening is included in Appendix IV). Clinical management of hepatitis B infection is discussed in Section 9.

7.3 Screening Part 2

Multiple visits may be conducted to complete all required procedures if necessary. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

7.3.1 Administrative, Behavioral, and Regulatory Procedures

- Behavioral eligibility information
- Locator information
- HIV post-test counseling (if indicated, i.e., for participants who required Western Blot (WB) testing due to discordant rapid test results at Screening Part 1)
- HIV/STI risk reduction counseling
- Offer of HIV counseling and testing for partners
- Provision of condoms
- Reimbursement
- Schedule next visit (if applicable)

7.3.2 Clinical Procedures

- Medical and menstrual history
- Current medications
- Urine collection
- Weight
- Height
- Physical exam

- Pelvic exam to include the following:
 - visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at www.conrad.org/colposcopy.htm
 - assessment of vaginal pH
 - vaginal fluid swabs for
 - dried smear for Gram stain assessment at the MTN NL
 - rapid test for Trichomonas
 - BV rapid test if clinically indicated
 - wet mount (KOH) for candidiasis if clinically indicated
 - storage for biomarker analyses at MTN NL
 - endocervical swab for biomarker analyses at MTN NL
 - ecto- and endocervical cells for Pap smear (at sites where Pap smears are the standard of care for women, and where cytopathology and referral services for dysplasia are available)
 - bimanual exam
- Blood collection if clinically indicated (e.g., if genital ulcer indicative of syphilis infection is observed)
- Disclosure of available test results
- Treatment of UTI and/or STI/RTIs (if indicated)
- Offer of STI testing and treatment for partner(s) (if indicated)
- Contraceptive counseling
- Provision of contraception if indicated per site SOP and MTN-003 SSP Manual

7.3.3 Laboratory Procedures

- Urine pregnancy test
- Dipstick urinalysis if clinically indicated (clinical indications may include but are not limited to urinary symptoms, or proteinuria or glycosuria detected at Screening 1)
- Urine SDA for chlamydia and gonorrhea if clinically indicated
- Syphilis serology if clinically indicated
- Prepare and store vaginal fluid slides for Gram stain assessment at MTN NL
- Prepare and store vaginal and endocervical swabs for biomarker analyses at MTN NL
- Rapid test for Trichomonas
- Rapid test for BV if clinically indicated
- Wet mount (KOH) for candidiasis if clinically indicated
- Pap smear interpretation if applicable (at selected sites where Pap smears are standard of care for women, and where cytopathology and referral services for dysplasia are available; not required if documentation of a non-exclusionary Pap smear result within the 12 months prior to enrollment is available)

7.4 Enrollment

7.4.1 Final Screening Procedures and Confirmation of Eligibility

Before proceeding with the enrollment or “on study” procedures in Section 7.5, the following procedures will be performed to confirm participant eligibility:

- Review of all prior screening documentation
- Update medical and menstrual history and/or current medications if applicable
- Re-confirmation (by participant self-report) of medical eligibility information assessed at Screening Part 1 (exclusionary medical conditions and medications)
- Re-confirmation (by participant self-report) of behavioral eligibility, specifically that the participant:
 - has not taken PEP for HIV infection within the six months prior to enrollment
 - has not been pregnant, given birth, or had a pregnancy terminated within the 42 days prior to enrollment
 - has not had a gynecologic or genital procedure within 42 days prior to enrollment
 - has not participated in any other research study involving drugs, medical devices, or vaginal products within 30 days prior to enrollment
 - is currently using an adequate method of contraception
 - is not currently breastfeeding
 - is not currently taking any of the medications listed in Exclusion Criterion 1j
- Dipstick urinalysis and pelvic exam components (e.g., visual inspection, BV rapid test, rapid test for Trichomonas, wet mount (KOH) for candidiasis, vaginal pH, bimanual exam) may be performed on the day of enrollment to confirm eligibility (STI/UTI treatment for participants and STI counseling/treatment for partner(s) to be provided if indicated)
- Urine collection and pregnancy test
- Blood collection and HIV serology (see Appendix II), HIV pre- and post-test counseling
- Provision of contraception if indicated per site SOP and MTN-003 SSP Manual
- Any other clinically indicated behavioral, clinical, or laboratory assessments
- If all eligibility criteria met, informed consent for enrollment

7.4.2 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for specimen storage and possible future research testing
- Locator information
- Behavioral risk assessment
- HIV/STI risk reduction counseling
- Provision of condoms
- Offer of HIV counseling and testing for partner(s)
- Randomization
- Provision of study product, instructions, and adherence counseling
- Reimbursement

- Schedule next visit if indicated

7.4.3 Clinical Procedures

- Urine collection
- Blood collection
- Disclosure of available test results
- Contraceptive counseling
- If indicated, hepatitis B vaccination or documentation of declination of vaccination

Note: Participants found to be HBV susceptible at screening will be given information and offered the HBV vaccine series starting at their enrollment visits. For enrolled participants who are susceptible but decline vaccination at enrollment, the vaccine series may be initiated at any time during follow-up. The hepatitis B vaccine is not considered a study product in VOICE.

7.4.4 Laboratory Procedures

- Urine pregnancy test
- HIV serology
- Plasma archive
- Dipstick UA (if performed to confirm eligibility on day of enrollment)
- Rapid test for Trichomonas (if performed to confirm eligibility on day of enrollment)
- Rapid test for BV if clinically (if performed to confirm eligibility on day of enrollment)
- Wet mount (KOH) for candidiasis (if performed to confirm eligibility on day of enrollment)

7.5 Follow-up Visits

All enrolled study participants will complete monthly follow-up visits targeted to occur every 28 days following the participant's study enrollment date (Day 0). Target dates are set based on the enrollment date, and do not change if subsequent actual visits take place before or after the target date.

Acknowledging that it will not always be possible to complete monthly follow-up visits on the targeted dates, follow-up visits may be completed within an approximate 4-week window around the target date (-14 days and +13 days from the target date).

For participants who do not complete scheduled visits within the allowable window, the visit will be considered "missed" and relevant CRFs will be completed to document the missed visit. However, for participants who miss visits at which pelvic exams, complete blood counts, serum chemistries, and/or plasma archive are specified to take place, these procedures must be conducted at the participants' next visit. See Section 7.6 for further procedural modifications that may be required during follow-up.

The last two scheduled visits for each participant are referred to as the PUEV and the Termination Visit, respectively. The PUEV will serve as the participant's last routine monthly follow-up visit and will include all monthly visit procedures, except that no study product will be dispensed. The Termination Visit will take place approximately eight weeks after the PUEV (i.e., eight weeks after the participant has discontinued product use). Window periods for the PUEV and Termination Visit will be specified in the MTN-003 SSP Manual (www.mtnstopshiv.org).

7.5.1 Administrative, Behavioral, and Regulatory Procedures

- Locator information:
 - At all visits
- Behavioral and study product adherence assessment (see Section 7.9):
 - Monthly
 - At PUEV
 - At Termination Visit (behavioral only)
- Study product sharing assessment and last dose recall:
 - Quarterly
 - At PUEV
- Intravaginal practices assessment:
 - Quarterly
 - At PUEV
 - At Termination Visit
- Social harms assessment:
 - Quarterly
 - At PUEV
 - At Termination Visit
- Perceived study product assessment:
 - At PUEV
- HIV pre- and post-test counseling:
 - Monthly
 - At PUEV
 - At Termination Visit
 - Additionally when needed/requested
- HIV/STI risk reduction counseling, offer of HIV counseling and testing for partner(s):
 - Monthly
 - At PUEV
 - At Termination Visit
 - Additionally when needed/requested

- Provision of condoms:
 - At all visits
- Study product supplies, instructions, and adherence counseling:
 - Monthly prior to PUEV
- Reimbursement:
 - At scheduled visits and per site SOP
- Schedule next visit:
 - At all scheduled visits except the Termination Visit (at Termination Visit, next visit is scheduled only if applicable)

7.5.2 Clinical Procedures

- Interval (i.e., since last visit) medical and menstrual history and concomitant medication review:
 - At all scheduled visits
 - Additionally at unscheduled visits in response to intercurrent symptoms/illnesses
- Contraceptive counseling:
 - At all visits
- Provision of contraception if indicated:
 - As needed at all visits
- Pelvic exam to include the following:
 - visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004:
 - Semiannually
 - At PUEV
 - Additionally when clinically indicated
 - assessment of vaginal pH:
 - At all pelvic exams
 - vaginal fluid swabs for dried smear for Gram stain assessment at MTN NL
 - Semiannually
 - At PUEV
 - vaginal fluid swab for rapid test for Trichomonas:
 - Annually
 - At PUEV

- Additionally when clinically indicated
- vaginal fluid swab for rapid test for BV:
 - When clinically indicated
- vaginal fluid swab for wet mount (KOH) for candidiasis:
 - When clinically indicated
- vaginal fluid swab for storage for biomarker analyses at MTN NL:
 - At all pelvic exams
- endocervical swab for biomarker analyses at MTN NL:
 - At all pelvic exams
- ecto- and endocervical cells for Pap smear (at selected sites):
 - At PUEV
 - When clinically indicated and/or per local clinical guidelines
- bimanual exam:
 - At all pelvic exams

Note: If a participant is menstruating at a study visit during which a pelvic exam is required, all other visit procedures will be conducted, and the participant will be scheduled to return to the clinic within approximately five days to complete her pelvic exam.

- Physical exam:
 - At Month 1
 - Quarterly
 - At PUEV
 - Additionally when clinically indicated
- Height:
 - As part of physical exams semiannually
 - At PUEV
- Weight:
 - As part of physical exams at Month 1, Quarterly, and PUEV
 - When blood is collected for creatinine testing (minimally at Month 1, Quarterly, at PUEV, and when clinically indicated)
 - Additionally when clinically indicated
- Urine collection:
 - At all scheduled visits
 - Additionally when clinically indicated

- Blood collection:
 - At all scheduled visits
 - When needed to perform confirmatory HIV testing per Appendix III
 - Additionally when clinically indicated
- Disclosure of available test results:
 - At all scheduled visits
 - Additionally when clinically indicated
- Treatment of UTI and/or STI/RTI:
 - When clinically indicated
- Offer of STI testing and treatment for partner(s):
 - When clinically indicated
- Hepatitis B vaccination (as indicated for consenting HBV susceptible participants):
 - At visits corresponding with recommended time points for hepatitis B vaccine series

7.5.3 Laboratory Procedures

- Urine pregnancy test:
 - At all scheduled visits
 - Additionally at unscheduled visits when a participant reports a missed menstrual period or has not had a pregnancy test in the last 28 days
- Urine SDA for chlamydia and gonorrhea:
 - Annually
 - At PUEV
 - Additionally when clinically indicated
- Dipstick urinalysis for protein, glucose, nitrites, and/or leukocyte esterase:
 - Month 1
 - Quarterly
 - At PUEV
 - When clinically indicated
- Preparation and storage of vaginal fluid slide for Gram stain assessment at the MTN NL:
 - Semi-annually
 - At PUEV
- Preparation and storage of vaginal and cervical swabs for biomarker analyses at the MTN NL:
 - When pelvic exam is performed

- Rapid test for Trichomonas:
 - Annually
 - At PUEV
 - Additionally when clinically indicated
- Rapid test for BV:
 - When clinically indicated
- Wet mount (KOH) for candidiasis:
 - When clinically indicated
- Pap smear interpretation (at selected sites only):
 - When Pap smear specimens are collected (see pelvic exam description above)
- HIV serology:
 - At all scheduled visits
 - Additionally when clinically indicated
- HBsAg test:
 - Annually if indicated (susceptible but not vaccinated)
 - At PUEV
 - Following PUEV as described in Appendix IV
 - Additionally when clinically indicated
- HBsAb
 - When clinically indicated
- Syphilis serology:
 - Annually
 - At PUEV
 - Additionally when clinically indicated
- Complete blood count with differential and platelets:
 - Semi-annually
 - At PUEV
 - Additionally when clinically indicated
- Serum chemistries:
 - Month 1
 - Quarterly
 - At PUEV
 - Additionally when clinically indicated
 - Additionally if required per Section 7.6.2

- Plasma archive:
 - Quarterly
 - At PUEV
 - At Termination Visit
 - If indicated (when blood is collected [each sample] for Sample 2 per Appendix III)
 - Additionally if required per Section 7.6.1
- PBMC archive:
 - If indicated (when blood is collected [each sample] for Sample 2 per Appendix III)
 - Additionally if required per Section 7.6.1
- HIV-1 RNA PCR:
 - If indicated (when blood is collected [each sample] for Sample 2 per Appendix III)
 - Additionally if required per Section 7.6.1
- CD4+ T cell count:
 - If indicated (when blood is collected [each sample] for Sample 2 per Appendix III)
 - Additionally if required per Section 7.6.1

Note: PK analyses will be performed via batched drug levels from plasma archive at selected time points (from quarterly specimens and PUEV at a minimum). These assays will be performed via procedures that will maintain appropriate blinding in the study.

7.6 Follow up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product

Participants who temporarily hold or permanently discontinue use of study product will not routinely be withdrawn from the study. Rather, every effort will be made to complete all protocol-specified visits and procedures with these participants with the exceptions and additions described below.

7.6.1 Participants Who Become Infected with HIV

Participants who become infected with HIV will be offered the option to continue follow-up visits per their original study schedule until their originally scheduled study exit date. For those who choose to be maintained in follow-up, protocol-specified procedures will continue except the following:

- HIV serology
- Provision of study product, instructions, product adherence counseling, adherence assessment, study product sharing assessment and last dose recall, partner (permanent discontinuation)

HIV/STI risk reduction counseling will be modified to address primary and secondary prevention for infected women.

Participants will be offered enrollment in MTN-015 (www.mtnstopshiv.org) at the visit when seroconversion confirmation test results are discussed with the participant.

For participants who delay or decline enrollment in MTN-015, the following procedures will be completed as part of the VOICE study; these procedures will be discontinued immediately if the participant enrolls in MTN-015:

- Plasma archive:
 - Months 1, 3, 6 and every 6 months post-seroconversion
- PBMC archive:
 - Months 1, 3, 6 and every 6 months post-seroconversion
- HIV-1 RNA PCR:
 - Months 1, 3, 6, and every 6 months post-seroconversion
- CD4+ T cell count:
 - Months 1, 3, 6 and every 6 months post-seroconversion
- HBsAb test:
 - 6 months after completion of HBV vaccine series

For the above procedures, the date of seroconversion is defined as the specimen collection date of Sample 1 as listed in the HIV Follow-up Testing Algorithm (Appendix III). If the window for the Month 1 post-seroconversion procedures has passed at the time that seroconversion is confirmed, the Month 1 post-seroconversion procedures may be omitted.

Plasma and PBMC collected at the above-listed time points, as well as when blood is collected for confirmatory HIV testing, will be shipped to the MTN NL and utilized for the following:

- Standard HIV resistance test
- Specialized HIV resistance test
- Blood TDF and FTC levels (Note: These assays will be performed via procedures that will maintain appropriate blinding in the study)
- Long-term archive and future research testing

7.6.2 Participants Who Become Infected with Hepatitis B

All protocol-specified study procedures will continue except the following:

- Provision of study product, instructions, product adherence counseling, adherence assessment, study product sharing assessment and last dose recall, (permanent discontinuation)

Participants assigned to oral study products who become infected with hepatitis B will additionally have AST and ALT tests performed 1, 2, and 3 months after discontinuing study product.

7.6.3 Participants Who Become Pregnant

All protocol-specified study procedures will continue except the following:

- Provision of study product, instructions, and adherence counseling. Product use may be resumed after birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff, provided the participant is not breastfeeding. For participants assigned to gel, a pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.
- Pelvic examination after 24 weeks of pregnancy

7.6.4 Participants Who Temporarily Hold or Permanently Discontinue Study Product Use (Initiated by Participant)

All protocol-specified study procedures will continue except the following:

- Provision of study product, instructions, and adherence counseling

7.6.5 Participants Who Are Temporarily Held or Permanently Discontinued from Study Product Use (Initiated by the Site Investigator)

All protocol-specified study procedures will continue except the following:

- Provision of study product, instructions, and adherence counseling (permanent discontinuation)

Guidance related to permanent discontinuation of study product, including consultation with the PSRT, is included in Section 9.

7.7 Interim Visits

Interim visits may be performed at any time during the study, for the following or other reasons:

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visit.
- For product-related reasons, e.g., a participant may need additional study product or want to discuss problems with adherence to product use.
- In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see also Section 9).
- For interim STI counseling and testing in response to STI symptoms.
- For interim HIV counseling and testing in response to presumed exposure to HIV.

- To provide participants with the results of confirmatory HIV test results, per the algorithm in Appendix III.
- For other reasons at participant request.

Given the specification of visit windows for this study, interim visits will occur when more than one visit takes place within an allowable visit window. For example, if a participant returns to the clinic two days after completing her month 1 follow-up visit to report a new symptom or illness, the second visit conducted in the Month 1 visit window will be considered an interim visit. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

7.8 Final Contact

Since participants' Termination Visits include laboratory testing for HIV, a final contact may be required to provide her additional study test results, and post-test counseling, if needed. In addition, for participants who become pregnant during study participation, an additional contact may be required to ascertain the participant's pregnancy outcome. Study sites may complete these contacts at the study site or at community-based locations, depending on site capacities and site and participant preferences. All final contacts will be documented in participant study records.

7.9 Behavioral Evaluations

Using ACASI and/or interview-administered questionnaires, the following behaviors will be assessed:

- Study product adherence
- Sexual activity, including frequency of vaginal and anal sex
- Condom use, including frequency of condom use when having sex and condom use at last sex
- Intravaginal practices
- Sharing of study products, including with whom products were shared (assess selling of products and product theft)

To ensure that study participants understand how to use ACASI and complete the behavioral assessments on their own, study staff will guide each participant through a practice session in ACASI.

The study questionnaire will include images that can be selected as response options by participants. For example, when participants complete the retrospective calendar that will assess on which days study product was used, they will be asked to select an image of the gel or tablet (depending upon arm) to indicate an affirmative response that study product was used.

7.10 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

Vital signs:

- Oral temperature
- Blood pressure
- Pulse
- Respirations

Measurements of:

- Weight
- Height (at Screening 2, semiannually and at PUEV)

Clinical assessments of:

- Head and eyes
- Ears, nose, and throat
- Neck
- Lymph nodes
- Heart
- Lungs
- Abdomen
- Extremities
- Neurological
- Skin
- Breasts

Additional assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

Pelvic exams will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at www.conrad.org/colposcopy.htm. The required sequence of procedures and specimen collection performed during pelvic during exam will be specified in the MTN-003 SSP Manual.

Participants for whom there is documentation of surgical sterilization may have contraceptive counseling omitted, in accordance with any relevant site SOPs.

7.11 Laboratory Evaluations

Local Laboratory

- Urine pregnancy test
- Dipstick urinalysis
- Lactic acidosis evaluation (may include bicarbonate, lactate, and/or other assays depending on site capacity and local standard of care)

Local, Regional, or Network Laboratory

The location of laboratory evaluations will depend on laboratory capacity.

- Urine pregnancy test
- Dipstick urinalysis
- HIV serology
- Syphilis serology
- Complete blood count with platelets, WBC, and differential
 - Hemoglobin
 - Hematocrit
 - Mean corpuscular volume
 - Platelets
 - White blood cells
 - Absolute neutrophil count
 - Percent neutrophils
 - Absolute lymphocyte count
 - Absolute monocyte count
 - Absolute eosinophil count
 - Absolute basophil count
- Serum chemistries
 - ALT
 - AST
 - Creatinine
 - Phosphate
- Trichomonas rapid test
- BV rapid test
- Vaginal pH
- Wet mount (KOH) for candidiasis
- Pap smear interpretation
- Plasma archive
- PBMC archive
- HIV-1 RNA PCR
- CD4+ T Cell Count
- Urine SDA for chlamydia and gonorrhea
- HBsAg
- HBsAb

Network Laboratories

- Gram stain assessment of vaginal fluid slides
- Biomarker analyses of vaginal swabs
- Biomarker analyses of endocervical swabs
- Standardized and specialized HIV-1 resistance tests
- Blood TDF level

- Blood FTC level

7.12 Primary HIV Endpoint Determination

All study sites will perform HIV testing per the algorithm in Appendix III for purposes of primary endpoint determination. Prior to study initiation, all sites will have validated this algorithm in accordance with the policies described in the MTN Manual of Operations (www.mtnstopshiv.org). All sites will participate in ongoing proficiency testing of their HIV testing procedures throughout the course of the study. The HIV test kits used at each site will be pre-approved by the MTN NL; at each testing time point when rapid tests are used, at least one FDA-approved rapid test kit will be used. All Western blot testing will be performed using FDA-approved test kits.

The MTN NL will verify HIV testing performed at the study site laboratories for purposes of eligibility determination and primary outcome ascertainment as follows:

- The NL will test study entry specimens from a 10 percent random sample of participants enrolled at each site for evidence of HIV infection using FDA-licensed tests. Study Entry specimens are collected at participants' Enrollment Visits. If any false-negative local lab results are identified, the NL will test the Study Entry specimens from another 20 percent of enrolled participants from that site.
- The NL will test the Study Entry and Seroconversion specimens from all study participants identified by the local labs as having become infected with HIV during the study follow-up period. Study Entry specimens are collected at participants' Enrollment Visits. Seroconversion specimens are collected at the time of specimen collection for confirmatory HIV testing, i.e., when Sample 2 in Appendices II and III is obtained. The NL similarly will test the Study Entry and Study Exit specimens from a random sample of participants (equal to the number of seroconversions) not identified by the local labs as having become infected with HIV during the study follow-up period. Study Exit specimens are collected at participants' final follow-up visits. All specimens will be tested for evidence of HIV infection using FDA-licensed tests. For seroconverters, Study Entry specimens also will be tested by RNA PCR. If any false-negative or false-positive local lab antibody test results are identified, the NL will test all Study Exit specimens from that site.

NL staff will follow-up directly with site staff to resolve any quality control or quality assurance problems identified through proficiency testing, on-site assessments, and/or confirmatory HIV testing.

In addition to all of the above, an endpoint adjudication committee will provide guidance on endpoint determination to the VOICE Protocol Team on an as needed basis. See the MTN MOP (www.mtnstopshiv.org) for detailed information on the composition, roles, and responsibilities of the endpoint adjudication committee.

7.13 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice, the HPTN-MTN Network Laboratory Manual (www.mtnstopshiv.org), DAIDS Laboratory Requirements (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Labs/>), MTN-003 Study Specific Procedures Manual (www.mtnstopshiv.org), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS). In cases where laboratory results are not available due to administrative or laboratory error, sites are permitted to re-draw specimens.

7.14 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/Labs/>).

7.15 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study as recommended by the CDC and NIH. All biological specimens will be transported using packaging mandated by CFR 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

Site IoRs are responsible for continuous close safety monitoring of all study participants, and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Co-Chairs, DAIDS Medical Officer, Protocol Safety Physician, and SCHARP Clinical Affairs Safety Associate will serve as the PSRT. The MTN SDMC prepares routine AE and clinical data reports (blinded to treatment assignment) for review by the PSRT, which meets via conference call approximately once per month or as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

The NIAID Vaccine and Prevention DSMB will monitor participant safety throughout the study. The DSMB routinely meets approximately every four months, and it is expected

that reviews of VOICE will take place approximately every eight months. At the time of these reviews, or at any other time, the DSMB may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

8.2 Adverse Events Definitions and Reporting Requirements

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all five study groups, and is applied to all groups beginning from the time of randomization. The term “investigational product” for this study refers to all six study products, as well as the study gel applicator.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience, except for possible life-threatening events, for which they are instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study CRFs. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product. Study staff also will report on CRFs the following subset of AEs reported by or observed in enrolled participants:

- All genital, genitourinary, and reproductive system AEs
- All fractures
- All AEs of severity Grade 2 or higher in the following categories: dizziness, headache, nausea, vomiting, diarrhea, abdominal pain, rash
- All AEs of severity Grade 3 or higher
- All serious AEs, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
- All AEs that result in permanent discontinuation of study product use
- All laboratory test abnormalities not otherwise associated with a reported clinical AE
- AEs that do not meet the above-listed criteria but do meet expedited reporting requirements per Section 8.3 below

For each study participant, AE documentation and reporting will be undertaken throughout the scheduled duration of follow-up, i.e., through completion of the participant's Termination visit. After the Termination Visit, only pregnancy outcomes that meet criteria for expedited adverse event (EAE) reporting (see Section 8.3 below) occurring among participants known to be pregnant at the Termination Visit will be reported.

The IoR/designee will grade the severity of each AE and, for AEs reported on CRFs, assess the relationship of the AE to study product:

- AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 and the Female Genital Grading Table for Use in Microbicide Studies (Appendix 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004), except that asymptomatic BV will not be a reportable AE. AEs not included in the Female Genital Grading Table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004. In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.
- The relationship of all AEs reported on CRFs will be assessed based on the Manual for Expedited Reporting of Adverse Events to DAIDS, dated May 6, 2004 (DAIDS EAE Manual), the product Package Inserts and Investigators Brochures, and the clinical judgment of the IoR/designee. The study products that must be considered when AE relationship are TDF tablet, FTC/TDF tablet, tenofovir 1% vaginal gel, and study gel applicator.

The DAIDS Table for Grading Adult and Pediatric Adverse Events, the Female Genital Grading Table for Use in Microbicide Studies, and the Manual for Expedited Reporting of Adverse Events to DAIDS are available on the DAIDS Regulatory Compliance Center (RCC) web site: rcc.tech-res-intl.com.

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the exit visit, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-faxed to SCHARP DataFax. For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the AE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The VOICE PSRT may advise

study staff as to whether any additional follow-up may be indicated on a case by case basis. For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log CRFs based on the re-assessments.

8.3 Expedited Adverse Event Reporting Requirements

Expedited Adverse Event Reporting to DAIDS

The EAE reporting requirements and definitions for this study and the methods for expedited reporting of AEs to the DAIDS Regulatory Compliance Center (RCC) Safety Office are defined in the DAIDS EAE Manual, available on the RCC website: <http://rcc.tech-res-intl.com/>. EAEs must be documented on the DAIDS EAE Reporting Form available on the RCC website: <http://rcc.tech-res-intl.com>. DAIDS EAE forms should be submitted to DAIDS through the RCC Safety Office (rccsafetyoffice@tech-res.com) or call 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710.

EAE Reporting Requirements for this Study

EAE Reporting Level

This study uses the Standard Level of expedited AE reporting as defined in the DAIDS EAE Manual.

Study Agents for Expedited Reporting to DAIDS

The study agents that must be considered in determining relationships of AEs requiring expedited reporting to DAIDS are: TDF tablet, FTC/TDF tablet, tenofovir 1% vaginal gel, and study gel applicator.

Grading Severity of Events and Reporting Period

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.2. After the end of the Protocol-defined EAE Reporting Period stated above, sites must report serious, unexpected, clinical suspected adverse drug reactions if the study site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

8.4 Regulatory Requirements

Information on all reported AEs will be included in reports to the U.S. FDA and other applicable government and regulatory authorities. Site IIRs/designees will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. Site IIRs/designees also will submit AE information and any other relevant safety information to their IRBs/ECs in accordance with IRB/EC requirements.

8.5 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example,

participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to responsible site IRBs/ECs at least annually, or according to their individual requirements. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-003 SSP Manual. While maintaining participant confidentiality, study sites may engage their Community Advisory Boards in exploring the social context surrounding instances of social harm, to minimize the potential occurrence of such harm.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to hold study product temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the IoR/designee should immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs. In this section, “oral study product” refers to both types of tablets to which a participant is randomized.

9.1 Grading System

AE severity grading is described in Section 8.2.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

9.3 General Criteria for Temporary Hold and Permanent Discontinuation of Study Product

A participant will be permanently discontinued from product use by the IoR/designee for any of the following reasons:

- Acquisition of HIV-1 infection; such participants will not resume product use at any time. Study product should be held beginning immediately upon recognition of the first reactive rapid HIV test. If via the algorithm in Appendix III the participant is determined to be HIV-uninfected, she may resume product use. The IoR/designee must permanently discontinue study product if HIV-1 infection is confirmed.

- Acquisition of hepatitis B infection; such participants will not resume product use at any time.

A participant will be temporarily held from study product for any of the following reasons:

- Pregnancy. A participant who becomes pregnant may resume product use after giving birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff, provided they are not breastfeeding. For participants assigned to gel, a pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.
- Breastfeeding. Product use may resume when the participant reports complete cessation of breastfeeding.
- Report of use of prohibited medications described in Section 6.8. Product use may resume when the participant reports no longer taking the prohibited medication, provided other reasons for temporary product hold/permanent discontinuation do not apply.
- Report of use of PEP for HIV infection. The participant may resume product use when she reports completion of PEP and is confirmed HIV negative based on testing performed at the study site per the algorithm in Appendix III.
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee. The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation. If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

9.4 Temporary Product Hold/Permanent Discontinuation in Response to Observed Adverse Events

Grade 1 or 2

In general, a participant who develops a Grade 1 or 2 AE regardless of relatedness to study product that is not specifically addressed below may continue product use.

Grade 3

Participants who develop a Grade 3 AE that is not specifically addressed below and is judged by the IoR/designee to be probably not or not related to study product may continue product use.

In general, and unless otherwise decided in consultation with the PSRT, the IoR/designee should:

- Temporarily hold the study product.
- Re-evaluate the participant at least weekly for up to 2 weeks.
- Resume study product if improvement to \leq Grade 2 is documented within 2 weeks.
- Permanently discontinue the study product if improvement to severity \leq Grade 2 cannot be documented within 2 weeks.

If product use is resumed and the same Grade 3 AE recurs at any time, the IoR/designee must consult the PSRT for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the study product.

Grade 4

A participant who develops a Grade 4 AE that is not specifically addressed below (regardless of relationship to study product) should have the study product held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT. In general, product use will not be resumed if the Grade 4 AE is considered probably not, possibly, probably, or definitely related to product use. If, in consultation with the PSRT, product use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study product must then be permanently discontinued.

9.5 Management of Specific Toxicities

Specific temporary product hold requirements are specified here in the context of clinical management of toxicities.

9.5.1 Nausea, Vomiting, and/or Diarrhea

The IoR/designee may treat a participant with Grade 1 or 2 nausea, vomiting, and/or diarrhea symptomatically (e.g., diet changes, antiemetics, and/or supportive fluids).

ORAL STUDY PRODUCT

For participants with Grade ≥ 3 or higher nausea and/or vomiting and/or diarrhea, the IoR/designee must:

- Place a temporary hold on oral study product
- Offer symptomatic treatment
- Order any clinically relevant laboratory analyses (per judgment of the IoR/designee)

If the condition(s) improve(s) to Grade ≤ 2 , the participant should resume oral study product. Note, all symptoms of nausea, vomiting, and/or diarrhea must improve to Grade ≤ 2 prior to resumption of study product. Should condition(s) not improve to Grade ≤ 2 within 7 days, the IoR/designee should consult the PSRT for guidance on

continuing temporary hold or progressing to permanent discontinuation of oral study product.

If following a Grade ≥ 3 event(s) the participant is permitted to resume oral study product, but has recurrence of the same event(s) at a Grade ≥ 3 level, the IoR/designee must:

- Place a temporary hold on oral study product
- Offer symptomatic treatment
- Order any clinically relevant laboratory analyses (per judgment of the IoR/designee)
- Consult the PSRT for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the oral study product.

VAGINAL STUDY PRODUCT

Unless other temporary product hold requirements apply, vaginal study product need not be held unless the IoR/designee has compelling evidence that the toxicity is probably or definitely related to vaginal study product. In this case, the IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

9.5.2 AST and/or ALT Elevations

Careful assessments should be done to rule out alcohol, non-study medication-related drug toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST and/or ALT of any grade. The IoR/designee must carefully assess the participant for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain or hepatomegaly. If the AST and/or ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent (if clinically indicated), should be undertaken.

If symptoms or signs of clinical hepatitis are present, the IoR/designee must temporarily hold oral study product and test the participant for hepatitis (including HBsAg plus any other testing indicated by the local standard of care). If hepatitis infection is confirmed, product use must be permanently discontinued.

ORAL STUDY PRODUCT

Grade 1

For a participant with normal (less than Grade 1) ALT and/or AST at study entry, an increase to Grade 1 even in an asymptomatic participant may be of concern. The IoR/designee must repeat the ALT and AST as soon as possible (at most within 1 week of a new Grade 1 ALT and/or AST). The participant may continue study product while the IoR/designee repeats the participant's ALT and AST, provided the participant is asymptomatic. In a participant with a confirmed Grade 1 ALT and/or AST who is asymptomatic, the IoR/designee may continue the participant's study product with continued close observation. In the case of symptomatic participants, study product will

be held temporarily and management (including resumption of study product) should be arranged in consultation with the PSRT.

Grade 2

The IoR/designee must repeat the ALT and AST as soon as possible (at most within 1 week) and then follow the participant weekly until levels are Grade ≤ 1 . The frequency of follow up may be altered at the discretion of the IoR/designee following consultation with the PSRT. Study product may continue at the discretion of the IoR/designee, provided the participant is asymptomatic. In the case of symptomatic participants, study product will be held temporarily and management (including resumption of study product) should be arranged in consultation with the PSRT.

Grade 3

The IoR/designee must temporarily hold study product and repeat the ALT and AST as soon as possible (at most within 1 week). The participant should then be followed weekly until levels are Grade ≤ 1 , at which point, with concurrence from the PSRT, study product may be resumed. If improvement to Grade ≤ 1 cannot be documented within three weeks, study product must be permanently discontinued.

If following a Grade ≥ 3 event(s) the participant is permitted to resume oral study product, but has one or more events (AST and/or ALT) at a Grade 3 level, the IoR/designee must perform the following:

- Place a temporary hold on oral study product
- Offer symptomatic treatment (if appropriate)
- Order any clinically relevant laboratory analyses (per judgment of the IoR/designee)
- Consult the PSRT for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the oral study product.

Grade 4

Study product should be permanently discontinued. The IoR/designee must follow the participant's ALT and AST at least weekly until levels are Grade ≤ 1 .

VAGINAL STUDY PRODUCT

Unless other temporary product hold/permanent discontinuation requirements guidelines apply, vaginal study product need not be held unless the IoR/designee has compelling evidence that the toxicity is probably or definitely related to vaginal study product. In this case, the IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the product hold temporarily, or progressing to permanent discontinuation.

9.5.3 Creatinine

ORAL STUDY PRODUCT

The IoR/designee should temporarily hold oral study product for any rise in creatinine greater than or equal to 1.5 x participant's baseline value (BL). The creatinine should be repeated as soon as possible (at most within 1 week). Product use may be resumed

when the creatinine level improves to $\leq 1.3 \times \text{BL}$. If product use is resumed and the creatinine level increases to $\geq 1.5 \times \text{BL}$, product use must be permanently discontinued.

VAGINAL STUDY PRODUCT

Unless other temporary product hold/permanent discontinuation requirements apply, vaginal study product need not be held. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

9.5.4 Creatinine Clearance

ORAL STUDY PRODUCT

If the creatinine clearance is $<50\text{mL/min}$, oral study product should be held and the test should be repeated as soon as possible (at most within 1 week of the receipt of the results). If a level of $<50\text{mL/min}$ is confirmed with retesting, study product should be permanently discontinued. If retesting cannot be completed within one week, all attempts should be made by the site to contact the participant for retesting within three additional working days. A participant who fails to undergo confirmatory testing within one week plus three additional working days will permanently discontinue oral study product.

If re-testing yields a result $\geq 50\text{mL/min}$, the IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

If clinical suspicion for renal failure exists, local medical resources with clinical expertise in renal failure must be engaged to the extent available.

VAGINAL STUDY PRODUCT

Unless other temporary product hold/permanent discontinuation requirements apply, vaginal study product need not be held. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

9.5.5 Lactic Acidosis

While occurrences in healthy adults are expected to be rare, lactic acidosis induced by ARV medication has been reported and may present with nonspecific complaints. In the absence of other explanatory conditions (e.g., acute viral hepatitis or bacterial infection), certain findings should trigger consideration of lactic acidosis. Such clinical findings include unexplained dyspnea, weight loss, nausea, vomiting, abdominal pain, and/or liver failure. Unexplained laboratory abnormalities which also warrant clinical consideration of lactic acidosis include low bicarbonate, hypoalbuminemia, elevated anion gap, elevated liver enzymes, and/or increased amylase.

ORAL STUDY PRODUCT

If significant suspicion for lactic acidosis is present according to the clinical judgment of the IoR/designee, oral study product must be held, and local medical resources with clinical expertise in lactic acidosis engaged to the extent available. The IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the

hold temporarily, or progressing to permanent discontinuation based on the results of clinical evaluation and laboratory testing.

VAGINAL STUDY PRODUCT

Unless other product hold requirements apply, vaginal study product may be continued at the discretion of the IoR/designee. Should the IoR/designee determine that a product hold is warranted, consultation with the PSRT is required.

9.5.6 Hypophosphatemia

ORAL STUDY PRODUCT

Grades 1 and 2

The phosphate test should be repeated within 2 weeks of the receipt of the results. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution. Unless other temporary product hold requirements apply, study product need not be held.

Grades 3 and 4

The phosphate test should be repeated within 1 week of the receipt of the results. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution, and other causes of low phosphate should be investigated. During the time that supplemental phosphate is provided to the participant and the time that testing is repeated, sites should follow temporary product hold/permanent discontinuation guidelines described in Section 9.4. If improvement to \leq Grade 2 can not be documented within one week, study product must be permanently discontinued.

VAGINAL STUDY PRODUCT

The IoR/designee should treat hypophosphatemia according to clinical management guidelines noted above for participants randomized to oral study product. However, unless other temporary product hold/permanent discontinuation requirements apply, vaginal study product need not be held. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

9.6 Proteinuria

Proteinuria will be assessed by urine dipstick. A finding of 1+ proteinuria should be confirmed with a second urine dipstick performed no earlier than one week but no later than 2 weeks after detection of the first 1+ proteinuria. Proteinuria of 2+ or greater does not need to be confirmed at a separate visit.

ORAL STUDY PRODUCT

The IoR/designee should temporarily hold oral study product in the following circumstances:

- Detection of 3+ or greater proteinuria at any visit. Oral study product should be held regardless of serum creatinine or phosphorus results obtained at the time of proteinuria detection. Urine dipstick testing and serum creatinine and phosphate should then be performed monthly for at least three months.

- Detection of 2+ proteinuria. Oral study product should be held until results of serum creatinine and phosphorus results obtained at the time of proteinuria detection are available. Product hold should continue if hold criteria outlined for serum creatinine and/or phosphorus are met. If neither value meets criteria for study product hold, oral study product should be resumed.
- Detection of 1+ proteinuria confirmed on two separate visits. Oral study product should be held only if serum creatinine or phosphorus results obtained at the time of detection of proteinuria meet hold criteria (Sections 9.5.3 and 9.5.6).

In cases of oral study product hold based on proteinuria, product use may be resumed following the resolution of proteinuria no earlier than three months after product cessation. If product use is resumed and proteinuria increases to 2+ or greater, product use must be permanently discontinued.

VAGINAL STUDY PRODUCT

The IoR/designee should manage proteinuria according to clinical management guidelines (pertaining to laboratory analyses) noted above for participants randomized to oral study product. However, unless other temporary product hold/permanent discontinuation requirements apply, vaginal study product need not be held. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

9.7 Glycosuria

Glycosuria will be assessed by urine dipstick. A finding of 1+ glycosuria should be confirmed with a second urine dipstick performed no earlier than one week but no later than 2 weeks after detection of the first 1+ glycosuria. Glycosuria of 2+ or greater does not need to be confirmed at a separate visit.

ORAL STUDY PRODUCT

The IoR/designee should temporarily hold oral study product in the following circumstances:

- Detection of 3+ or greater glycosuria at any visit. Oral study product should be held regardless of serum creatinine or phosphorus results obtained at the time of proteinuria detection. Urine dipstick testing and serum creatinine and phosphorus should then be performed monthly for at least three months.
- Detection of 2+ glycosuria. Oral study product should be held until results of serum creatinine and phosphorus results obtained at the time of glycosuria detection are available. Product hold should continue if hold criteria outlined for serum creatinine and/or phosphorus are met (Sections 9.5.3 and 9.5.6). If neither of these values meets criteria for study product hold, oral study product should be resumed.
- Detection of 1+ glycosuria confirmed on two separate visits. Oral study product should be held only if serum creatinine or phosphorus results obtained at the time of detection of glycosuria meet hold criteria.

In cases of oral study product hold based on glycosuria, product use may be resumed following the resolution of glycosuria no earlier than three months after product cessation. If product use is resumed and glycosuria increases to 2+ or greater, product use must be permanently discontinued.

VAGINAL STUDY PRODUCT

The IoR/designee should manage glycosuria according to clinical management guidelines noted above for participants randomized to oral study product. However, unless other temporary product hold/permanent discontinuation requirements apply, vaginal study product need not be held. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

9.8 Pap Smear

The IoR/designee should manage Pap smear results according to current guidelines of the American Society for Colposcopy and Cervical Pathology, unless other local guidelines are available.

ORAL STUDY PRODUCT

Unless other temporary product hold/permanent discontinuation guidelines apply, oral study product need not be held. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

VAGINAL STUDY PRODUCT

The IoR/designee must temporarily hold vaginal study product for participants with a high-grade squamous intraepithelial lesion or more severe abnormality identified on Pap smear. Product use also may be held in response to lower grade abnormalities, if local standards of care require clinical colposcopy and/or biopsy to assess lower grade abnormalities. The period of temporary product hold will begin on the day of the clinical evaluation, biopsy, and/or treatment of the abnormality. Alternatively, the temporary hold may be initiated one to two days prior to the day of clinical evaluation, biopsy, and/or treatment, if per local standards of care the participant is advised to avoid sexual intercourse on these days. The period of temporary hold will continue after biopsy and/or treatment of the abnormality until a clinically acceptable resolution for the biopsy and/or treatment has occurred according to the judgment of the IoR/designee. Study staff will obtain medical records documenting the evaluation, biopsy, and/or treatment of the abnormality and, assuming adequate treatment is confirmed, will perform a pelvic exam after the evaluation/biopsy/treatment date to confirm healing of the cervix. Thereafter, assuming no contraindications are identified on pelvic exam, product use will be resumed.

9.9 Genital Sexually Transmitted Infection/Reproductive Tract Infection

The IoR/designee should manage STI/RTI per current WHO guidelines, available at <http://www.who.int/en/>. Observed single dose treatment should be provided whenever possible. Vaginally applied medications should not be used, except that vaginal azoles should be used to treat symptomatic candidiasis among pregnant women.

ORAL STUDY PRODUCT:

Oral study product need not be held in the event of genital STI/RTI requiring treatment, unless other temporary product hold/permanent discontinuation requirements apply. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

VAGINAL STUDY PRODUCT

Vaginal study product need not be held in the event of an STI/RTI requiring treatment, unless other temporary product hold/permanent discontinuation guidelines apply. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

9.10 HIV Infection

A participant who has a positive rapid test for HIV must have study product held. If the participant is subsequently determined to be HIV-uninfected according to the algorithm in Appendix III, study product may be resumed. If HIV infection is confirmed, study product will be permanently discontinued by the IoR/designee. Participants identified as infected with HIV will be managed or referred for management according to the local standard of care.

Participants who become infected with HIV will be offered participation in MTN-015, the MTN Seroconverter Study, which also includes provisions for the clinical management and/or referral of participants infected with HIV. It is anticipated that all VOICE sites will have MTN-015 activation prior to or concurrently with the initiation of the VOICE protocol. Participants will be referred for HIV-1 care and treatment, according to local guidelines; this referral process may also occur via MTN-015 if the participant chooses to enroll in that study. Written SOPs for referral for HIV-1 care and treatment are in place at each study site. Study site investigators have identified facilities offering psychological and social services and medical care, including ART, to people infected with HIV-1 in the study countries. Some of the research sites are part of health care institutions that provide HIV-1 care and support, and can refer women to those services. Other sites have established referral agreements with programs to expand access to ART, such as those funded by the US President's Emergency Plan for AIDS Relief.

The level of care provided at the referral sites will be at a level that meets or exceeds the community standard for HIV-1 care. At every study visit, study staff will actively follow-up on prior referrals to HIV-1 care and support services, to determine whether the participant sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. Additional counseling also may be needed to help ensure the participant receives appropriate care. All follow-up actions, outcomes, counseling, and plans for next steps will be documented in participant study records. Results of study laboratory testing may be helpful in clinical management; these results will be provided to the participant and her medical provider in real-time.

9.11 Hepatitis B Infection

If symptoms or signs of clinical hepatitis are present, the IoR/designee must temporarily hold oral study product and test the participant for hepatitis (including HBsAg plus any other testing indicated by the local standard of care). If hepatitis infection is confirmed, product use must be permanently discontinued.

Participants identified as infected with hepatitis B (acute or chronic active infection, according to algorithm in Appendix IV) will be managed or referred for management according to the local standard of care. Participants identified as infected with hepatitis B will permanently discontinue study product. Following permanent discontinuation of study product, participants in the oral arm identified as infected with hepatitis B will have scheduled laboratory and clinical evaluations to monitor for hepatitis B flare, as noted in Section 7; if deemed clinically necessary by the IoR/designee, these evaluations may continue following the end of the study follow-up period.

9.12 Pregnancy

All study participants are required to be using an effective method of contraception according to Section 5.2 at the Enrollment Visit. Study staff will provide contraceptive counseling to enrolled participants as needed throughout the duration of study participation and will facilitate access to contraceptive services through direct service delivery. Study staff also will provide participants with condoms and counseling on use of condoms ideally during every sex act during study participation.

Pregnancy testing will be performed at all study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The expected maximum time from conception to permanent discontinuation of study product will be approximately six weeks. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

A participant who is pregnant at the Termination Visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). Pregnancy outcomes will be reported on relevant CRFs; outcomes meeting criteria for EAE reporting also will be reported on EAE forms.

A participant who becomes pregnant during the course of the study will have study product held as per Section 7.6.3, but may resume study product after delivery, or spontaneous or elective termination of the pregnancy, provided she is not breastfeeding. Study product will be held after pregnancy while women report breastfeeding. Participants who successfully complete a pregnancy during the study will be encouraged to breastfeed, according to current WHO recommendations. Study product will be resumed once a participant reports cessation of breastfeeding, as long as other temporary product hold or permanent discontinuation rules do not apply. For participants assigned to gel, a pelvic exam must be performed prior to resumption to

confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.

Participants who become both pregnant and HIV-infected will have expedited HIV-1 resistance testing performed at the MTN NL to provide information about possible resistance that might impact the efficacy of ART regimens to reduce mother-to-child HIV-1 transmission. The participant will be referred to local providers for antenatal care, and prevention of mother-to-child transmission services. HIV testing for infants will be provided by the study if not otherwise accessible by the participant.

A participant who becomes pregnant during the course of study participation may be offered participation in MTN-016, the Prevention Agent Pregnancy Exposure Registry. This registry study is anticipated to capture pregnancy outcomes as well as infant health information, (including growth and development), to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy.

9.13 Compression Fracture

A participant noted to have a decrease in height of 1.5 inches or more during follow-up as measured by study staff will have measurement repeated. If the decrease is confirmed by repeat measurement, the IoR/designee will order radiography to rule out vertebral fracture, unless the participant is pregnant, in which case radiography may be delayed until the pregnancy is completed.

ORAL STUDY PRODUCT

If radiography confirms vertebral compression fracture, oral study product must be permanently discontinued.

VAGINAL STUDY PRODUCT

Unless other temporary product hold/permanent discontinuation requirements apply, vaginal study product need not be held. Should the IoR/designee determine that a temporary product hold is warranted, consultation with the PSRT is required.

9.14 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, including the Office of Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date, pending consultation with the PSRT.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

This is a Phase 2B, multi-site, five-arm, randomized, placebo-controlled trial. A total of approximately 4200 participants will be randomly assigned in a 1:1:1:1:1 ratio to each of the following five study groups:

- TDF group (TDF 300 mg and FTC/TDF placebo)
- FTC/TDF group (TDF placebo and FTC/TDF 200 mg/300 mg)
- Oral placebo group (TDF placebo and FTC/TDF placebo)
- Vaginal tenofovir 1% gel group
- Vaginal placebo gel group

The study is double-blinded within each mode of administration (oral or vaginal) but it is open-label with respect to the mode of administration. Each participant will complete a minimum of 12 months and a maximum of 33 months of study product use. Based on the expected HIV baseline incidence rates at the sites, the accrual and follow-up plan should achieve the target of 217 HIV seroconversions (i.e., 94 endpoints per pairwise-comparison) needed for appropriate statistical power for the study primary objectives. At the end of follow-up with product use, all participants will be followed off-product for an additional approximate 8 weeks to evaluate the incidence of delayed HIV seroconversion (a secondary endpoint).

10.2 Study Endpoints

Primary safety endpoints

Consistent with the primary safety study objective to evaluate the extended safety of daily tenofovir 1% gel, oral TDF, and oral FTC/TDF in women at risk for sexually transmitted HIV infection, the following primary safety endpoints will be assessed:

- Grades 2, 3, and 4 clinical and laboratory AEs (as defined by the DAIDS AE Grading Table including Addendum 1 - Female Genital Grading Table for Use in Microbicide Studies)

Primary effectiveness endpoint

Consistent with the primary study objective to estimate the effectiveness of daily tenofovir 1% gel compared to a vaginal placebo gel, and the effectiveness of oral TDF and oral FTC/TDF compared to an oral placebo in preventing HIV infection among at-risk women, the following primary effectiveness endpoint will be assessed:

- HIV infection as measured by seroconversion according to the algorithm in Appendix III at the end of the study product use period (i.e., at the start of the additional 8 weeks of follow-up off product)

Secondary endpoints

- **Adherence/Behavioral**

Consistent with the secondary objectives to evaluate adherence to daily regimens of vaginal gel (tenofovir 1% gel and placebo) vs. oral tablets (TDF, FTC/TDF, and placebo) used for pre-exposure prophylaxis (PrEP) to prevent HIV infection, and to examine whether sexual activity, condom use, and intravaginal practices change over time in women who use either daily vaginal gel (tenofovir 1% gel and placebo) or daily oral tablets (TDF, FTC/TDF, and placebo), the following secondary endpoints will be assessed:

- Self-reported use of study product (including frequency and last time product used), frequency of sexual activity (including vaginal and anal sex), frequency of condom use, condom use at last sex, intravaginal practices, study product counts

- **HIV-1 Drug resistance**

Consistent with the secondary objective to assess the occurrence of HIV-1 drug resistance in women who acquire HIV-1 infection while using study product, the following secondary endpoint will be assessed:

- HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by genotypic methods

- **Pharmacokinetic**

Consistent with the secondary objective to evaluate the PD relationship between plasma drug concentrations and the study outcomes (i.e., HIV seroconversion, toxicity, report of AEs or evidence of cervicovaginal inflammation, viral resistance), the following secondary endpoint will be assessed:

- AUC, C_{max} , and C_{min}

- **Delayed seroconversion**

Consistent with the secondary objective to assess the incidence of HIV seroconversion across study arms between the PUEV and the Termination Visit the following secondary endpoint will be assessed:

- HIV infection as measured by seroconversion (according to the algorithm in Appendix III) during the approximate 8 weeks of follow-up off study product between the PUEV and the Termination Visit

10.3 Primary Study Hypotheses

Primary safety endpoints

The VOICE protocol team hypothesizes that all three active study products will be safe, well-tolerated and acceptable for once daily use among healthy sexually active women. Therefore, the null hypothesis is that there will be no difference in the safety profile between daily regimens of active products and placebo.

Primary effectiveness endpoint

To achieve an overall effect of preventing HIV infection at the population level, a minimum bound above 0% for the effectiveness in individual efficacy trials needs to be achieved to offset any negative indirect effects potentially induced by an increase in risky behavior (e.g., sexual disinhibition) and/or in changes in condom usage. Indeed, mathematical modeling has shown that for an HIV vaccine to be effective at the population level, the minimum (direct) efficacy may need to be 30% or greater.^{74,75} Recently, similar mathematical models suggest that the (direct) efficacy of oral PrEP should be above 25-50%.⁷⁶ Similarly, the (direct) efficacy of vaginal microbicides may also need to be above 25-50% to offset potential changes in condom usage.^{57, 77}

Based on this, several of the ongoing or planned oral PrEP trials are powered to rule out a lower effectiveness between 10% and 30%. The VOICE protocol team has set the minimum lower bound for the effectiveness at 25% for both the oral and vaginal products. Therefore the null hypothesis is that the active products will be no more than 25% effective. That is, the trial is powered to detect effectiveness of at least 55% and to rule out effectiveness of 25% or lower.

10.4 Sample Size and Power Calculations

Primary effectiveness endpoint

Phase 2 extended safety trials of vaginal microbicides and oral PrEP regimens neither provide any evidence regarding the effectiveness of these regimens for the prevention of HIV infection, nor provide evidence of effectiveness associated with biological or surrogate markers. Given this, moving directly from Phase 2 trials to Phase 3 trials involving several thousand participants is a risky strategy, and a potentially inefficient use of time and resources. Recognizing this, the HPTN 035 team used a Phase 2B screening trial design as described in Fleming and Richardson.⁷⁸ Typically, the number of events in a Phase 2B screening trial that would be required for an efficient licensure strategy would be about one-fourth to one-third of the number of events that would be needed in a Phase 3 trial powered for licensure with the strength of evidence of at least one-and-a-half Phase 3 studies (false-positive error rate of 0.0025).⁷⁸

VOICE uses this licensure strategy, such that the trial size is about one-third of the size of a Phase 3 trial to detect at least 55% effectiveness while ruling out a lower effectiveness of $\leq 25\%$ with 90% power and a false positive error rate of 0.25% (i.e., 0.0025) where product effectiveness is defined as $100 \times [1 - (\text{product infection rate} / \text{placebo infection rate})]$. On the log scale, a false-positive error rate of 0.0025 is

approximately midway between the false-positive error rates associated with the strength of evidence from 1 and 2 traditional Phase 3 studies (0.025 and 0.000625, respectively). In the context of the HPTN 035 trial, it follows from discussions with the Food and Drug Administration that a false-positive error rate of 0.0025 should be used for hypothesis testing for each product if a single Phase 3 trial were being considered for product registration. Although the approach above was used in the context of vaginal microbicides, the same rationale holds for oral PrEP regimens where similar strength of evidence would be needed to be support a change of product labeling.

Based on the above parameters, 94 events per-pairwise comparison are needed for a Phase 2B screening trial to detect 55% effectiveness while ruling out a lower effectiveness of 25% with 90% power and a false-positive error rate of 0.25%. Note that the usual formula for determining the number of endpoints is appropriate for moderate effectiveness for the null and alternative hypothesis. The following variance inflation factor needs to be applied for null and/or alternative hypotheses for relative risks outside the range of 0.50 and 2.00:

$$((1+R_0)(1+R_0)/(8R_0))+((1+R_1)(1+R_1)/(8R_1))$$

Note, R_0 and R_1 are the relative risks under the null and alternative hypothesis, respectively (see formula on page 395 of Fleming and Harrington for more details).

The derivation follows directly from Fleming and Harrington, 1991, pages 394-395. Equations 4 and 5 on page 394 give the general result for the information matrix upon which the variance is derived. When β is near zero, we get the familiar result in (d) on the top of page 395. However when β is not near zero (i.e., when $\exp(\beta)$ is below 0.5 or greater than 2.0 which is the case for this protocol), the more exact solution provided above should be used.

Based on the formula given in Fleming and Harrington with the above variance inflation factor, 282 events per-pairwise comparison would be required for a Phase 3 trial which yields 94 events per-pairwise comparison for a Phase 2B screening trial (one-third of 282).^{78,79} Thus a total of 217 endpoints are required, 94 for the pairwise comparison between placebo gel and tenofovir 1% gel and 123 for the two pairwise comparisons for the oral arms: oral placebo vs. oral TDF and oral placebo vs. oral FTC/TDF (assuming an effectiveness of 55% for oral TDF and oral FTC/TDF).

At the end of the trial, the decision guidelines for each of the three active products are as follows:

- If the estimated effectiveness is greater than 58.0%, consider the product effective while ruling out effectiveness $\leq 25\%$ with the strength of evidence of at least one-and-a-half Phase 3 studies (i.e., with a false-positive error rate of 0.0025). Proceed to licensure or change of label.

- If the estimated effectiveness is between 50.0% and 58.0%, consider the product effective while ruling out effectiveness $\leq 25\%$ with strength of evidence equal to that of at least a single Phase 3 study (i.e., with a false-positive error rate of 0.025). Evidence from a subsequent Phase 3 study (or another on-going trial) with a false-positive error rate of 0.025 may be required for licensure or change of label.
- If the estimated effectiveness is between 33.3% and 50.0%, consider the product effective with strength of evidence equal to that of at least a single Phase 3 study (i.e., with a false-positive error rate of 0.025 against a null alternative of 0% effectiveness) but effectiveness $\leq 25\%$ cannot be ruled out. Consider the product to be effective, but effectiveness may be too low to achieve a positive total effectiveness at the population level. More evaluation may be required to assess the population level effect.
- If the estimated effectiveness of a candidate product is less than 33.3%, exclude the candidate product from further testing for HIV prevention.

Note that the above-listed statements represent decision guidelines. The point estimates of product effectiveness and associated false-positive error rates specified in these guidelines are based on the assumptions related to study size, although every effort will be made to fulfill these assumptions. In the event that they are not borne out, alternative p -values may be associated with observed point estimates. In this case action taken with regard to declaring effectiveness, seeking licensure, and/or planning further studies will be consistent with the intent of the guidelines, but based on the actual point estimates and p -values observed.

The operating characteristics for this decision guideline can be derived from Table 6 and can be summarized:

- The false-positive error rate of the guideline is low. If a product is truly ineffective (0% true effect), there is only 0.4% chance of proceeding with another Phase 3 trial and $<0.1\%$ chance of declaring the product to be effective with enough strength of evidence for licensure (or change of label). Moreover, there is 97.5% chance of excluding the product from further testing.
- The false-negative error rate of the guideline is low. If the candidate product is truly effective with a true effect of 55%, there is only a 2.8% chance of excluding the product from further evaluation and there is a 37.0% chance of declaring the product to be effective with enough strength of evidence for licensure (or change of label) and a 32.7% chance of declaring the product effective but without sufficient strength of evidence for licensure (or change of label). Moreover, there is a 27.5% chance of declaring the product effective but effectiveness lower than 25% could not be ruled out.

- The power to proceed directly to licensure is very high for a very effective product. If a product's true effect is 65%, then there is an 81.2% chance that the product would be declared effective with enough strength of evidence for licensure (or change of label) and only a 0.09% (i.e., 9 out of 10 000) chance that it would be excluded from further evaluation.

Table 6: Probabilities of Study Outcomes According to Various Levels of True Effect. Probability of Obtaining an Observed Effect (OE)

True Effect	OE < 33.3%	OE > 33.3% but < 50.0%	OE > 50.0% but < 58.0%	OE > 58.0%
0%	0.9750	0.0246	0.0004	0.0000
5%	0.9565	0.0426	0.0009	0.0000
10%	0.9264	0.0714	0.0021	0.0001
15%	0.8794	0.1154	0.0048	0.0003
20%	0.8101	0.1784	0.0106	0.0009
25%	0.7141	0.2609	0.0225	0.0025
33.3%	0.5000	0.4184	0.0691	0.0125
35%	0.4489	0.4483	0.0854	0.0173
40%	0.3028	0.5073	0.1477	0.0422
45%	0.1741	0.5019	0.2278	0.0962
50.0%	0.0816	0.4184	0.3015	0.1985
55%	0.0280	0.2748	0.3268	0.3704
58.0%	0.0125	0.1860	0.3015	0.5000
60%	0.0065	0.1319	0.2666	0.5949
65%	0.0009	0.0405	0.1460	0.8126
70%	0.0001	0.0065	0.0445	0.9490

Power under more moderate alternative hypotheses (i.e., < 55%) is given in Table 7. Power in the last row is relatively low since this Phase 2B design is using one third of the endpoints needed for a fully powered Phase 3 trial with a false positive rate of 0.25% required for licensure. On the other hand, power in the first row is moderate to high which leads to low probabilities of discarding a product from further evaluation. For instance, the probabilities of discarding a product from further evaluation are: 3%, 8%, 17%, and 30% if the true effects are 55%, 50%, 45%, and 40%, respectively.

Table 7: Power Under More Moderate Alternative Hypotheses

Null Hypothesis	False Positive Error Rate	Alternative Hypothesis				
		55%	50%	45%	40%	35%
0%	2.50%	97%	92%	83%	70%	55%
0%	0.25%	86%	71%	54%	37%	23%
<=25%	2.50%	70%	50%	33%	19%	10%
<=25%	0.25%	37%	20%	10%	4%	2%

Primary safety endpoint

For this analysis, a safety and toxicity endpoint is defined as the occurrence of the primary safety endpoint described in Section 10.2. Assuming that each candidate product will be compared separately to its corresponding placebo, a 5% significance level for a two-sided test (i.e., a 2.5 % false positive rate), 1420 p-y of follow-up per arm (see Section 10.5), and a pooled (pooled across active and placebo) safety and toxicity rate of 10% (i.e., 10 safety and toxicity endpoints per 100 p-y), the study has 90% power to detect a (hazard) rate ratio of $\leq 67\%$. This corresponds to safety and toxicity rates in placebo and active arms of 8 and 12 per 100 p-y, respectively. Table 8 displays the statistical power achieved for different safety and toxicity rates and (hazard) rate ratios.

Table 8: Statistical Power by Safety/Toxicity Rate and Hazard Rate Ratio

Safety/Toxicity Rate (per 100 p-y) (pooled over active and placebo)	Hazard Rate Ratio (placebo over active)						
	0.50	0.55	0.60	0.65	0.70	0.75	0.80
2.5%	83.7%	71.8%	58.2%	44.7%	32.8%	23.0%	15.5%
5.0%	98.5%	94.5%	86.1%	72.8%	56.6%	40.3%	26.4%
7.5%	99.9%	99.2%	96.2%	88.3%	74.2%	55.7%	37.2%
10.0%	>99.9%	99.9%	99.0%	95.3%	85.2%	67.9%	46.8%
12.5%	>99.9%	>99.9%	99.9%	98.2%	92.0%	77.5%	55.8%
15.0%	>99.9%	>99.9%	>99.9%	99.4%	95.7%	84.3%	63.4%
17.5%	>99.9%	>99.9%	>99.9%	99.8%	97.8%	89.4%	70.2%
20.0%	>99.9%	>99.9%	>99.9%	99.9%	98.9%	92.9%	75.8%
22.5%	>99.9%	>99.9%	>99.9%	>99.9%	99.5%	95.3%	80.6%
25.0%	>99.9%	>99.9%	>99.9%	>99.9%	99.7%	96.9%	84.4%
27.5%	>99.9%	>99.9%	>99.9%	>99.9%	99.9%	98.0%	87.7%
30.0%	>99.9%	>99.9%	>99.9%	>99.9%	99.9%	98.7%	90.3%
32.5%	>99.9%	>99.9%	>99.9%	>99.9%	>99.9%	99.2%	92.4%

10.5 Participant Accrual, Follow-up and Retention

A total of approximately 4200 women will be enrolled in 21 months with each site expected to enroll between approximately 300 and 600 women. Periodically during the accrual period, the MTN SMC, DSMB, and/or the Protocol Team will review performance data from each study site — including accrual rates, retention rates, protocol adherence measures, data quality measures, and HIV incidence rates — to determine whether enrollment slots should be shifted across sites to achieve the study objectives more efficiently and to determine when to discontinue accrual.

The VOICE Protocol Team will make every effort to discontinue accrual approximately 12 months prior to when the targeted number of incident HIV infections (i.e., n=217) will be observed.

Each enrolled participant will be followed, for a minimum of 12 months, through the study end date or for a maximum of 33 months, whichever occurs first, not including the approximate 8 week period between the scheduled PUEV and Termination Visit. The study end date will be set as the date upon which a total of 217 incident HIV infections have been observed. Based on the assumptions listed below, the targeted number of incident infections is expected to be reached approximately 12 months after the date upon which the last participant enrolls in the study. Thus, it is expected that participants will be followed for a minimum of 12 months and a maximum of 33 months, depending on when they enroll in the study and when the targeted number of infections is reached, not including the time between the PUEV and the Termination Visit. Sample size calculations are based on equal randomization to the five study treatment groups and the following assumptions:

- Expected participant accrual rates.
- Expected average annual baseline HIV seroincidence rates.
- Average annual retention rate of 90 percent.

Note that 90% retention per year is used to be conservative for the sample size calculations; however retention of 95% per year will be the target.

The assumed HIV seroincidence rates are averages of best available estimates based on ongoing or recently completed research studies and/or other available epidemiologic information from populations as similar as possible to the study population. In particular, estimates from populations receiving condom counseling were used when available.

Each study site will establish participant retention procedures to target lost-to-follow-up rates that do not exceed the HIV infection rate among local study participants, to minimize potential bias associated with loss-to-follow-up. However, the assumed average retention rate of 90 percent reflects past performance at the study sites and was factored into the sample size calculations to adjust for the increase in variability associated with these rates.

Given the above assumptions, and assuming a 55% effect of each of the candidate products, a total of approximately 1420 p-y of follow-up are expected to be accrued in each of the five study arms, and approximately 226 incident HIV infections are expected to be observed throughout the course of the study. The anticipated average baseline HIV rate in the placebo arms is 4.76% per year while the anticipated average HIV rate for the entire trial is 3.19% assuming 55% effectiveness for all three active products (3.45% and 3.01% for the topical and oral arms, respectively). For comparison, the target HIV rate for the HPTN 035 trial was 4.42% per year, and several HPTN 035 sites will participate in the VOICE study.

If needed, the protocol team could reasonably increase the sample size by 20% at each participant site (i.e., an increase of 3 to 4 months of the accrual period) and increase the follow-up by 6 months. This would yield an increase of about 50% in p-y which would

allow an average annual baseline HIV seroincidence rate as low as of 3.05 per 100 p-y (compared to the slightly conservative assumption of 4.76%). The selection of sites for VOICE is based on a demonstrated baseline HIV rate of at least 3.00%. Given that the protocol team has achieved high retention of participants in trials with long follow-up, the follow-up could be increased by an additional 6 months which would yield a total increase of about 80% in p-y. The resulting total number of p-y allows an average annual baseline HIV seroincidence rate as low as of 2.54% which is well below of what is currently observed in the VOICE participating sites.

10.6 Randomization

Enrolled participants will be assigned at random to one of the five study arms in a 1:1:1:1:1 ratio. The randomization scheme will be stratified by site and will be generated and maintained by the MTN SDMC. The SDMC will provide two sets of sealed, opaque randomization envelopes to each study site. The two sets are linked by sequential envelope number. One set of envelopes is stored and used in the study clinic. The other set is stored and used in the study pharmacy. The clinic envelopes will contain an assignment to vaginal or oral product. Clinic staff will assign these envelopes in sequential order by envelope number to eligible study participants. Assignment of the clinic randomization envelope is considered the effective act of participant enrollment/randomization. Clinic staff will prepare a written prescription that, among other things, documents the randomization envelope number to which the participant was assigned and the assignment to vaginal or oral product. Prescriptions for these participants will be delivered to pharmacy staff members who will dispense study product according to the information contained in the corresponding pharmacy randomization envelope. The pharmacy envelopes contain coded (blinded) information indicating the specific oral or vaginal product to which participants are assigned.

10.7 Blinding

Within each mode of administration, both study staff and participants will be blinded to the random assignments of participants to the study treatment arms. The mode of administration cannot be blinded. Within each oral and vaginal arm, study products will be supplied in identical packaging. Randomization documentation and other pharmacy records will be stored in a secure location in the site pharmacy (apart from the rest of the participant file). This information must not be accessible to study staff members who complete other study procedures with participants. Blinding will be maintained until all data are entered into the study database, all study endpoint data and other data included in the final analysis have been cleaned and verified, and the data are ready for final analysis. This will be explained to participants as part of the informed consent process. There are no circumstances under which it is expected that unblinding will be necessary for provision of medical treatment or to otherwise protect the safety of study participants. As described in Section 9, in the event that an IoR/designee is concerned that a participant might be put at undue risk by continuing product use, the IoR/designee may discontinue product use by this participant, however knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an IoR/designee feels that specific product knowledge is necessary to protect participant safety, the IoR/designee will notify the PSRT to

consider and rule upon the request. All study participants will be administered a brief unblinding assessment at their PUEVs in which they will be asked to report which study product they think they received in the study. The DSMB will be provided with unblinded product coding information with closed study reports upon request.

10.8 Data and Safety Monitoring and Analysis

10.8.1 Study Monitoring Committee (SMC)

In addition to the safety monitoring done by the PSRT (described in Section 8), the MTN SDMC will prepare study progress reports for review by the MTN SMC. The SMC will conduct interim reviews of study progress (pooled over study arms), including rates of participant accrual, retention, rates of adherence to study product, and HIV rates. These reviews will take place approximately every 4 to 6 months, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Typically, as much as possible, a SMC review is planned 2 – 4 weeks prior to a DSMB review such that recommendations from the SMC are passed along to the DSMB. This process allows the DSMB to focus less on trial operational issues and more on safety. However, all data presented to the SMC are also presented to the DSMB.

Based on the assumptions of Section 10.5, the target HIV rate is 3.19% for the entire trial. As a guideline during SMC review, the observed HIV rate will be compared to the lower one-sided 90% confidence interval computed by using the current number of p-y and the expected number of endpoints under the assumption of a 3.19% per year HIV rate. If the observed HIV rate is substantially lower than the lower confidence bound, the VOICE protocol team may need to develop plans for increasing the accrual and/or the length of follow-up (see Section 10.5). The target HIV rate may need to be revised if the accrual and follow-up plans are modified by the VOICE protocol team. Based on prior performance the sites have adequate additional capacity to effectively respond to seroincidence rates much lower than those initially used for the power calculations.

Note that the monitoring of the trial target HIV rate as described above was successfully implemented in HPTN 035. Further monitoring of the HIV rates will be performed by the DSMB which will ensure that the target number of primary endpoints will be achieved for each mode of administration (i.e., vaginal and oral).

10.8.2 Data and Safety Monitoring Board (DSMB)

DSMB reviews of study safety data will be conducted approximately every eight to twelve months. A no-data DSMB meeting will be scheduled prior or close to study initiation where the protocol and the complete interim monitoring plan will be presented to the DSMB members. At subsequent DSMB reviews, besides safety and efficacy data presentations, tables will be prepared for these reviews to assess the study conduct operational characteristics (e.g., accrual, adherence, retention, HIV incidence). That information will be compared to the protocol assumptions, and alterations will be made to the study design (e.g., increase or decrease in accrual and/or follow-up and/or

number of sites) if recommended by the DSMB. Study conduct operational characteristics are also reviewed by the SMC more frequently. Recommendations and minutes made by the SMC are forwarded to the DSMB.

Monitoring Quality of Study Conduct Operational Characteristics and Implementation

The study may be terminated or modified for poor accrual/recruitment, adherence/product use, retention, and/or low HIV acquisition rate. The design of the trial allows the partial termination of the trial either by terminating one mode of administration (i.e., topical or oral) and/or one of the oral active arms.

Monitoring of Safety and Efficacy Endpoints

The DSMB may recommend early termination of the study or modification when there is clear evidence of benefit, futility, or harm, or may recommend continuation of the study if the balance between potential benefit and harm remains adequate. Therefore, the DSMB may recommend stopping or modifying the study early in the following situations:

Clear evidence of serious safety problems including:

- An excess in frequency of any AEs (judged by the DSMB to be harmful to the participants) in one of the active product arms.
- An excess in frequency of any SAEs (Grade 4 and higher) in one of the active product arms.
- An excess in frequency of the primary safety endpoints as defined in Section 10.2 in one of the active product arms.
- An excess in frequency of primary HIV endpoints in the vaginal placebo gel arm (in comparison to the placebo oral arm) which might be indicative of a negative effect of the placebo vaginal gel on the vaginal microenvironment.

Clear evidence of benefit:

- A statistically significant difference in the rate of HIV infection between one of the active product arms and its corresponding placebo arm (appropriately adjusted for sequential monitoring of the trial)

Note that given the Phase IIb design and the strength of evidence required for licensure or change of label (i.e., a one-sided p-value of 0.25% at the final analysis), it is highly unlikely that this trial could be stopped early for clear evidence of benefit. For example, the nominal one-sided p-value to stop for benefit when the trial has reached its halfway point (i.e., 50% of the information has accrued) is on the order of 1×10^{-5} using an O'Brien-Fleming type guideline. This is indeed a very stringent stopping criterion for benefit but the stopping guideline needs to be very stringent because the licensure requirements are very stringent. This situation is currently being faced in the monitoring of the HPTN 035 trial.

Clear evidence of futility:

- Futility is defined to be results sufficient to rule out that the rate of HIV infection in one of the active product arm is smaller than the rate of HIV infection in the corresponding placebo arm leading to a lack of difference in the rate of HIV infection between the two arms appropriately adjusted for the sequential monitoring of the trial.

Note that the futility stopping rules will be based on a null hypothesis of no reduction (i.e., 0% effectiveness) with a false positive error rate of 2.5% since some components of the decision guideline describe in Section 10.4 include a null hypothesis of no reduction with a false positive error rate of 2.5%. The rationale for this is the current lack of any proof of concept for microbicide and oral PREP effectiveness for women at risk of sexual acquisition of HIV. While the protocol team does strongly believe effectiveness of these interventions would need to rule out less than 25% effectiveness to be a viable public health intervention, demonstrated effectiveness > 0% that does not rule out 25% would still offer hope of a potentially effective prevention methodology, albeit needing further evaluation. Therefore, the protocol team would propose to the DSMB only stopping for futility if an intervention shows no evidence of reduction in HIV infection rates.

Interim and final analyses will be adjusted to maintain an overall type I error rate. Adjustments will be based on Lan and DeMet's implementation of the O'Brien-Fleming grouped sequential stopping boundary with the time scale measured on the cumulative number of primary endpoints.⁸⁰ This implementation will permit early stopping only for very strong positive or negative effects and maintains nearly all of the nominal power for the final analysis. As stated above, a null hypothesis of no effect (effectiveness equals 0%) along with a false positive error rate of 2.5% will be used for setting the futility stopping rules, while a null hypothesis of at least a 25% effectiveness along with a false positive error rate of 0.25% will be used for setting the clear benefit stopping rules.

The DSMB may request additional analyses of the safety, toxicity, and/or effectiveness data from this study. The Statistical Analysis Plan for this study will provide further details on the interim monitoring strategy including the specifics of the above guidelines and other relevant details.

10.8.3 Data Analysis

When the use of descriptive statistics to assess group or site characteristics or differences is required, the following methods will be used: for categorical variables, the number and percent in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum). Typically, within-arm assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired

t-test or Wilcoxon signed-ranks test (for continuous variables). In general, when use of formal testing to assess differences between arms is required, the following methods will be used: for binomial response variables, chi-square tests and logistic regression; for continuous variables, t-tests and linear regression, or nonparametric methods if data are non-Normal. To assess the adequacy of the randomization, participants will be compared for baseline characteristics including demographics, pelvic examination, and laboratory measurements using descriptive statistics.

Primary Safety Analysis

For each of the three active products, safety and toxicity data from participants in the active product arm of the study will be compared to that from participants in the corresponding placebo arm. Incidence rates of safety and toxicity endpoints will be compared using Andersen Gill Proportional Hazards Models stratified by site and robust variance estimates.⁸¹ For this analysis, a safety and toxicity endpoint is defined as the occurrence in a participant of any primary safety endpoint described in Section 10.2 during follow-up.

In addition, the above analysis will be supplemented by performing an analysis that allows recurring events in individual participants. This analysis will be performed using the Andersen Gill Proportional Hazards Models stratified by site and robust variance estimates adjusting for the correlation of events within participants.

AEs will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific AE will be tabulated by severity and by relationship to treatment regimen. For the calculations in these tables, each participant's AE will be counted once under the maximum severity or the strongest recorded causal relationship to study product.

For each of the three active products, all AEs will be grouped by body system and a *p*-value and confidence interval for the relative risk (active product: corresponding placebo) of each AE will be calculated, as well as the difference in rates between treatment groups (active product – corresponding placebo) and its confidence interval. To safeguard against too many “false positive” safety findings, the statistical significance of the *p*-values will be assessed after a multiplicity adjustment.⁸² Finally, a listing of EAEs reported to the DAIDS Safety Office will provide details of the event including severity, relationship to study product, onset, duration and outcome.

Boxplots of local laboratory values will be generated for baseline values and for values measured during the course of the study. Each boxplot will show the 1st quartile, the median, and the 3rd quartile. Outliers, or values outside the boxplot, will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

Note that all of the above analyses will be conducted under the intention-to-treat (ITT) principle. However, participants off study product and/or those who are non-adherent that are included in these analyses could potentially lower the rate of safety and toxicity

endpoints in the active product arms. Therefore a 'per-protocol' analysis, where time off-product is excluded from the analysis, will be used to explore the sensitivity of the conclusions obtained with the safety analysis under the ITT principle.

Primary Effectiveness Analysis

For each of the three active products, the primary analysis will be performed under the ITT principle and using the HIV infection status at the end of product use (i.e., excluding the last 8 weeks of follow-up with no product use). To assess the effectiveness of each of the active products, HIV incidence rates will be calculated for each study treatment arm and the effect of each candidate active product on HIV incidence will be determined using Cox Proportional Hazards models stratified by site where the active product arm is compared to its corresponding placebo. Product effectiveness will be expressed as a percent reduction in the HIV incidence rate (i.e., $100 \times [1 - (\text{active product HIV infection rate} / \text{corresponding placebo HIV infection rate})]$). The primary analysis will be formally based on the decision guideline that was used to determine the study sample size and operating characteristics (see Section 10.4). The decision guideline should not be interpreted as a strict decision rule, but as a guideline derived from formal statistical procedures that will be factored into a broader scientific perspective regarding the public health benefit of the candidate products and how they compare to their respective placebo.

This primary effectiveness analysis will be supplemented by a secondary analysis where person-time of women that have been off product will be excluded from the analysis (i.e., per-protocol analyses). Extension of the Cox Proportional Hazards models stratified by site will be use for these analyses.

Analysis of Main Secondary Endpoints

HIV-1 Drug Resistance

In this study, ART resistance can be expected to arise in participants receiving active oral and topical regimens. For each of the three active product arms, the Mantel-Haenszel (M-H) method stratified by site will be used to compute an overall test statistic for comparing the proportion of HIV-1 drug resistance in women who acquire HIV while in the study with that observed in the corresponding placebo arm. A two-sided p -value will be computed using the chi-square approximation of the distribution of the M-H statistic. Each of these three comparisons will involve relatively small denominators for the proportions. Indeed, the number of HIV infections in each arm could vary from 20 to 70 such that the statistical power for these comparisons is low for detecting small differences between arms. However, assuming conservatively that HIV-1 drug resistance will be observed in 5% of seroconverters in both placebo arms, the study has moderate (>50% - <80%) power to detect absolute differences of 15% or larger (i.e., 20% or higher of HIV-1 drug resistance among seroconverters that were randomized to the active product versus 5% in the corresponding placebo arm). Power for this objective could range from 39% to 87% depending on the assumptions on the available sample size for these analyses. If 45 seroconverters per arm are

available for these comparisons, the power would be 71%, which would be considered moderate.

Delayed Seroconversions

In the study performed by Peterson, et al., evaluating the safety and preliminary effectiveness of TDF 300 mg daily versus placebo for prevention of HIV-1 infection in women in a Phase 2 double-blind study conducted at three sites in West Africa, HIV seroconversion was observed in 2/427 participants in the TDF arm (0.86 per 100 p-y) and 6/432 participants in the placebo group (2.48 per 100 p-y).³⁷ Three and six months of extended follow-up without product use at the Ghana and Cameroon sites, respectively, yielded six new seroconversions (all at the Cameroon site), four in the TDF arm and two in the placebo arm. Although these numbers are too small for making any reliable conclusion, it is conceivable that the oral active product could potentially mask an infection until product use is stopped. If this is the case, the potential effectiveness observed during follow-up with product use could be lost a short while after product use is discontinued.

To investigate this hypothesis, each participant will be followed for an additional approximate 8 weeks at the end of follow-up with product use. Study products will not be used during this extended follow-up of 8 weeks. This analysis will be performed only if the observed effectiveness in at least one of the oral active arms is above the lower limit of the decision guidelines for the primary effectiveness analysis (i.e., > 33.3%). For each of the three active products, the proportion of women positive at the 8 weeks extended follow-up visit but negative at the end of follow-up with product use in the active product arm will be compared to the proportion in the corresponding placebo arm. The Mantel-Haenszel (M-H) method stratified by site will be used to compute an overall test statistic for comparing these proportions. A two-sided *p*-value will be computed using the chi-square approximation of the distribution of the M-H statistic.

If there are no differences in the number of seroconversions between the placebo arms and the active product arms, this would argue strongly against the occurrence of delayed seroconversion from infection suppressed by active product. However, if there are significantly more seroconversions in one or more of the active product arms, then each seroconversion occurring between the Product Use End Visit and the Termination Visit, regardless of study arm, will be investigated to assess the timing of infection as follows. Specifically, stored plasma from the Product Use End Visit and the Termination Visit will be tested for the presence of HIV-1 RNA using FDA-approved ultrasensitive assays. The frequency of detectable HIV-1 RNA at the Product Use End Visit will be compared across study arms. A higher frequency of HIV-1 RNA detection at the Product Use End Visit in one or more of the active products arms would be consistent with suppressed HIV-1 infection by study product.

Assuming that 85% of randomized women will participate in the extended follow-up and a 5% HIV infection rate per year, about 30 seroconversions (six in each of the five arms) are anticipated during that extended follow-up. A total of 27 events per pairwise comparison is required to ensure 80% power to detect a 3.5 fold or larger increase with

a false-positive error rate of 2.5%, i.e., a proportion of 2.94% (21/714) in the active product arm versus 0.84% (6/714) in the corresponding placebo arm. To achieve this power, at least 15 delayed seroconversions would need to be detected in each of the active arms during the extended follow-up of 8 weeks. Depending on the magnitude of the observed effectiveness, this represents a substantial proportion of undetected seroconversions during follow-up with product use that would need to be detected during the extended follow-up of 8 weeks (40% to 75%).

The above analysis will be supplemented by an ITT analysis similar to the one performed for the primary effectiveness analysis where the entire follow-up of participants will be included in the analysis (i.e., including the 8 week post treatment follow-up). A lower estimate of effectiveness is expected from this analysis even in the absence of any delayed seroconversion since the inclusion of about 10% of follow-up off treatment (i.e., 8 weeks off treatment over an average of 24.5 months of total follow-up) would reduce the effectiveness by an absolute magnitude of about 5% (e.g., 50% effectiveness instead of 55% effectiveness).

Adherence and Sexual Behavior

An important secondary analysis will focus on adherence to study treatment strategy and sexual behavior. Self-reported adherence to product use and sexual behavior will be measured on a monthly and quarterly basis. Besides self-reported product use, the main self-reported sexual behavior outcome that will be used in these analyses is the proportion of sexual acts, vaginal and anal, unprotected by condom.

For adherence, this data structure will permit the following:

- Estimation of adherence rates
- The testing of differences in adherence between the active product and its corresponding placebo for each of the three active products
- The testing of trends over time in adherence rates, and
- The examination of the relationship between adherence and HIV infection.

Descriptive statistics will be used to estimate (1) at selected time points. Since the analysis will involve repeated observations, generalized estimating equations (GEE) methods and robust variance estimates, will be used to evaluate statistical significance and compute confidence intervals for (2) and (3). Cox proportional hazards models with robust variance estimates will be used for (4) with HIV infection as the endpoint. Similar analyses as described above will be performed for the sexual behavior outcome. The relationship between adherence, sexual behavior and risk of incident HIV infection will also be examined. For this analysis, a Cox proportional hazards model with HIV infection as the endpoint and treatment arms, time-dependent adherence, and sexual behaviors as covariates will be fit to the data.

Pharmacokinetics

Blood plasma levels of tenofovir, times of prior tenofovir doses, and participant characteristics will be used to build a population model of tenofovir PK to include

parameters for tenofovir clearance and volume of distribution. Participant covariates to be explored for inclusion in the model will include study site, creatinine clearance, height, weight, adherence, and medical co-morbidities. Participant-specific tenofovir exposure estimates will be estimated based on this model and PK (tenofovir)–PD (seroconversion outcome) relationships will be explored. Adherence data will be evaluated as an explanatory variable in these models. Further, AEs and tenofovir resistance will also be explored as PD outcome variables in PK–PD models.

Depending on the availability of data from other studies supporting model building relating intracellular tenofovir diphosphate to extracellular tenofovir concentrations, individual intracellular tenofovir diphosphate levels will be estimated for use in expanding the building of PK-PD models to explain variation in seroconversion and other outcomes explained by intracellular drug levels.

Exploratory Analysis

Using similar methods as those used for the effectiveness analysis (but without the use of the decision guideline), the following relative effectiveness measures will be evaluated using a five percent two-sided *p*-value:

- Active oral TDF versus active oral FTC-TDF
- Active oral TDF versus active vaginal gel
- Active oral FTC-TDF versus active vaginal gel
- Placebo oral versus placebo vaginal gel

Note that the study is not powered to detect these relative effectiveness measures. The number of primary endpoints involved for each of these comparisons could vary anywhere from 40 to 70 primary endpoints for (1), (2), or (3) and up to 130 endpoints for (4). Therefore, the study has marginal power to detect a relative effectiveness of 50% and above. Precise power computations cannot be done without making very strong assumptions regarding the effectiveness of each of the three active products.

Furthermore, methods similar to those described for the primary safety analysis will be used to compare the safety and toxicity profiles for the above four comparisons.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents. Non-ACASI data are transferred to the MTN SDMC, entered, and cleaned using the DataFax data management system.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/>).

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, for each of the three investigational products tested, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval for each of the three study products for the indication in which they were studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US FDA is notified.

Study records must be maintained on site for the entire period of study implementation. Thereafter, instructions for record storage will be provided by DAIDS. No study records may be moved to an off-site location or destroyed prior to receiving approval from DAIDS.

11.3 Quality Control and Quality Assurance

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/ClinicalSite/QMPPolicy.pdf>)

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by PPD (Wilmington, NC) in accordance with Requirements for On-Site Monitoring of DAIDS Funded and/or Sponsored Clinical Trials (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/ClinicalSite/OnsiteMonitor_Reqs.pdf). Study monitors will visit the site to do the following:

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, GCP guidelines, and applicable regulatory requirements (US and non-US), including US Code of Federal Regulations (CFR) Title 45 Part 46 and Title 21 Parts 50, 56, and 312.
- Perform source document verification to ensure the accuracy and completeness of study data
- Verify proper collection and storage of biological specimens
- Verify proper storage, dispensing, and accountability of investigational study products
- Assess implementation and documentation of internal site quality management procedures
- Assess site staff training needs

The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN CORE, SDMC, and NL; NIAID, and local and US regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR will have obtained IRB/EC approval and the protocol will have been submitted to the FDA. The IoR will permit audits by the NIH, CONRAD, Gilead Sciences, Inc., the FDA, or any of their appointed agents.

Accurate and thorough community education efforts may enhance participants' understanding of HIV prevention studies and of clinical research in general. The MTN CORE Community Program staff has initiated and plans continuation of strategies to inform site community representatives and community educators on important issues related to the VOICE study, including but not limited to general research and DSMB literacy, microbicide and HIV prevention education, risks of study product sharing, and interpretation of trial results, among others.

13.1 Institutional Review Boards/Ethics Committees

Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms, and study-related documents (such as participation education and recruitment materials) are reviewed by an IRB/EC responsible for oversight of research conducted at the study sites. Any amendments to the protocol must be approved by the responsible IRBs/ECs prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs/ECs must review the study at least annually. Each IoR/designee will make safety and progress reports to the IRBs/ECs at least annually and within three months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. In addition, the results of all DSMB reviews of the study will be provided to the IRBs/ECs. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office in accordance with the DAIDS Protocol Registration Policy and Procedures Manual.

13.2 Protocol Registration

Each study site will complete protocol registration with the DAIDS RCC Protocol Registration Office. Protocol registration material can be sent electronically to

epr@tech-res.com. For questions regarding protocol registration, please call (301) 897-1707 or email Protocol@tech-res.com. For additional information, refer to the protocol registration documents located at <http://rcc.tech-res.com/forms.htm>. Protocol registration must occur as a condition for site-specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE (FHI) staff will notify each study site when all activation requirements have been met by issuing a site-specific study activation notice. Study implementation may not be initiated until the activation notice is issued. The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB/EC(s) and the RCC prior to implementing the amendment.

13.3 Study Coordination

DAIDS holds the IND applications for this study. Copies of all regulatory documents submitted to this IND by DAIDS are forwarded by DAIDS to Gilead Sciences, Inc. and CONRAD, for cross-referencing with other INDs for the study products. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS, CONRAD, and Gilead Sciences, Inc.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chairs and DAIDS Medical Officer. Study implementation will also be guided by a common study-specific procedures manual that provides further instructions and operational guidance on conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN CORE, SDMC, NL and other designated members of the Protocol Team.

Close coordination between protocol team members is necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. The PSRT will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the DSMB.

13.4 Risk Benefit Statement

13.4.1 Risks

General

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Pelvic examination may cause mild discomfort and/or vaginal bleeding or spotting. Disclosure of HIV and STI status may cause worry, sadness or

depression. Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions.

Although study sites make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Participants in sites requiring partner notification in response to diagnosed STI or HIV infection could have problems in their relationships with their sexual partners. Participants also could have problems in their partner relationships associated with use or attempted use of study products. In addition, participants could misunderstand the current experimental status of the study products (i.e., their unknown safety and unproven efficacy) and as a result increase their HIV risk behaviors while in the study.

Data on participant risk behaviors and the occurrence of other potential social harms will be collected from all participants on a quarterly basis. The DSMB will monitor trends in risk behaviors over time based on these data, as well as the occurrence of other potential social harms, and advise the Protocol Team if any follow-up action is required.

Hepatitis B Vaccine Series

Study sites will provide the hepatitis B vaccine series to HBV susceptible participants. Though there is some variation among AEs reported with different types of hepatitis B vaccine; in general the most frequently reported adverse reactions regardless of brand are injection site soreness and fatigue. Other common reactions (approximately 1% to 10% of injections) include injection site reactions (such as induration, erythema, and/or swelling), fever >37.5°C, headache and dizziness.

Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with hepatitis B vaccines. It is also not known whether hepatitis B vaccines can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity, though current WHO opinion is that the vaccine can be given during pregnancy if clinically indicated.

Nursing Mothers: It is not known whether hepatitis B vaccines are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when hepatitis B vaccines are administered to a nursing woman.

Antiretroviral Drugs

Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in persons receiving ARV drugs. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Nucleotide Analogues

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported with the use of ARV nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

Oral TDF Tablet

The following side effects have been associated with the use of tenofovir:

- Upset stomach, vomiting, gas, loose or watery stools
- Dizziness
- Abdominal pain
- Lack of energy
- Kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas
- Shortness of breath
- Rash
- Low phosphate
- Increase of liver functions tests in children
- Allergic reaction, which may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath or a general feeling of illness
- Changes in bone growth and strength were seen in study animals given tenofovir. Bone thinning has been seen in adults and children taking tenofovir.

Persons co-infected with Hepatitis B and HIV may have increases in liver function tests, and symptoms associated with hepatitis may worsen if tenofovir is stopped. TDF is a pregnancy category B medication. No controlled human studies have been completed among HIV-1 infected or uninfected pregnant women. No data on excretion of TDF in human breast milk have been reported.

FTC/TDF Tablet

No new or unexpected side effects are observed with the FTC 200 mg/TDF 300 mg combination tablet than those observed when each drug is given separately. The following side effects have been associated with the use of FTC: headache, dizziness, tiredness, inability to sleep, unusual dreams, loose or watery stools, upset stomach (nausea) or vomiting, abdominal pain, rash, itching, skin darkening of the palms and/or soles, increased cough, runny nose, abnormal liver function tests, increases in pancreatic enzyme, increased triglycerides, and increased creatine phosphokinase. In persons co-infected with Hepatitis B and HIV, liver function tests may increase, and symptoms associated with hepatitis may worsen if FTC is stopped. FTC is a pregnancy category B medication. No controlled human studies of FTC among pregnant women

have been conducted. No data on excretion of FTC/TDF in human breast milk have been reported.

Tenofovir 1% Gel

Administration of tenofovir gel intravaginally at 0.3% and 1% concentrations in the HPTN 050 Phase1 study resulted in minimal local irritation and little or no systemic AEs were identified. Although 92% of participants reported at least 1 AE, 87% of those reported AEs were mild, and 70% of the AEs were limited to the genitourinary tract. Four severe AEs were reported, with only one, lower abdominal pain, thought to be product-related. The risks associated with tenofovir gel are believed to be less than those identified for systemic use. Some of the possible side effects of the study gel are dryness, itching, burning, or pain in the genital area.

In the HPTN 050 Phase1 study of tenofovir gel, serum PK analysis in a subset of participants demonstrated that there is no clinically significant systemic toxicity. Fourteen of 25 women with PK results had low, but detectable, serum tenofovir levels. Given that Phase 1 data demonstrate measurable plasma concentrations of tenofovir in some participants, participants with hepatitis B infection might be at risk for development of tenofovir resistant hepatitis B. However, participants with known hepatitis B infection will not be eligible for enrollment. It is not known what effect tenofovir gel could have on the HIV virus or HIV disease progression in HIV-infected participants or their partners. There is a theoretical risk that tenofovir absorbed systemically from oral TDF or vaginal tenofovir gel could result in mutations of the HIV virus in participants who become infected with HIV during the study, or their partner, if the partner is infected with HIV. Limited resistance data from HPTN 050 show no new resistance mutations in plasma or cervicovaginal lavage specimens after 14 days of tenofovir gel use. No participant had high level tenofovir mutations (e.g., K65R).

In a male tolerance study of tenofovir 1% gel, there were few genital findings observed after product use and all findings were classified as mild, small in size and required no treatment. The most common symptoms included mild pain (burning, irritation, discomfort) and pruritus. All reported urogenital symptoms were felt to be mild.

13.4.2 Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of safe and effective interventions to prevent HIV transmission. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, pelvic examination, and routine laboratory testing related to blood, liver, and kidney function. Participants will be provided STI treatment in accordance with WHO guidelines free of charge, and offered STI testing and treatment for their partners. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their

community. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals. Participants identified as HBV susceptible will be offered the Hepatitis B virus vaccine series free of charge.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to both screening and enrollment. Written informed consent also will be obtained for long-term specimen storage and possible future testing, although consent for specimen storage is not required for study participation. A separate informed consent form will be utilized for the Bone Mineral Density Substudy. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to Good Clinical Practices (GCP) and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/ClinicalSite/SourceDocPolicy.pdf>). Participants will be provided with copies of the informed consent forms if they are willing to receive them.

Each study site is responsible for developing study informed consent forms for local use, based on the templates in the Appendices that describe the purpose of screening and of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template forms into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

In addition to informed consent forms, the Protocol Team will work with study staff and community representatives to develop locally-appropriate materials about the study and a standardized approach to the informed consent process to be implemented at all study sites, which will be detailed in the study-specific procedures manual.

The informed consent process will cover all elements of informed consent required by research regulations. In addition, the process specifically will address the following topics of import to this study:

- The unknown safety and unproven efficacy of the study products.
- The need to practice safer sex behaviors regardless of study treatment group.
- The importance of participants in all five study groups to the success of the study.
- The importance of adherence to the study visit and procedures schedule.
- The potential medical risks of study participation (and what to do if such risks are experienced).
- The potential social harms associated with study participation (and what to do if such harms are experienced).
- The real yet limited benefits of study participation.

- The distinction between research and clinical care.
- The right to withdraw from the study at any time.

The informed consent process will include an assessment of each potential participant's understanding prior to enrollment and randomization of concepts identified by the protocol team as essential to the informed consent decision. Participants who are not able to demonstrate adequate understanding of key concepts after exhaustive educational efforts will not be enrolled in the study. For quality assurance purposes, similar assessments of participant understanding will be undertaken among a sub-sample of participants during follow-up; results will be used to provide feedback and recommendations to the Protocol Team and relevant study site staff to optimize the informed consent process.

13.6 Access to Effective Products

Should this study provide evidence of the effectiveness of TDF, FTC/TDF and/or tenofovir 1% gel in preventing HIV infection, it will be critical to provide access to the effective product(s) to study participants, their communities, and the worldwide population at risk for HIV infection in a timely manner. In preparation for this study, discussions have begun with Gilead Sciences, Inc. and CONRAD to ensure such access. Considerations under discussion include licensing agreements and preferred pricing arrangements for the study communities and other resource-poor settings.

While this study is ongoing, the MTN will continue these discussions. In addition, discussions will be initiated with other public and private funding sources such as the WHO, UNAIDS, Gates Foundation, and appropriate site government agencies that may be able to purchase product supplies in bulk and offer them at low or no cost to the study communities and other resource-poor communities most in need of the product(s). Operations and marketing research also may be conducted to determine how best to package and distribute the products, and maximize their acceptability and use, in at-risk populations.

13.7 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- DAIDS, NICHD, NIMH, and/or its contractors, including study monitors

- Representatives of Gilead Sciences, Inc. and CONRAD
- Representatives of the MTN CORE, SDMC, and/or NL
- The US FDA and/or other government and regulatory authorities
- Site IRBs/ECs

13.8 Special Populations

13.8.1 Pregnant Women

Women who test positive for pregnancy at screening or enrollment visits will not be eligible to participate in this study. A urine pregnancy test will be performed on all women at all scheduled study visits, and additionally at interim visits if indicated; the IIR/designee will discontinue study product among participants who test positive for pregnancy. During the informed consent process, women will be informed that the study products are not methods of contraception and that their effects on a developing human fetus are unknown.

Oral TDF and oral FTC/TDF are both classified by the US FDA as a pregnancy category B drug. For both products, animal studies have failed to demonstrate risk to the fetus, but there are no adequate and well-controlled studies in pregnant women completed to date. As new data become available related to safety of study products for pregnant women, summaries of this information will be compiled by the MTN and circulated to the study sites, so that women have up-to-date information on risk/benefit decisions related to the study products. The MTN will provide updates on an annual basis, with additional updates more frequently in the case more timely data become available.

13.8.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets “Justifications for Exclusion” criteria for younger children as set forth by the NIH. Specifically, “insufficient data are available in adults to judge potential risk in children” and “children should not be the initial group to be involved in research studies.” Oral TDF and oral FTC/TDF are not currently approved for children under 18 years old. This study does not plan to enroll children under 18 years old.

13.9 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort.

13.10 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases including HIV identified among study participants to health authorities. Participants will be made aware of reporting requirements during the informed consent process.

13.11 Access to HIV-related Care

13.11.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV testing time point. Testing will be performed in accordance with the algorithms in Appendices II and III. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will emphasize the unknown efficacy of the study products in preventing HIV infection. In accordance with the policies of the NIH, participants must receive their HIV test results to take part in this study. Condoms will be provided to participants throughout the duration of their participation.

13.11.2 Care for Participants Identified as HIV-Infected

Care for participants identified as HIV-infected is described in Section 9.10.

13.12 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, CONRAD, Gilead Sciences, Inc., the US FDA, the OHRP, other government or regulatory authorities, or site IRBs/ECs.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies and a Clinical Trial Agreement between CONRAD, Gilead Sciences, Inc. and NIAID will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS, NICHD, NIMH, CONRAD, and Gilead Sciences, Inc., for review prior to submission.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR 1	SCR 2	ENR	MLY	QRT	SEM	ANN	PUEV	TERM
	Up to and including 56 days		Day 0	Must occur -14 days or + 13 days of scheduled visit				Specified in SSP	
Informed Consent	X		X						
Demographics	X								
Locator Information	X	X	X	X	X	X	X	X	X
Behavioral Eligibility	X	X	X						
Review Screen Documentation			X						
Behavioral Risk Assessment			X	X	X	X	X	X	X
Adherence Assessment				X	X	X	X	X	
Prod. Sharing/Dose Recall					X	X	X	X	
Intravaginal Practices Assess.					X	X	X	X	X
Social Harms Assessment					X	X	X	X	X
Reimbursement	X	X	X	X	X	X	X	X	X
Schedule Next Visit	▲	▲	▲	X	X	X	X	X	▲
Test Results	X	X	X	X	X	X	X	X	X
Randomization			X						
HIV Pre/Post-Test Couns.	X	▲	X	X	X	X	X	X	X
HIV/STI Risk Red. Couns.	X	X	X	X	X	X	X	X	X
STI/UTI Treatment	▲	▲	▲	▲	▲	▲	▲	▲	▲
Offer HIV Test/Couns. Partners	X	X	X	X	X	X	X	X	X
Offer STI Couns./Tx. Partners	▲	▲	▲	▲	▲	▲	▲	▲	▲
Contraceptive Couns.	X	X	X	X	X	X	X	X	X
Medical Eligibility	X		X						
Med./Mens. History		X	X	X	X	X	X	X	X
Current Medications		X	X	X	X	X	X	X	X
Weight	X	X		■	X	X	X	X	▲
Height		X				X	X	X	
Blood Collection	X	▲	X	X	X	X	X	X	X
Urine Collection	X	X	X	X	X	X	X	X	X
HBsAg	X			▲	▲	▲	▲	X	▲
HBsAb	X			▲	▲	▲	▲	▲	▲
Hepatitis B Vaccination			▲	▲	▲	▲	▲	▲	▲
UA	X	▲	+	■	X	X	X	X	▲
Urine hCG	X	X	X	X	X	X	X	X	X
Urine SDA for GC/CT	X	▲		▲	▲	▲	X	X	▲
Rapid Test-Trichomonas		X	+	▲	▲	▲	X	X	▲
Rapid Test-BV		▲	+	▲	▲	▲	▲	▲	▲
Complete Blood Count	X			▲	▲	X	X	X	▲
Serum Chemistries	X			■	X	X	X	X	▲
Plasma Archive			X	▲	X	X	X	X	X
Blood PK Analyses					X	X	X	X	
Syphilis Serology	X	▲		▲	▲	▲	X	X	▲
HIV Serology	X		X	X	X	X	X	X	X
Physical Exam		X		■	X	X	X	X	X
Pelvic Exam Visual Inspection		X	+	▲	▲	X	X	X	▲
Vaginal pH		X	+	▲	▲	X	X	X	▲
Vaginal Wet Mount		▲	+	▲	▲	▲	▲	▲	▲
Vag./Endocerv. Swabs Storage		X		▲	▲	X	X	X	▲
Gram Stain		X				X	X	X	
Pap Smear		▲●		▲●	▲●	▲●	▲●	●	▲●
Bimanual Exam		X	+	▲	▲	X	X	X	▲
Study Product, Instr., Adher.			X	X	X	X	X		
Condoms	X	X	X	X	X	X	X	X	X
Contraception	▲	▲	▲	▲	▲	▲	▲	▲	▲
Perceived Product Assessment.								X	

X = required, ▲ = as indicated, ● = at sites with capacity where local standard of care, ■ = first monthly visit, + = UA, pelvic exam components, and other relevant assessments may be done on day of ENR to confirm eligibility

Note: ENR includes procedures conducted as part of final screening procedures and confirmation of eligibility. Monthly visit procedures also occur at quarterly, semiannual, and annual visits; likewise, quarterly visit procedures occur at semiannual and annual visits, and semiannual visit procedures occur at annual visits.

Note: If Sample 2 is drawn (per Appendix III), blood is also collected for the following analyses: Plasma archive, CD4+ T-cell count, HIV-1 RNA PCR, and PBMC archive.

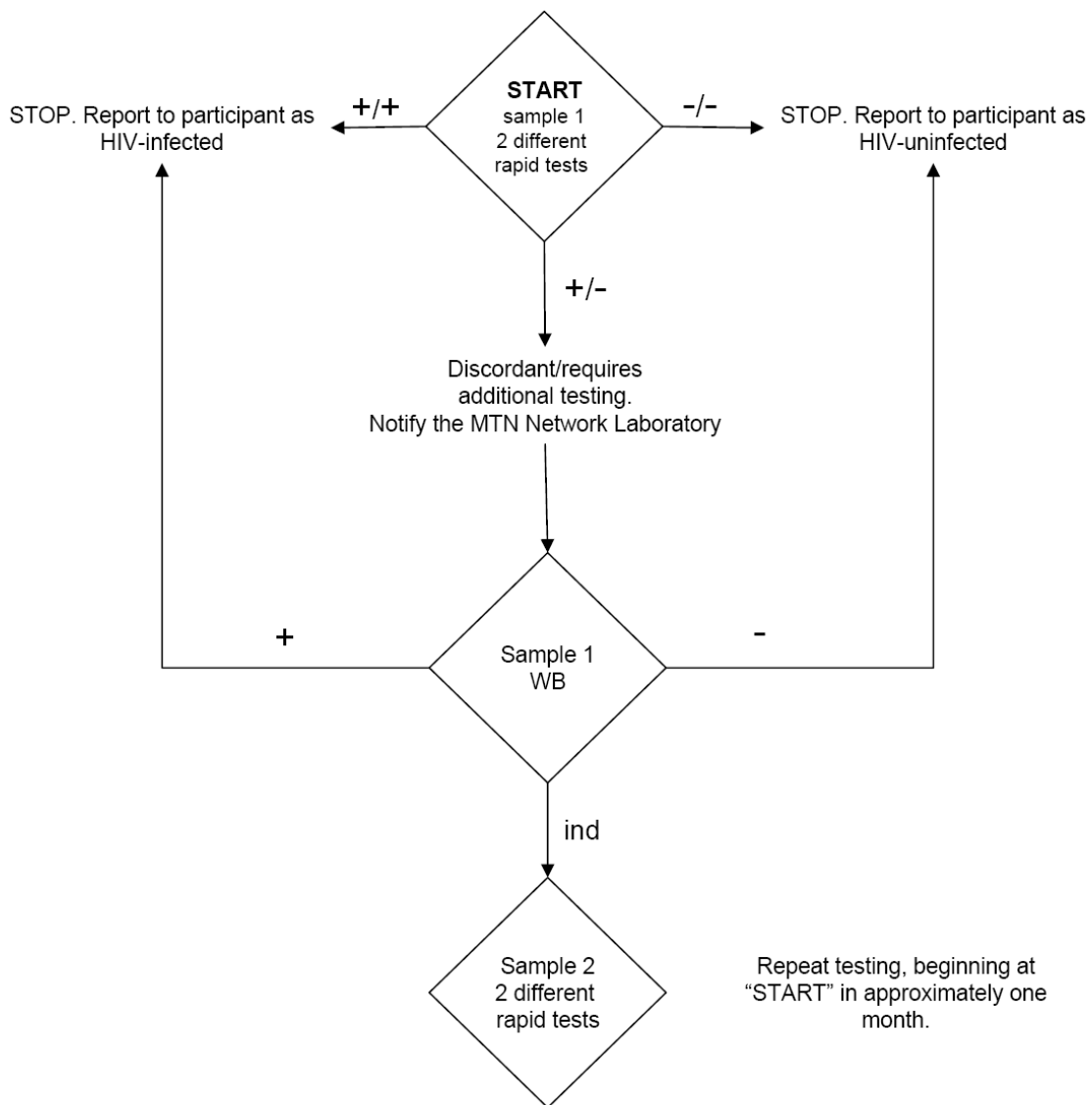
Note: For hepatitis B susceptible participants randomized to oral study product who do not receive hepatitis B vaccination, HBsAg additionally is checked annually and 6 months after PUEV; serum chemistries are checked 3 and 6 months after PUEV.

SCHEDULE OF POST-HIV-1 SEROCONVERSION LABORATORY PROCEDURES

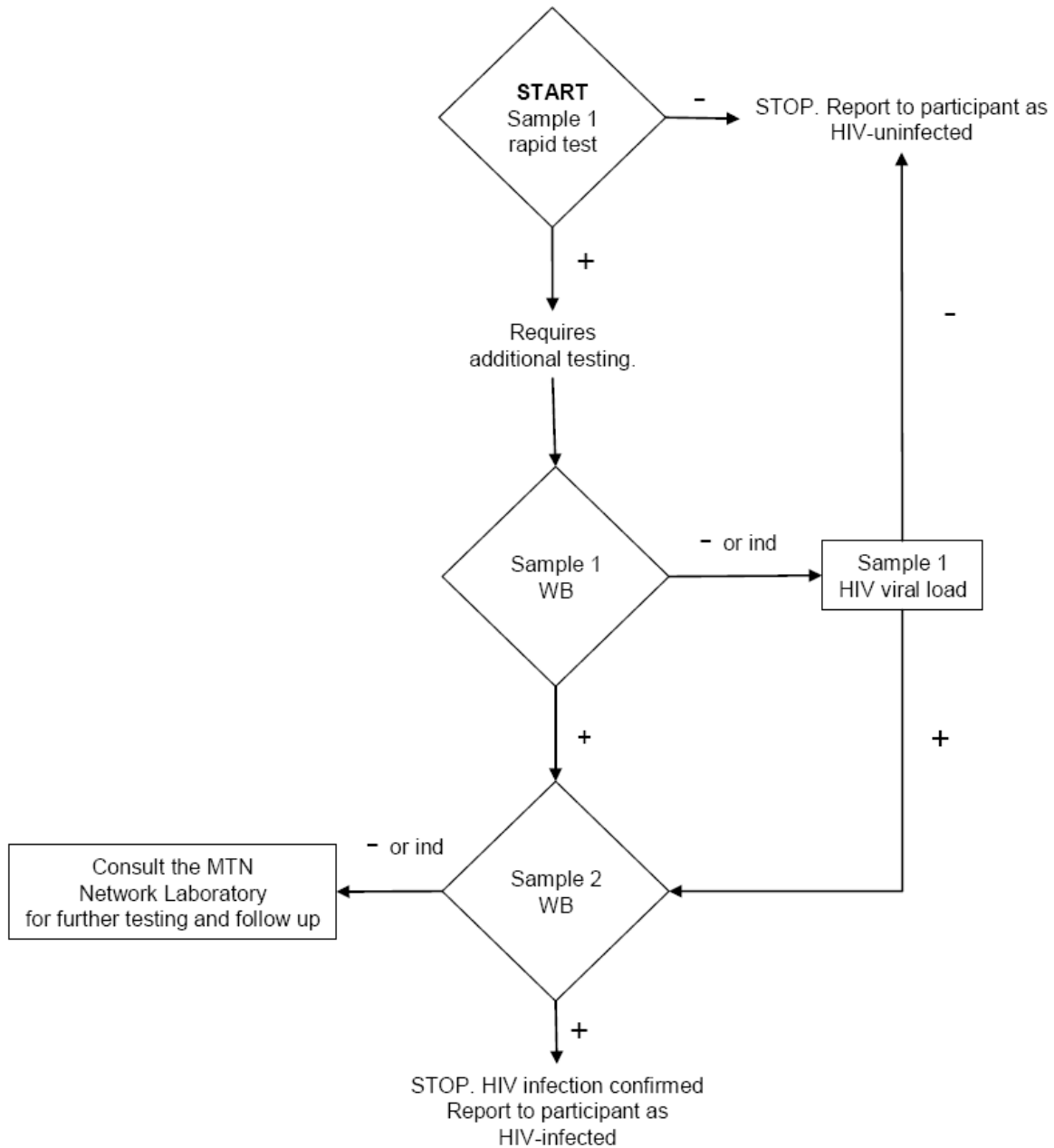
	Post-Seroconversion Time Points				Time Since Completion of Hepatitis B Vaccine Series
	1-month	3-months	6-months	Q6-months	6-months
Plasma Archive	X	X	X	X	
PBMC Archive	X	X	X	X	
HIV-1 RNA PCR	X	X	X	X	
CD4+ T Cell Count	X	X	X	X	
HBsAb					X

APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING (SCREENING)

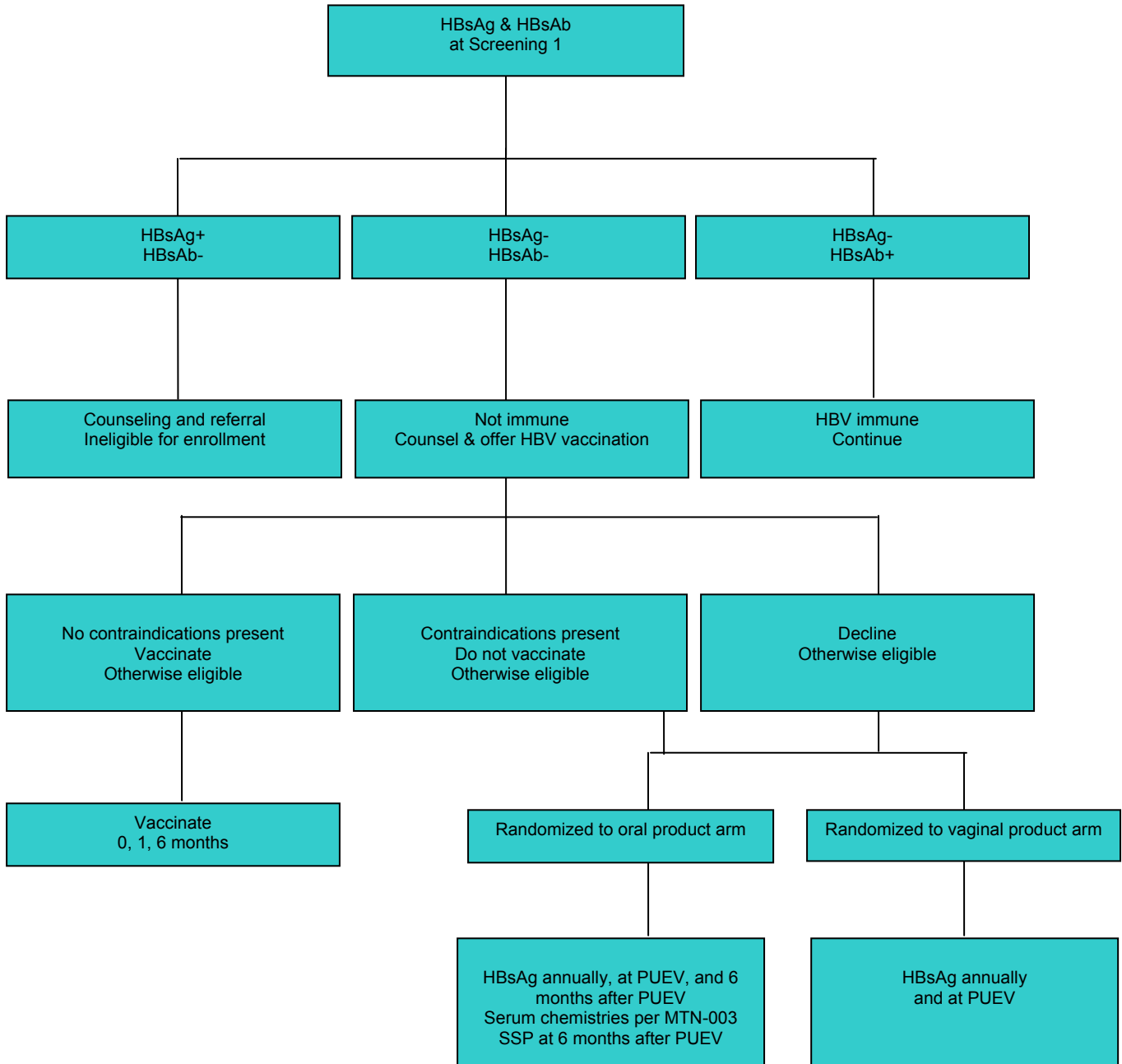
Algorithm for HIV antibody testing (screening)



APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING (FOLLOW-UP AND PRIMARY ENDPOINT DETERMINATION)



APPENDIX IV: ALGORITHM FOR MANAGEMENT OF HEPATITIS B SEROLOGIC ASSAYS ASSESSED AT SCREENING



APPENDIX V: SAMPLE INFORMED CONSENT FORM (SCREENING)

**SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH**

MTN-003/VOICE

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

May 22, 2008

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

Short Title for the Study: Vaginal and Oral Interventions to Control the Epidemic (VOICE)

INFORMED CONSENT

You are being asked to volunteer for screening tests to find out if you are eligible for a research study known as the VOICE study. The VOICE study is for women who could get Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immune Deficiency Syndrome, or AIDS. The study is testing whether certain drugs can prevent HIV in women. The screening tests include interview questions, urine and blood tests, a physical exam, and an exam of your vagina. The United States National Institutes of Health is funding the study. We expect that about 4200 women will be enrolled in this study at different sites in Africa.

Before you decide whether to have the screening tests, we would like to explain the purpose of the screening tests, the risks and benefits to you, and what is expected of you. This consent form might contain some words that are unfamiliar to you. Please ask questions about anything you do not understand or want to learn more about.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the screening tests that will be discussed with you. Once you understand the screening tests, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

Before you learn about the screening tests, it is important that you know the following:

- Your participation is voluntary: you do not have to have the screening tests if you do not want to.
- You may decide not to have the screening tests, or to withdraw from the screening tests at anytime, without losing your regular medical care.

- If you decide not to have the screening tests, you can still join another research study later, if one is available and you qualify. However, you cannot join the VOICE study if you are taking part in another study of drugs, medical devices or vaginal products. You are asked to tell the study staff about any other studies you are taking part in, or thinking of taking part in. This is very important for your safety.
- You are only being asked to have the screening tests at this time. Even if you agree to have the screening tests, you do not have to join the VOICE study.
- Some people may not be able to join the VOICE study because of information found during the screening tests.
- You will receive the results of the screening tests even if you are not eligible to join the VOICE study.
- If new information is learned about the study, or the study products, you will be told about this as soon as possible.

PURPOSE OF THE SCREENING TESTS AND THE STUDY

The purpose of the screening tests is to find out if you are eligible for the VOICE study.

The VOICE study is testing 3 products:

- A gel that is put in the vagina called tenofovir gel
- A tablet that is taken by mouth, called tenofovir.
- A tablet that is taken by mouth, called Truvada. Truvada is a combination of tenofovir and another medication called emtricitabine.

There are two main purposes of the VOICE study. The first purpose is to find out if the three products listed above will protect women from getting HIV through vaginal sex. The second purpose is to find out if there are any bad effects when women use these products over a long period of time.

PROCEDURES

If you agree to have the screening tests, you will have 3 visits. Depending on your screening test results, more visits may be needed, as described below. All screening tests must be done within 8 weeks. If all tests are not done within 8 weeks, and you still want to find out if you are eligible for the VOICE study, you will have to start the screening tests over from the beginning.

Visit 1:

Your first visit will happen after you read, discuss, understand and sign or make your mark on this form. Study staff will help you understand the form and answer your questions before you sign or mark this form. The procedures done at this visit will take about 2 hours.

- The study staff will ask you where you live and other questions about you, your medical health, and your sexual practices.
- If these questions show that you may be eligible for the VOICE study, you will give urine for a pregnancy test. If you are pregnant you are not eligible for the VOICE study. The study staff will refer you to available sources of medical care and other

services you may need. If the study is still open after your pregnancy, you can come back here to find out if you are eligible then.

- If you are not pregnant, you will talk with study staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex. You will be asked to give a blood sample (XX mL) and have HIV testing. It will take about 20-40 minutes to get your HIV test result. You will be told your result as soon as it is available, on the same day you have the test. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive but also not clearly negative. In that case, we will do more tests until we know your status for sure. You must receive your HIV test results to be in the research study. If the test shows that you have HIV, you will not be eligible for the research study. The study staff will tell you about other studies you may be eligible for, if any. They will refer you to available sources of medical care and other services you may need. Your partner(s) may also have access to free HIV counseling and testing if needed.
- If the tests show that you do not have HIV, the study staff will:
 - Measure your weight
 - Talk with you about contraception
 - Test your urine for:
 - Chlamydia and gonorrhea. These are infections passed through sex.
 - Common urine infections and the health of your kidneys
- Test your blood for:
 - Syphilis. This is an infection passed through sex.
 - Health of your blood, liver and kidneys.
 - Hepatitis B. This is an infection of the liver that can be passed from mother to baby, through sex or through body fluids infected with hepatitis B. If the tests show that you have hepatitis B that is active in your liver, you will not be eligible for the VOICE study. If the tests show that you have had hepatitis B in the past, but it is no longer active in your liver, or that you are immune to hepatitis B because of a prior immunization, you may be eligible for the VOICE study.
- Give you condoms
- Give you treatment for urine infections and infections passed through sex, if needed
- Give you referrals for other services if you or your partner(s) need them.

The results of the tests listed above will be available within 1-2 weeks after your visit. You will come back for another visit when the results are available. No blood collected at this visit will be kept or used for any other tests other than those listed above.

Visit 2:

The procedures done at this visit will take about 2-3 hours. This visit does not require an additional informed consent form. The study staff will:

- Review and update your contact details, if needed.
- Tell you your test results from Visit 1 and what they mean. If the results show that you might have some health problems, you may not be eligible for the VOICE study. Study staff will refer you to available sources of medical care and other services you

may need. Later, if these problems resolve, you can come back to find out if you are eligible at that time.

- Talk with you again about HIV and other infections passed through sex, and how to avoid these.
- Give you condoms.
- Talk with you about your health and what medications you take.
- Test your urine for infections and to check on the health of your kidneys.
- Test your urine for pregnancy. If you are pregnant, you will not be eligible for the VOICE study. If you are not pregnant, study staff will talk with you about contraception and give you contraception if you need it.
- Measure your height and weight.
- Examine your body, including your genital area and inside your vagina.
 - The study staff will collect fluid from your vagina with a swab to test for infections. These infections are called trichomoniasis, candidiasis, and bacterial vaginosis (BV). Some fluids also will be collected to test for factors that could affect the chances of getting HIV.
 - [*For selected sites only*: Study staff will also collect samples from your cervix to test for abnormalities that could mean you have cervical cancer, or that could lead to cervical cancer. This test is called a “Pap test”.
- Give you treatment for urine infections and infections passed through sex, if you need it.
- Give you referrals for other health services if you need them.

If you have no health problems or infections requiring treatment, you may be eligible for the VOICE study. You will come back for another visit in 1-2 weeks. If you had a sore or other problem seen in your vagina at today’s visit, you will be given treatment, if needed, and have another exam at your next visit. If the problem is resolved when you come back, you may be eligible for the VOICE study.

Visit 3 (Final Screening Procedures/Confirmation of Eligibility):

The screening tests done at this visit will take 1-2 hours. Study staff will:

- Tell you your test results from visit 2, and what they mean.
- Ask questions to update the information from your first two visits.
- Test your urine for infections and to check on the health of your kidneys, if needed.
- Test your urine for pregnancy. If you are pregnant, you will not be eligible for the VOICE study. If you are not pregnant, study staff will talk with you about contraception and give you contraception if you need it.
- Talk with you about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex. You will give blood (XX mL) and have HIV testing. It will take about 20-40 minutes to get your HIV test results. You will be told your results as soon as they are available. You will talk with the study staff about the meaning of your results and how you feel about them. Sometimes HIV tests are not clearly positive but also not clearly negative. In that case, we will do more tests until we know your status for sure. You must receive your HIV test results to be in the VOICE

study. If the tests show you have HIV, you will not be eligible for the VOICE study. The study staff will tell you about other studies you may be eligible for, if any. They will refer you to available sources of medical care and other services you may need.

The study staff then will review all of your screening test results. If the results show that you are eligible for the VOICE study, the study staff will fully explain the study to you and answer any questions you have. If you decide to take part in the VOICE study, you will be asked to sign another consent form.

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws:

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, small clot, or infection where the needle goes into your finger or arm.

Risks of Genital Exams:

You may feel discomfort during the exam of your genital area and inside your vagina. You may have a small amount of vaginal bleeding which will stop shortly after the exam.

Other Possible Risks:

You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other infections passed through sex, and your test results. You may become worried while waiting for your test results. If you have HIV or other infections, knowing this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the screening tests. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your HIV status could also cause problems between you and your partner. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

BENEFITS

You may get no direct benefit from the screening tests. However, you will have a physical exam, a genital exam, and tests to check on the health of your blood, liver, and kidneys. If these tests show that you might have health problems, you will be referred for medical care and other services available to you. [*For selected sites only:* If your Pap test result is abnormal, you will be referred for treatment at [insert provider/center].]

You will get counseling and testing for HIV. You will get free condoms. If you are infected with HIV, you will be referred for medical care, counseling, and other available services that could be of help to you. You will get counseling and testing for other infections passed through sex. If you have these infections, you will be offered

treatment for them, if needed. You can bring your partner here for HIV counseling and testing and treatment for infections passed through sex. For other health problems that cannot be treated at this clinic, the study staff will refer you to other places where you can get medical care.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING TESTS WITHOUT YOUR CONSENT

You may be withdrawn from the screening tests without your consent for the following reasons:

- You are found to not be eligible for the VOICE study.
- The VOICE study is stopped or canceled.
- The study staff feel that having the screening tests would be harmful to you.
- You are not willing to find out your HIV test result.
- You are not able to attend clinic visits or complete the screening tests.
- Other reasons, decided by the study staff.

COSTS TO YOU

There is no cost to you for the screening tests. Treatments available to you and/or your partner(s) from the study for infections passed through sex (other than HIV) will be given free of charge.

REIMBURSEMENT

[*Sites to insert information about local reimbursement:*] You will receive [\$xx] for your time, effort, and travel to and from the clinic at each scheduled screening visit.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff will use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes other studies conducted by [site name] and studies conducted by other researchers that study staff know about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the organization that supplies tenofovir gel (CONRAD)
- the company that makes tenofovir tablets and Truvada tablets (Gilead Sciences)

[*Sites to include/amend the following if applicable:*] [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other

infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [health authority].

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of having the screening tests. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the screening tests, or if you have a research-related injury, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert physical address and telephone number].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert physical address and telephone number].

SIGNATURES

[Insert signature blocks as required by the local IRB/EC:] If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to have the screening tests, please sign your name or make your mark below.

Participant Name (print)	Participant Signature/Mark	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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Witness Name (print)	Witness Signature	Date
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APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)

SAMPLE INFORMED CONSENT FORM DIVISION OF AIDS, NIAID, NIH

MTN-003/VOICE

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

May 22, 2008

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

Short Title for the Study: VOICE

INFORMED CONSENT

You are being asked to volunteer for a research study known as VOICE. The VOICE study is for women who do not have but could get Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immune Deficiency Syndrome, or AIDS. The study is testing whether certain products can prevent HIV in women. The United States National Institutes of Health is funding this study.

Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, what is expected of you, and what you can expect of us. This consent form might contain some words that are unfamiliar. Please ask questions about anything you do not understand or want to learn more about.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary: You do not have to take part in the study if you do not want to.
- You may decide not to take part in the study, or to leave the study at any time, without losing your regular medical care.
- If you decide not to take part in the study, you can still join another study later, if one is available and you qualify. However, you cannot join the VOICE study if you are taking part in another study of drugs, medical devices or vaginal products. You are asked to tell the study staff about any other studies you are taking part in, or thinking of taking part in. This is very important for your safety.

PURPOSE OF THE STUDY

The VOICE study is testing 3 products.

- A gel that is put in the vagina called tenofovir gel.
- A tablet that is taken by mouth, called tenofovir.
- A tablet that is taken by mouth, called Truvada. Truvada is a combination of tenofovir and another medication called emtricitabine.

There are two main purposes of the VOICE study. The first purpose is to find out if the three products listed above will protect women from getting HIV through vaginal sex. The second purpose is to find out if there are any bad effects when women use these products over a long period of time.

Tenofovir gel, tenofovir tablets and Truvada tablets are “experimental” for HIV prevention. This means **we do not know if they work to protect against HIV**. This study is being done to find that out.

Tenofovir gel is not approved for use in the general community. Tenofovir tablets and Truvada tablets are used to treat people who have HIV. The tablets are generally safe when used as treatment for HIV. These tablets are not a cure for HIV/AIDS, but they are very effective for improving the health of people who have HIV/AIDS. Although these tablets improve the health of people with HIV, **we do not know if they work to protect against HIV**.

The United States Food and Drug Administration (US FDA) has been informed of this study and has permitted it to be conducted. [The [local authority] also has permitted the study to be conducted.]

About 4200 women will be enrolled in the study at different sites in Africa. About [approximate site-specific accrual target] women will be in the study here at [study site]. The whole study will take about three years to finish. Each woman will be in the study from about 14 to 36 months.

STUDY GROUPS

There are five study groups. If you decide to take part in the study, you will be placed in one of the five groups. Your group will be chosen “by lot” [or other equivalent local term, for example, like flipping a coin or throwing dice] to be in one of these groups. You cannot choose your group, and the study staff cannot choose your group for you. You have an equal chance of being placed in any of the five groups. Once you are in a group, you cannot change to another group.

Women in two of the groups will get a gel to insert in the vagina once a day. One of these groups will get tenofovir gel and one group will get a placebo gel. The placebo gel is a gel that looks and feels like tenofovir gel, but it does not have the ingredients from tenofovir gel that might protect against HIV.

Women in the three other groups will get two tablets to take by mouth once a day.

- One group will get tenofovir tablets and the placebo for Truvada tablets.
- One group will get Truvada tablets and the placebo for tenofovir tablets.
- One group will get two placebo tablets (placebo for tenofovir tablets and placebo for Truvada tablets).

The placebo tablet for tenofovir looks and feels like a tenofovir tablet, but does not have the ingredients that may protect against HIV. The placebo tablet for Truvada looks and feels like a Truvada tablet, but does not have ingredients that might protect against HIV.

All five groups are very important to this study. Women in all groups will have the same study visits. All women will get condoms and counseling on how to avoid HIV and other infections passed during sex.

No matter what study group you are in, you must remember that we do not know if the gel or tablets work to protect women from getting HIV. The only known way to protect against getting HIV during sex is to use a condom every time you have sex.

Gel Groups

If you are in a group that gets gel, neither you nor the study staff will know which gel you are getting. Both gels come in the same type of applicator. They look and feel about the same. You will be able to find out which gel that you got after the end of the study. Until then, no one will be told.

If you are in a group that gets gel:

- You will be given applicators containing the gel at each scheduled study visit.
- You will be given instructions on how to use the gel. For your safety, it is important that you only use the gel in your vagina, as instructed by study staff.
- You will be asked to insert the gel in your vagina once a day, at the same time every day.
- You will be asked to bring all unused applicators you have left from your previous visit to your next visit.
- You will be asked not to give your gel to anyone or use anyone else's gel or tablets.

Tablet Groups

If you are in a group that gets tablets, neither you nor the study staff will know which tablets you are getting. You will be able to find out which tablets that you got after the end of the study. Until then, no one will be told.

If you are in a group that gets tablets:

- You will be given bottles containing tablets at every scheduled study visit. One bottle will contain one type of tablet (tenofovir or placebo) and the other bottle will contain the other type of tablet (Truvada or placebo). The tablets in the two bottles will not look the same. One tablet is larger than the other, and one has a

darker color than the other. You should not mix the two types of tablets together. You should keep the tablets in the bottles they come in. The bottles will have packets inside to keep the tablets dry. You should not remove the packets from the bottles.

- You will be asked to take one tablet from each bottle once a day, at the same time every day.
- You will be asked to bring all tablets and bottles you have left from your previous visit to your next visit.
- You will be asked not to give your tablets away or use anyone else's study tablets or gel.

It is very important that you do not ever share tablets or gel with anyone else who is either in or not in the study.

STUDY PROCEDURES

If you decide to take part in the study, your first visit will continue today, after you read, discuss, understand, and sign or make your mark on this form. Study staff will help you understand the form and answer your questions before you sign or mark this form.

Today, after you decide to sign or mark this form, you will find out if you will get gel or tablets to use while in the study. You will answer interview questions about your sexual practices. You will give 2 teaspoons [or local equivalent] of blood that the study staff will keep frozen here while you are in the study. If needed, they will test this blood later in the study to help check on your health.

If your screening tests show that you do not have immunity to hepatitis B (immunity means protection against infection), you will be offered the hepatitis B vaccine. If you choose to get hepatitis B vaccine, you will have this vaccine three times (today, in one month, and again in six months). If you choose not to get the hepatitis B vaccine, you will be tested for hepatitis B every 12 months. You may also be tested for hepatitis B if you have signs or symptoms of hepatitis B during the study.

If you decide to enroll in the study, after today you will be in the study from 14 to 36 months, depending on when you join. You will have a study visit here every month while you are in the study. The procedures done at these visits will take 2 – 3 hours.

At most visits, you will:

- Tell study staff if you had any health problems since your last visit.
- Tell study staff about any medications, herbal treatments and supplements you are taking.
- Give urine for a pregnancy test.
- Have your weight measured.
- Have a physical exam.
- Talk with study staff about contraception, and get contraception if you need it.
- Tell study staff any new information on where you live and how to keep in contact with you. They will use this information to remind you of visits. If you miss a visit,

the study staff will try to contact you by [site-specific methods]. They also may visit your home. They will try to reach you through the contact people that you list. If they talk to these people, they will not say why they want to reach you.

- Answer questions about your sexual practices, reproductive health, and use of gel or tablets. Some of these questions will be asked by computer. The questions asked by the computer will be shown on the computer screen and read to you through earphones. You do not need to know how to read to answer the computer questions. The study staff will show you how to use the computer. You can practice using the computer and ask the study staff any questions you may have. Then you will answer questions using the computer by yourself. You will answer each question by marking your answer on the computer screen.
- Bring your remaining unused gel applicators or tablets and bottles to be counted by study staff.
- Talk with study staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex. You will give [about 5-10 mL [or local equivalent] of blood from your arm or finger] for HIV testing. When we do HIV testing for this study, we first do two tests that give results in 20-40 minutes. You will get results of these tests when they are available. If the tests show that you may have HIV infection, we will do another different test to confirm the result. This test takes 1-2 weeks, so you will come back at that time to get the results. If that test shows that you have HIV, we will test your blood again and repeat the test one more time. You will talk with study staff about the meaning of your results and how you feel about them. If both of these tests show that you have HIV, a sample of your blood will be sent to the US to make sure your test results are correct. This is something that the US National Institutes of Health requires for HIV prevention studies. Sometimes HIV tests are not clearly positive but also not clearly negative. In that case, we will do more tests until we know your status for sure. You must receive your HIV test results to stay in the study.
- Give blood (xx mL or local equivalent) and urine for tests of the health of your blood, liver, and kidneys.
- Give blood for tests to check the amount of medication (Truvada or Tenofovir) in your blood.
- Get the results of tests done at the visit and at the previous visit.
- Get treatment for most types of infections passed during sex if you need it.
- Get referrals for other medical care and services if you need them.
- Get condoms.
- Talk with study staff about using gel or tablets every day and get new supplies of gel or tablets.

Every 6 months (2 times per year), you also will:

- Have your height measured
- Have an exam of your genital area and inside your vagina. The study staff will collect fluid from your vagina with a swab to test for infections if they suspect you have infections (Trichomoniasis, candidiasis, and BV). Some fluids also will be collected by swab to test for factors that could affect the chances of getting HIV.

Every 12 months (once per year), you also will:

- Have a blood test for syphilis, a urine test for gonorrhea and chlamydia, and a vaginal fluid test for Trichomonas. These are infections passed through sex.
- Be tested for hepatitis B if you chose not to take the hepatitis B vaccine

At your end of product visit, you will:

- Have all of the procedures listed above, except that you will not receive any more gel or tablets. You will not use any more gel or tablets after this visit.

At your end of study visit (the final scheduled study visit), you also will:

- Answer questions about:
 - Your sexual practices and the study gel or study tablets.
 - Your relationships with others.

AT ANY TIME IN THE STUDY

If you have health problems that may be caused by infections passed through sex, you will:

- Have an exam of your genital area and inside your vagina.
- Give blood, urine, and/or vaginal fluid to test for infections passed through sex. Some fluids also will be collected by swab to test for factors that could affect the chances of getting HIV.
- Get treatment for most types of infections if you need it.

If you become infected with hepatitis B, you will:

- Stop using gel or tablets, but stay in the study as originally planned.
- Give blood to test for liver problems, if you are in the group that gets tablets
- Be given referrals for medical care and other services you may need.

If you become infected with HIV

You will be provided with condoms and counseling to help prevent you from getting HIV. However, it is still possible that you could get HIV.

As described above, if you may have been infected with HIV, you will have at least three HIV tests to confirm your results. Each time blood is drawn for these tests, you will also give blood (XX mL) for tests of the amount of HIV in your blood and your CD4+ T-cell count. The CD4+ T-cell count is a test that measures the amount of damage HIV has done to your immune system. The immune system is the part of the body that fights off germs and infections.

If the HIV tests confirm that you have been infected with HIV, you will stop using gel or tablets, but stay in the study as originally planned. If you do not have your unused study products with you, a study staff person may go with you to your home to collect study products.

Study staff will give you counseling and referrals for medical care and other services available to you. They also will refer you to another study called “MTN-015” which you

will have the option of joining. If you decide not to join the MTN-015 study, you will be asked to have additional blood drawn 1, 3, 6 and every six months after your HIV infection was detected. This blood will be used to check:

- Your CD4+ T-cell count.
- The amount of HIV in your blood
- Whether the HIV in your blood is resistant to medications used to treat HIV

Six months after you finish the hepatitis B vaccines (if this applies to you), your blood also will be tested to see if the vaccine worked to protect you against hepatitis B.

POSSIBLE FUTURE TESTS

Some of the blood and vaginal fluids that you give during this study may be left over after all of the study tests are completed. The study staff also would like to keep your leftover blood and vaginal fluids. You will be asked to sign a separate consent form to give permission for that. Even if you do not give permission to store your blood and vaginal fluids after the study, you can still be in this study.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may:

- Feel discomfort or pain when your blood is drawn.
- Feel dizzy or faint.
- Have a bruise, swelling, small clot, or infection where the needle goes in your arm or finger

When you have genital exams, you may:

- Feel discomfort in your genital area and inside your vagina.
- Have a small amount of vaginal bleeding which will stop shortly after the exam.

When you answer computer questions:

There are few risks to you from answering the computer questions. Your answers to the questions will be stored on a larger computer here at [study site] that can only be accessed by authorized study staff. Your answers then will be transferred to the same place where your study forms are sent. As with all of your study information, every effort will be made to keep your personal information confidential. Your answers will be identified by your study number only (not your name). However, absolute confidentiality cannot be guaranteed.

Gel Groups

If you are in a group that gets gel, the gel could cause some bad effects. We do not yet know all the bad effects of the gels. Some, but not all, women who used the gels in other studies have had:

- Dryness, itching, burning feeling, or pain in the genital area.
- Vaginal candidiasis (a kind of vaginal infection).
- Discharge from the vagina.

- Irritation in the genital area.

You could have these effects or other effects that we do not know about.

A small amount of tenofovir may pass from the gel in your vagina into your blood. If this happens, we do not know if it might cause bad effects.

Tablet Groups

If you are in a group that gets tablets, the tablets could cause some bad effects. We do not yet know all the effects of the tablets.

About 5 out of 100 people with HIV taking the tenofovir or Truvada tablets have these occasional side effects:

- Upset stomach, vomiting, gas, loose or watery stools
- Dizziness or headache
- Abdominal pain
- Lack of energy/general body weakness
- Mild problems of kidney function that are only detected by laboratory tests
- Shortness of breath or cough
- Rash, including allergic reaction
- Anxiety
- Joint pain, muscle pain, or other pain syndrome
- Fever

Fewer than 5 out of 100 people with HIV taking tenofovir or Truvada tablets have:

- Skin discoloration/darkening of the palms and/or soles of the feet

Potentially serious side effects are rare, but include:

- Liver function problems
- Serious kidney damage or failure
- Low phosphate levels (a chemical in the blood) or protein or sugar in the urine
- Inflammation or swelling and possible damage to the pancreas
- Bone softening
- Allergic reaction
- Lactic acidosis (which can produce shortness of breath, nausea, abdominal pain, and liver problems)

You could have these side effects or other side effects that we do not know about.

Both Gel and Tablet Groups

If you become infected with HIV while using gel or tablets, it is possible that the medications in Truvada (tenofovir and emtricitabine) would not work against the HIV in your body. If this happened, it could limit your options for HIV treatment. It is for this reason that you must stop using gel or tablets if you become infected with HIV. Study

doctors are available to discuss this with you. They can also do blood tests that will show which HIV medications might work best for you.

Other Possible Risks:

If you get the vaccine for hepatitis B, you may have side effects related to the vaccine, such as pain at the place where you got the injection, or feeling tired, both of which should last only a day or two.

We do not know if there are other risks if you use herbal treatments or supplements while you are using gel or tablets. Please tell study staff if you are using any herbal treatments or supplements.

You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other infections passed through sex, and your test results. You may become worried while waiting for your test results. If you have HIV or other infections, knowing this could make you worried. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality while you are having the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your HIV status could also cause problems between you and your partner. If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

Some other studies of HIV prevention have found an unexpected higher risk of getting HIV among study participants. This could happen in any prevention study, including the VOICE study. Because of this, the study staff will remind you of the importance of using condoms to protect against HIV.

Very rarely, some of the bad effects listed in this form, such as liver problems, may cause death if they are very severe.

Pregnancy and Breastfeeding

We do not know if tenofovir gel, tenofovir tablets, or Truvada tablets have any effect on pregnancy, the fetuses of women who use the gels or tablets when pregnant, or the babies of women who use the gels or tablets when breastfeeding. Because of this, pregnant women and women who are breastfeeding must not join this study. Women who join the study must use effective contraception and must have monthly pregnancy tests while in the study. Effective contraception includes hormonal methods (such as the birth control pill or shot), intrauterine contraceptive device (IUCD); and sterilization of you or your partner. You should not use spermicides as a method of contraception while participating in the VOICE study.

If you become pregnant during the study, the study staff will refer you to available sources of medical care and other services you or your baby may need. The study does not pay for this care. You will stop using gel or tablets, but will keep coming here for study visits as originally planned. We will change the study procedures as needed to protect your health while you are pregnant. For example, we will not examine or collect fluids from your vagina after 24 weeks of pregnancy. If you have a baby, we will ask you to have a study visit after the birth, so that we can find out about the birth.

Depending on when you become pregnant, you may be able to start using your gel or tablets again after your pregnancy and if you are not breastfeeding. The study staff will talk more with you about this after your pregnancy.

BENEFITS

You may get no direct benefit from being in this study. **We do not know if tenofovir gel, tenofovir tablets, or Truvada tablets work to protect against HIV.** Also, the gel or tablets you are getting may be placebo gel or tablets. Because of this, study staff will remind you of the importance of using condoms to protect against HIV.

You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV prevention. This is true no matter what study group you are in.

You will have physical exams and genital exams. You will have tests to check on the health of your blood, liver, and kidneys. If these tests show that you might have any health problems, you will be referred for medical care and other services available to you. [*For selected sites only:* If your Pap test result is abnormal, you will be referred for treatment at the [insert name of provider/center].] If your blood tests show that you have never had hepatitis B before, you may benefit from getting hepatitis B vaccine for free.

You will get counseling and testing for HIV. You will get free condoms. You can bring your partner(s) here for HIV counseling and testing and testing for other infections passed through sex. If you or your partner(s) have infections passed through sex, other than HIV infection, you will be offered medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will be referred for medical care, counseling, and other services available to you.

There may be no direct benefits to you from answering the computer questions. However, information learned about the computer questions may help researchers improve the way they collect information about women's sexual behaviors.

NEW INFORMATION

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the gels or tablets may be causing bad effects, or that clearly shows that the gels or tablets are very effective in protecting against HIV, you will be told about

this. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY HAVE TO STOP TAKING THE STUDY DRUG EARLY

You may have to stop using gel or tablets if you:

- Become infected with HIV.
- Become infected with hepatitis B.
- Become pregnant.
- Are breastfeeding.
- Are taking certain medications that affect your kidneys.
- Are taking medication called PEP for possible recent exposure to HIV infection.
- *[sites to include if applicable:]* Are using the vaginal gel and are found to have certain abnormalities on Pap smear
- Are unable or unwilling to follow study procedures or instructions.
- Could be harmed by continuing to take gel or tablets.

Even if you stop using gel or tablets, you will stay in the study and have your monthly visits as planned.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be withdrawn from the study without your consent for the following reasons:

- The study is stopped or canceled.
- The study staff feel that staying in the study would be harmful to you.
- You are not willing to find out your HIV test results.
- You are not able to attend clinic visits or complete the study procedures.
- Other reasons, decided by the study staff.

If you withdraw early from the study, we will ask you to come in for a final visit with all the exams and tests listed above.

ALTERNATIVES TO PARTICIPATION

There are no gels or tablets known to protect against HIV during sex. **The only known way to protect against HIV during sex is to use a condom every time you have sex.**

[Sites to include/amend the following if applicable: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing, hepatitis B vaccine, and contraception. We will tell you about those places if you wish.]

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you and/or your partner(s) from the study for infections passed through sex will be given free of charge.

REIMBURSEMENT

[Sites to insert information about local reimbursement:]

You will receive [\$xx] for your time, effort, and travel to and from the clinic at each scheduled visit.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff will use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes other studies conducted by [site name] and studies conducted by other researchers that study staff know about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the organization that supplies tenofovir gel (CONRAD)
- the company that makes tenofovir tablets and Truvada tablets (Gilead Sciences)

[Sites to include/amend the following if applicable:] [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [health authority].

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of study participation. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about the study, or if you have a research-related injury, you should contact [insert name of the investigator or other study staff] at [insert telephone number and/or physical address].

If you have questions about your rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert physical address and telephone number].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert physical address and telephone number].

SIGNATURES

[Insert signature blocks as required by the local IRB/EC:] If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to have the study, please sign your name or make your mark below.

Participant Name (print)	Participant Signature/Mark	Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

APPENDIX VII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)

**SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH**

MTN-003/VOICE

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

May 22, 2008

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

Short Title for the Study: VOICE

INTRODUCTION

You have decided to take part in the VOICE study, which is funded by the United States National Institutes of Health. While you are in the VOICE study, there may be some blood and vaginal fluids taken from you that might be useful for future research. You are being asked to agree to the storage of this blood and vaginal fluid. This consent form gives you information about the collection, storage, and use of your blood and vaginal fluid. The study staff will talk with you about this information. Please ask study staff any questions you may have. You will be asked to sign or make your mark on this form to indicate whether you agree to have your blood and vaginal fluid stored and tested in the future. You will be offered a copy of this form to keep.

HOW WILL YOU GET THE BLOOD AND VAGINAL FLUID FROM ME?

You have agreed to have blood and vaginal fluid collected and tested as part of the VOICE study. During the study, your stored blood and vaginal fluid will be tested to check on your health and to see if you have HIV or other infections passed through sex. The study staff would like to keep any blood and vaginal fluid that is leftover, after the VOICE study is done, to use for future testing. If you agree to this, no additional blood and vaginal fluid will be taken from you. Only leftover blood and vaginal fluid will be kept and used for future testing.

HOW WILL YOU USE MY BLOOD AND VAGINAL FLUID?

Your blood and vaginal fluid will only be used to look for additional evidence of infection with HIV or other agents; damage caused by infection; or your body's response to infection. For instance, researchers may look at your blood cells and substances in your blood and vaginal fluid called proteins and chemicals. They also may look at your genes (DNA), since your genes might affect your response to disease in important ways. Your genes might make you more likely or less likely to becoming infected, make your responses to infection or to treatment either stronger or weaker, or make HIV

progress either more rapidly or more slowly. No other kinds of genetic test will be done by anyone on your stored blood without first explaining the test to you and obtaining your permission. Some of these tests may be done outside of your country.

The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored blood and vaginal fluid. This is because research tests are often done using ways that are experimental, so the results do not usually help doctors manage your health. If a rare situation comes up in which the researchers decide that a test result is important for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your contact information. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name and contact information.

Your blood and vaginal fluid will not be sold or used directly to produce commercial products. Research studies wishing to use your blood and vaginal fluid will be reviewed by the National Institutes of Health and a special committee at the researcher's institution (an Institutional Review Board). The role of this committee is to protect you and other research volunteers from harm.

HOW LONG WILL YOU KEEP MY BLOOD AND VAGINAL FLUID?

There is no time limit on how long your blood and vaginal fluid will be stored.

HOW WILL MY BLOOD AND VAGINAL FLUID BE STORED?

Your blood will be stored at special facilities that are designed to store samples safely and securely. Some of these facilities are outside of your country. The storage facilities are designed so that only approved researchers will have access to the samples. Some employees of the storage facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you.

DOES STORAGE OF MY BLOOD AND VAGINAL FLUID BENEFIT ME?

There are no direct benefits to you. The benefit of doing research on stored blood and vaginal fluid includes learning more about HIV infection.

WHAT ARE THE RISKS?

There are few risks related to storing your blood and vaginal fluid. When tests are done on the stored blood and vaginal fluid, there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes), it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the true parent of a child) or problems getting a job or insurance.

WHAT ABOUT CONFIDENTIALITY?

To keep your information private, your blood and vaginal fluid will be labeled with a code that can only be traced back to your research clinic. Your name and other personal

information will be protected by the research clinic. When researchers are given your stored blood and vaginal fluid to study, they will not be given your personal information.

The results of future tests will not be included in your health records. Any publication about the results of future tests will not use your name or identify you personally. The researchers will do everything they can to protect your privacy. Every effort will be made to keep your personal information confidential. However, it is not always possible to guarantee confidentiality. Your personal information may be disclosed if required by law.

Your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- study staff
- study monitors
- the organization that supplies tenofovir gel (CONRAD)
- the company that makes tenofovir tablets and Truvada tablets (Gilead Sciences)

WHAT ARE MY RIGHTS?

Allowing your blood and vaginal fluid to be stored is completely voluntary. If you decide not to have any blood or vaginal fluid stored other than what is needed to complete the VOICE study, you can still remain in the VOICE study, and your leftover blood and vaginal fluid will be destroyed. If you decide now that your blood and vaginal fluid can be stored for future research, you may change your mind at any time. However, you must contact your study doctor or nurse and let them know that you no longer want your samples used for future research. Your blood and vaginal fluid will then not be used and will be destroyed.

WHAT DO I DO IF I HAVE QUESTIONS?

If you have questions about the storage and future testing of your blood and vaginal fluid, contact [insert the name of the investigator] at [insert physical address and telephone number].

If you have questions about your rights related to the storage and future testing of your blood and vaginal fluid for research, contact [insert the name or title of person on the Institutional Review Board] at [insert physical address and telephone number].

If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert physical address and telephone number].

SIGNATURES

Please carefully read the statements below and think about your choice. No matter what you decide it will not affect your participation in the VOICE study or your medical care. Please initial or mark your choice and sign or make your mark below.

[Insert signature blocks as required by the local IRB/EC, yes/no boxes may be used for each specimen type:]

I agree to allow the following leftover samples to be stored for future testing.

Blood
 Vaginal Fluid

OR

I do not agree to allow any of my leftover blood or vaginal fluid to be stored for future testing.

Participant Name (print)	Participant Signature	Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

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