

MTN-018

**Committed to Having Options for Interventions to Control the Epidemic:
a Follow-up Study to MTN-003**

Microbicide Trials Network

**Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
Eunice Kennedy Shriver US National Institute of Child Health and Human
Development
US National Institute of Mental Health
US National Institutes of Health**

**Grant #:
UM1 AI 068633-06**

DAIDS Protocol #: 11818

IND# 55,690

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Version 1.0

September 6, 2011

MTN-018

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LIST OF ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
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
CAB	Community Advisory Board
CDC	Centers for Disease Control
CDM	clinically driven monitoring
CFR	Code of Federal Regulations
CI	confidence interval
CONRAD	Contraceptive Research and Development Organization
CORE	Coordinating and Operations Center
CRF	case report form
CRPMC	Clinical Research Products Management Center
CWG	Community Working Group
d4T	stavudine
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EC	ethics committee
EC ₅₀	50% effective concentration
EFV	efavirenz
ELISA	enzyme-linked immunosorbant assay
FDA	Food and Drug Administration
fmol	femtomol
FHCRC	Fred Hutchison Cancer Research Center
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HEC	hydroxyethylcellulose
HEENT	Head, ears, eyes, nose and throat
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HR	hazard ratio

IATA	International Air Transport Association
IND	investigational new drug
IoR	Investigator of Record
iPrEx	Pre-exposure Prophylaxis Initiative
IRB	Institutional Review Board
LDMS	Laboratory Data Management System
µg	microgram
mg	milligram
MTN	Microbicide Trials Network
ng	nanogram
NIAID	National Institute of Allergy and Infectious Disease
NICHHD	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
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PK	pharmacokinetic(s)
PMPA	9-R-2-phosphonomethoxypropyl adenine
PMPApp	tenofovir diphosphate
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development
PrEP	pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
PTID	Participant identification number
QD	quaque die (daily)
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure
SSP	study specific procedures
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
ULN	upper limit of normal
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VS	vital signs
WB	Western blot
WHO	World Health Organization
ZDV	zidovudine

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MTN-018

**Committed to Having Options for Interventions to Control the Epidemic:
A Follow-up Study to MTN-003**

INVESTIGATOR SIGNATURE FORM

Version 1.0

September 6, 2011

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 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 product(s) 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-018

Committed to Having Options for Interventions to Control the Epidemic: A Follow-up Study to MTN-003

PROTOCOL SUMMARY

- IND Sponsor:** Division of AIDS, NIAID, US NIH
- Protocol Chairs:** Gita Ramjee, PhD, Nyaradzo Mgodzi, MBChB, and Sharon Riddler, MD, MPH
- Sample Size:** Up to approximately 4,300
- Accounting for exclusion of HIV-infected VOICE participants, as well as those lost to follow-up
- Study Population:**
- VOICE Cohort.** Up to approximately 4,000 former VOICE participants who are healthy, HIV-uninfected, not pregnant or breastfeeding, who meet MTN-018 eligibility criteria; and
- Non-VOICE Cohort.** Up to approximately 300 healthy, HIV-uninfected women who are not pregnant or breastfeeding and meet MTN-018 eligibility criteria, but with no previous history of participation in VOICE or other HIV prevention trials.
- Study Sites:** VOICE sites
- Study Duration:** Total study duration will include the following:
- Approximately 6-9 months for accrual
 - Approximately 12 months of scheduled study product use per participant; may be less depending when participant enrolls
 - Approximately 2 months of follow-up off of study product per participant
- Study Products:** May include any study product(s) found to be safe and effective in VOICE.
- Active products in VOICE include the following:
- tenofovir disoproxil fumarate (TDF) 300 mg tablet
 - emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) 200 mg/300 mg tablet
 - tenofovir 1% gel

Although specific study products and their suppliers are mentioned by name throughout the protocol, it is assumed that not all study products may be included in the final version of MTN-018 to be implemented by study sites.

If both TDF and FTC/TDF are found to be safe and effective in VOICE, it is anticipated that only one of those oral study products would be selected for MTN-018.

Following analysis of VOICE study results, study products will be selected via a formal process, anticipated to include input from the VOICE Protocol Team. The following factors will be considered for each VOICE study product during the MTN-018 study product selection process:

- Level of effectiveness (decreased risk of HIV transmission, $P < 0.05$)
- Safety and tolerance profile
- Resistance mutations detected among HIV seroconverters
- Emerging data from other HIV prevention and treatment studies involving VOICE study products
- Other factors that may impact the feasibility of widespread use, e.g., cost-effectiveness

Study Design:

Phase 3B, open-label, multi-site, randomized trial

Following the release of VOICE results and VOICE participant unblinding, and assuming that at least one safe and effective product will be identified in VOICE, eligible VOICE participants as well as a Non-VOICE Cohort would have the option to enroll in MTN-018.

If only one product is selected to move forward in MTN-018, all participants would receive that product.

If more than one product is selected to move forward in MTN-018, participants will select a study product at the Enrollment Visit; former VOICE participants will have the opportunity to select a product to which they were not originally randomized in VOICE.

Should more than one product move forward in MTN-018, at Month 1, participants will confirm their desire to continue with the study product chosen at the Enrollment Visit, or request a change in study product. All changes in product selection

following the Month 1 Visit must be approved by the IoR/designee. In general, one participant-initiated switch in study product will be permitted following Month 1; however, this does not preclude study product changes initiated by the IoR/designee for other reasons (e.g., toxicity or significant personal reasons, such as those impacting personal safety).

Participants will be randomized at Month 1 to one of two strategies for follow-up on study product:

- Monthly follow-up (Monthly Arm)
- Quarterly follow-up (Quarterly Arm)

Participants have approximately 12 total months of scheduled follow-up on study drug. Approximately two months after the Month 12 Visit, participants will return for final HIV testing to assess for potential delayed seroconversion.

Study Regimen:

Daily use of study product (non-coitally dependent)

Study Groups:

Final study groups will depend on selection of study product(s) for MTN-018. Participant preferences for study product will impact the size of study groups.

1. Vaginal gel - monthly
2. Vaginal gel - quarterly
3. Oral tablet - monthly
4. Oral tablet - quarterly

Graphic representations of study groups and their scheduled follow-up are provided in Figures 1 and 2.

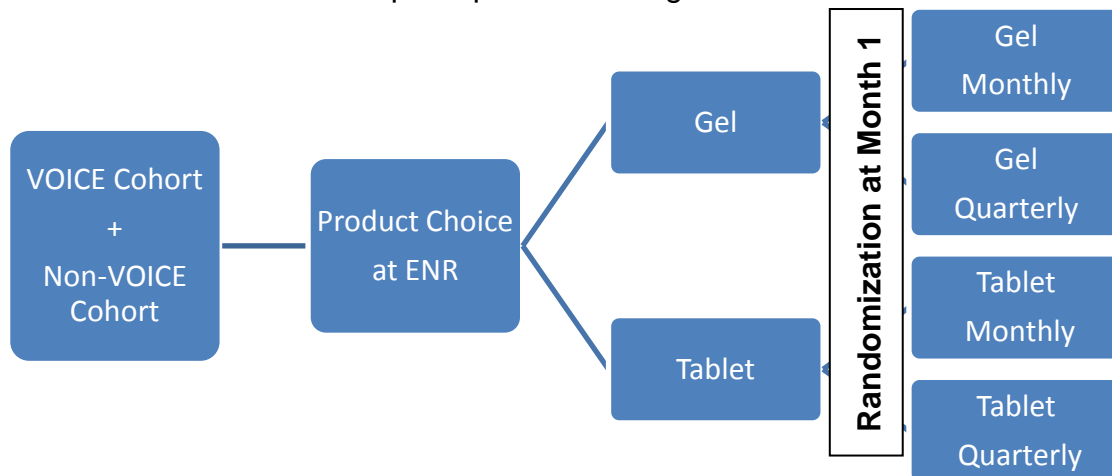


Figure 1: Study Groups

Note: **Study implementation will not occur until this protocol is modified.** It is assumed that following the analysis of VOICE results, the following will occur, among other steps necessary for activation of the study:

- Sponsor determination as to whether MTN-018 will be implemented
- Selection of MTN-018 study product(s)
- Finalization of follow-up schedules for safety assessments pending final review of safety trends in VOICE
- Modification of Version 1.0 of MTN-018 Protocol

Planned Substudies (see Figure 3)

MTN-018B – Breastfeeding

MTN-018B will enroll former VOICE participants who are breastfeeding into a protocol similar to CHOICE, except that participants will not be randomized to monthly vs. quarterly follow-up. Participants will choose their study product (if more than one product is selected for CHOICE). Mothers and their infants will be followed monthly to assess potential impact of study product use on infant health and growth, as well as key breastfeeding indicators (duration of exclusive breastfeeding and timing at weaning). MTN-018B will be open to women who are breastfeeding at the time of initiation of CHOICE, as well as those who deliver while CHOICE is open and subsequently initiate breastfeeding.

MTN-018C – Pregnancy

MTN-018C will enroll former VOICE participants who are pregnant at screening or enrollment for (or become pregnant during) CHOICE into a protocol similar to CHOICE, except that participants will not be randomized to monthly vs. quarterly follow-up. Participants will choose their study product (if more than one product is selected for CHOICE). Mothers will be followed monthly to assess potential impact of study product use on key pregnancy and perinatal outcomes. Mothers and infants will be offered participation in MTN-016, the Prevention Agent Pregnancy Exposure Registry, already activated at all planned MTN-018 sites.

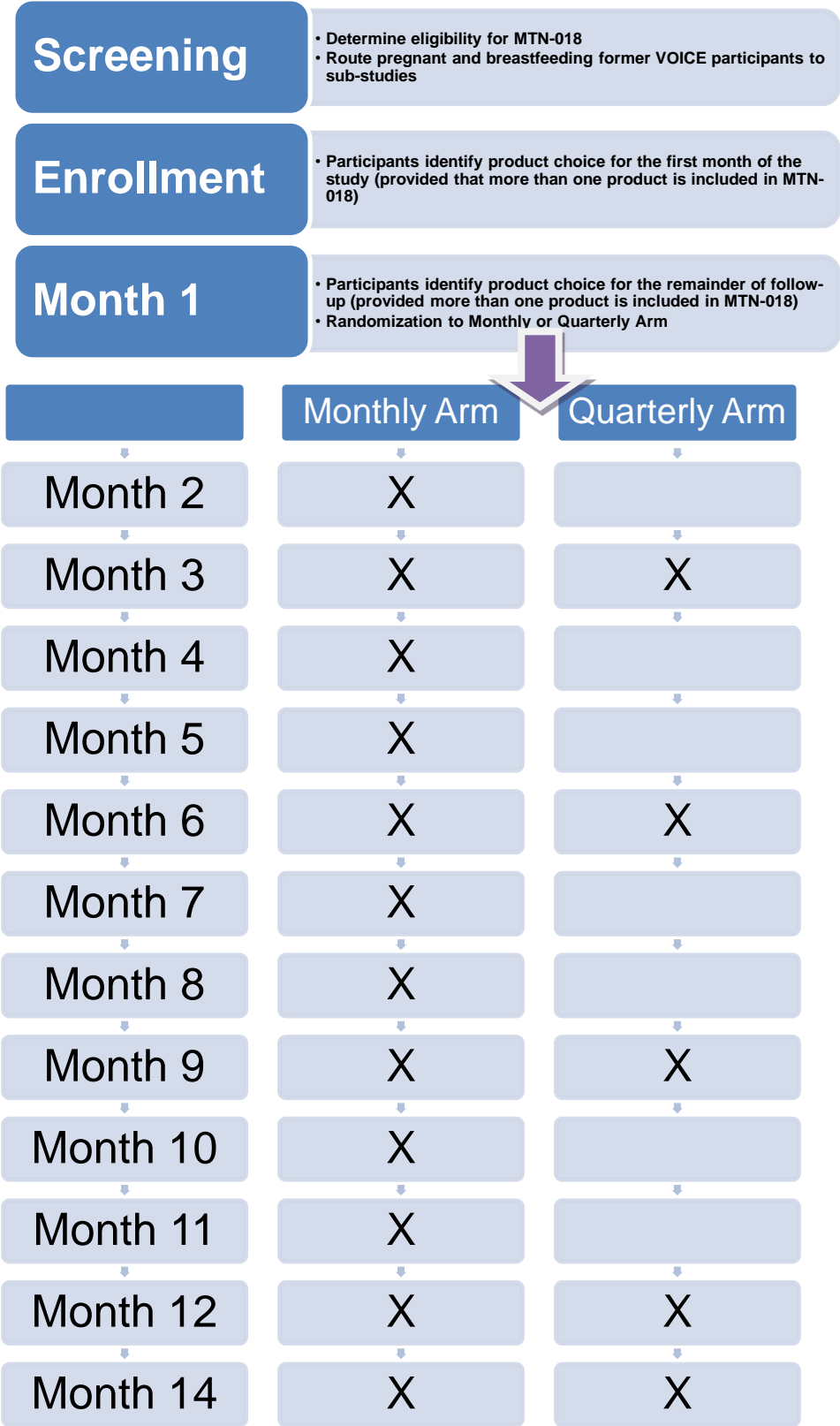


Figure 2: MTN-018 Visit Schedule

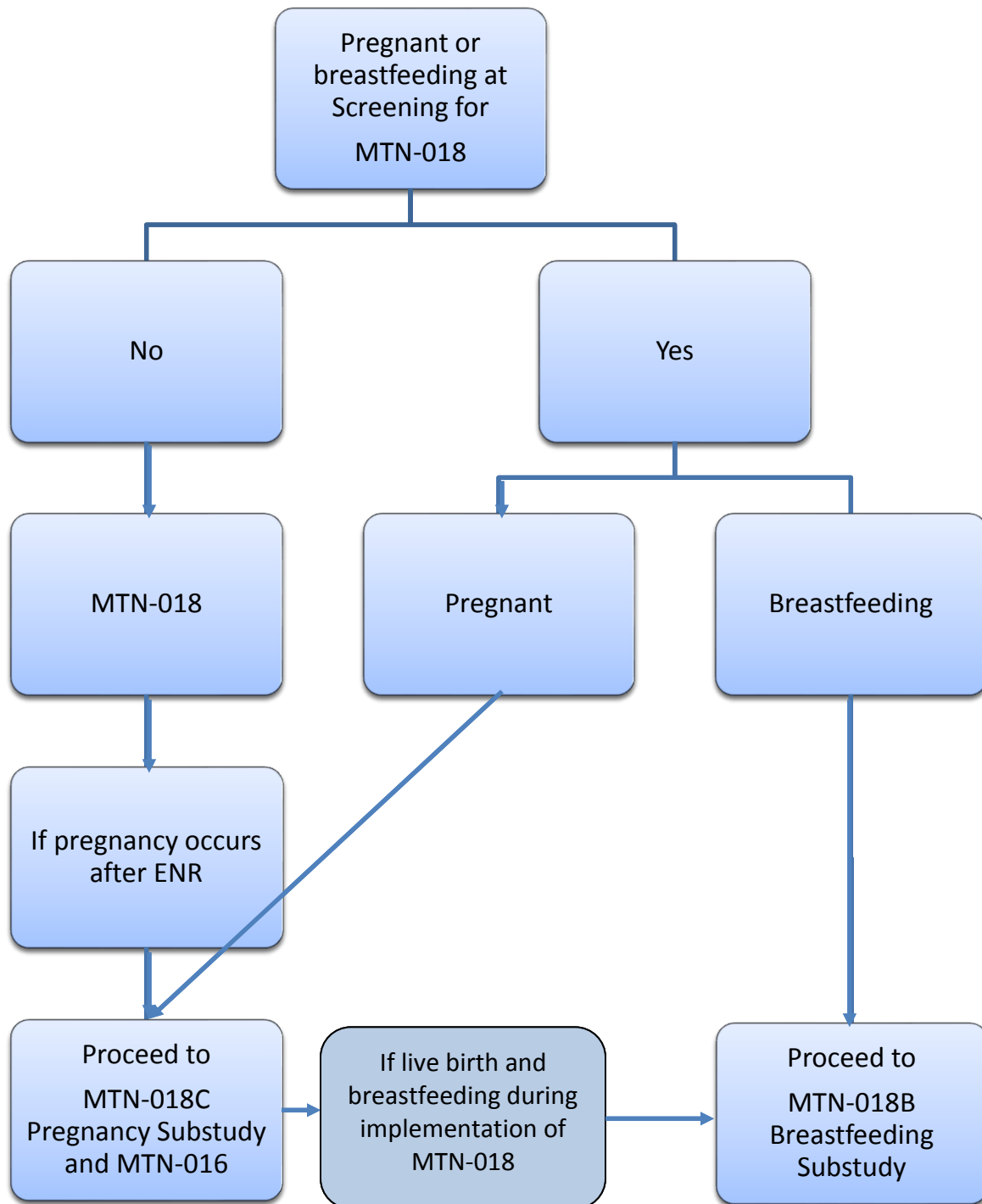


Figure 3: MTN-018 Sub-studies

STUDY OBJECTIVES

Primary Objectives

1. **Safety.** To compare the safety profiles associated with two different strategies of follow-up for participants taking daily study product
2. **Amount of Time Off Study Product.** To compare total amount of time off product associated with two different strategies of follow-up for participants taking daily study product

Primary Endpoints

1. **Safety**
 - Grade 3 and higher clinical AEs
 - Grade 2 and higher laboratory AEs for the following categories
 - AST
 - ALT
 - Creatinine
2. **Amount of Time Off Study Product**
 - Days off study product due to
 - Adverse events (AEs)
 - Investigator-initiated product hold/discontinuation
 - Participant-initiated product hold/discontinuation

Secondary Objectives

1. **Drug Resistance.** To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using study product who are monitored for HIV seroconversion monthly and quarterly
2. **Product Choice (if more than one product is selected to move forward in MTN-018).** To identify the determinants of product choice and product switching within the VOICE and Non-VOICE Cohorts
3. **Adherence.** To compare study product adherence between the VOICE cohort and the Non-VOICE cohort
4. **HIV Seroconversion Outcomes.** To describe participant HIV seroconversion outcomes associated with each study group

Secondary Endpoints

1. **Drug Resistance.** HIV-1 drug resistance mutations among participants who acquire HIV-1, as measured by standard genotype analysis and more sensitive methods to detect low frequency drug-resistant variants
2. **Product Choice (if more than one product is selected to move forward in MTN-018).** Study product selection and switching by participant
3. **Adherence.** Study product counts, participant self-report, study drug levels, and/or remote data collection, at sites with capacity
4. **HIV Seroconversion Outcomes.** HIV infection as defined by protocol algorithm

Exploratory Objectives

1. **Pharmacokinetics.** To evaluate the potential relationship between plasma drug concentrations and study outcomes
2. **Product Choice.** To compare product choice by VOICE arm (active vs. placebo)
3. **Study Product Diversion.** To describe product sharing, selling, and theft and to assess whether these vary by visit schedule (Monthly vs. Quarterly Arms) and among Quarterly Arm by timing of study product resupply
4. **Adherence.** To compare adherence by follow-up interval (Monthly vs. Quarterly)
5. **Perceptions of Efficacy.** To determine if understanding of partial efficacy affects product choice, adherence and risk behavior
6. **Product Use Patterns.** To determine if use of product is linked to timing of sex and if this differs by product
7. **Condom Use.** To measure differences in reported condom use by product
8. **Acute Seroconversion.** To establish the predictive value of participant-identified clinical signs to predict HIV seroconversion in a population of women at risk of HIV

Exploratory Endpoints

1. **Pharmacokinetics.** Drug levels in blood
2. **Product Choice.** Participant responses to questionnaire
3. **Sharing, Selling and Theft.** Participant responses to questionnaire

4. **Adherence.** Study product counts, participant self-report, and remote data collection at sites with capacity
5. **Perceptions of Effectiveness.** Participant responses to questionnaire
6. **Product Use Patterns.** Participant responses to questionnaire
7. **Condom Use.** Participant responses to questionnaire
8. **Acute Seroconversion.** Number of HIV seroconversions detected using participant-identified clinical signs in a population of women at risk of HIV infection

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Committed to Having Options for Interventions to Control the Epidemic: a Follow-up Study to MTN-003

Short Title: CHOICE

Protocol Number: MTN-018

Date: September 6, 2011

1.2 Sponsor and Monitor Identification

Sponsor: DAIDS/NIAID/NIH
6700 B Rockledge Dr.
Bethesda, MD 20892 USA

Sponsor: US NICHD
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Bethesda, MD 20892 USA

Sponsor: US NIMH
6001 Executive Blvd.
Rockville, MD 20852 USA

Co-Sponsor: CONRAD
1611 North Kent St., Suite 806
Arlington, VA 22209 USA

Co-Sponsor: Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404 USA

Monitor: Pharmaceutical Product Development (PPD), Inc.
929 North Front St.
Wilmington, NC 28401-3331 USA

1.3 Medical Officer

Medical Officer: Jeanna Piper, MD
6700 B Rockledge Dr.
Bethesda, MD 20892 USA

1.4 Network Laboratory

Laboratory: MTN Network Laboratory
204 Craft Ave.
Pittsburgh, PA 15213 USA

1.5 Data Center

Data Center: Statistical Center for HIV/AIDS Research & Prevention (SCHARP)
Fred Hutchison Cancer Research Center (FHCRC), 1100 Fairview
Ave. N., LE-400, PO Box 19024
Seattle, WA 98109-1024 USA

1.6 Study Operations

Study Operations: FHI
PO Box 13950
Research Triangle Park, NC 27709 USA

2 INTRODUCTION

2.1 Antiretroviral Drugs for HIV Prevention

2.1.1 Pharmacovigilance for Antiretroviral Drugs for HIV Prevention

In July 2010, the announcement of the results of CAPRISA 004 changed the landscape of HIV prevention.¹ For the first time, and after several unsuccessful attempts at proof-of-concept for topical chemoprevention of HIV, CAPRISA 004 showed a 39% reduction in the acquisition of HIV among women using a coitally dependent regimen of 1% tenofovir (TFV) gel, compared to women using placebo gel. Shortly thereafter in November 2010, the Pre-exposure Prophylaxis Initiative (iPrEx) study found a 44% reduction in HIV acquisition among men who have sex with men and transgender women randomized to a daily regimen of an oral antiretroviral (ARV) used for HIV treatment, emtricitabine/tenofovir disoproxil fumarate (FTC/TDF, Truvada[®]) vs. oral placebo.²

While these results were major breakthroughs for HIV prevention research, the scientific, regulatory, and advocacy communities are in agreement that further study is required to ensure that these interventions, if approved and rolled out widely, will be used optimally and safely by populations in need. These study results, combined with growing preclinical evidence of tenofovir effectiveness in the macaque challenge models^{3 4} have established the need to anticipate the possibility that the VOICE trial will demonstrate the effectiveness of one or more of the study products: 1% TFV gel, tenofovir disoproxil fumarate (TDF) tablet and FTC/TDF.

There are many factors which must be considered before an effective pre-exposure prophylaxis (PrEP) or microbicide intervention would be rolled out in the broader community. An appropriate rollout strategy for ARV-based prevention will balance practical constraints, community desires, need to prioritize appropriate subgroups at highest risk for HIV acquisition and thus most likely to benefit, and need for sufficient safety monitoring, among other competing priorities in public health. While implementation research on PrEP and microbicide rollout will be vital for optimizing the public health impact of a successful intervention, this research will ideally occur with a clear understanding of the framework required by adequate toxicity monitoring. It is recognized that pharmacovigilance is one key piece of a larger research agenda around the implementation of antiretroviral-based prevention.

The evaluation of the safety of the three formulations of tenofovir in MTN-003 or Vaginal and Oral Interventions to Control the Epidemic (VOICE) among healthy HIV-uninfected women has been necessarily rigorous, incorporating a multi-tiered system of pharmacovigilance that relies on participant report, clinician judgment, and an intensive regimen of laboratory-based monitoring. In one year alone, the typical participant in VOICE follow-up has a minimum of 13 scheduled face-to-face visits with multiple clinicians and counselors, 13 tests for HIV, 13 pregnancy tests, four sets of chemistry panels, two complete blood counts, and two complete pelvic exams. Adverse findings identified during follow-up are reviewed by clinicians at the site, network and sponsor level, and (in summary) by an independent data monitoring committee. This intensive system of pharmacovigilance is as appropriate in a clinical research setting as it is ultimately unsustainable, and potentially unnecessary, in a public sector delivery system, where concerns would be raised that the frequent follow-up used in VOICE would be complex, costly, burdensome, and not feasible in resource-constrained settings. When considering how ARV drugs might safely be monitored for prevention in such settings, it is useful to look at precedents from the HIV/AIDS treatment field.

The Development of AntiRetroviral Therapy in Africa (DART) trial was designed to investigate whether delivery of antiretroviral therapy (ART) with or without routine monitoring of CD4-cell counts for efficacy, and hematology and biochemistry for safety, led to similar outcomes in HIV-infected patients receiving ART who had already fulfilled clinical and CD4-count criteria to start ART.⁵ HIV ART is often managed without routine laboratory monitoring in Africa; however, prior to the DART trial, the effect of this approach was unknown. This trial investigated whether routine toxicity and efficacy monitoring of HIV-infected patients receiving ART had an important long-term effect on clinical outcomes in Africa.

In this open, non-inferiority trial in three centers in Uganda and one in Zimbabwe, 3321 symptomatic, ART-naive, HIV-infected adults with CD4 counts less than 200 cells per μL , starting ART, were randomly assigned to laboratory and clinical monitoring (LCM; n=1659) or clinically-driven monitoring (CDM; n=1662). Hematology, biochemistry, and CD4-cell counts were done every 12 weeks. In the LCM group, results were available to clinicians; in the CDM group, results (apart from CD4-cell count) could be requested if

clinically indicated and Grade 4 toxicities were available. Co-primary endpoints were new World Health Organization (WHO) stage 4 HIV events or death, and serious adverse events. Non-inferiority was defined as the upper 95% confidence limit for the hazard ratio (HR) for new WHO stage 4 events or death being no greater than 1.18. Analyses were by intention to treat.

5-year survival was 87% (95% confidence interval (CI) 85–88) in the CDM group and 90% (88–91) in the LCM group. There were 122 (7%) and 112 (7%) participants, respectively, lost to follow-up over median 4.9 years' follow-up. 459 (28%) participants receiving CDM versus 356 (21%) LCM had a new WHO stage 4 event or died (6.94 [95% CI 6.33–7.60] vs. 5.24 [4.72–5.81] per 100 person-years; absolute difference 1.70 per 100 person-years [0.87–2.54]; HR 1.31 [1.14–1.51]; $P=0.0001$). Differences in disease progression occurred starting in the third year on ART, whereas higher rates of change to second-line treatment were noted in LCM from the second year. 283 (17%) participants receiving CDM versus 260 (16%) LCM had a new serious adverse event (HR 1.12 [0.94–1.32]; $P=0.19$), with anemia being the most common (76 vs. 61 cases).

The results of DART indicate that ART can be delivered safely without routine laboratory monitoring for toxic effects, but differences in disease progression suggest a role for monitoring of CD4-cell count from the second year of ART to guide the switch to second-line treatment. These findings combined with the recently published WHO guidance (Antiretroviral Therapy for HIV infection in Adults and Adolescents: Recommendations for a public health approach, 2010 revision) are an important context when identifying possible strategies for monitoring ARV use in HIV-uninfected healthy women.

The use of ARVs for HIV prevention in healthy populations poses special challenges for public health. At the community level, the needs of the HIV-infected population must be taken into consideration, especially given the gaps existing in ARV treatment in resource-challenged areas of the HIV/acquired immunodeficiency syndrome (AIDS) epidemic. Risks and benefits at the individual and community level associated with ARV use for HIV prevention merit further study, and the safety of study participants must remain the highest priority in any trial, including MTN-018.

MTN-018 will obtain additional safety data on VOICE study products desired by regulators, and examine the potential for quarterly monitoring for ARV-based prevention agents. The monitoring strategy in this protocol reflects the input from a broad set of contributors, including VOICE site investigators, Microbicide Trials Network (MTN) physicians and scientists, MTN VOICE Community Working Group (CWG) members, HIV treatment and prevention advocates, and other stakeholders in the delivery of a successful HIV prevention agent. As a quarterly monitoring strategy is investigated, opportunities also exist to obtain critical information on adherence, potential development of antiretroviral resistance in participants newly HIV-infected, and possible diversion of study products, via sharing, selling, and/or theft.

2.1.2 Anticipating Community Concerns

In an effort to hear potential community concerns about MTN-018, opinions were gathered from VOICE site community education staff, Community Advisory Board members, and VOICE site community stakeholders on the MTN-018 trial concept. A range of opinions was noted, but several key themes emerged from the communities' feedback.

Although respondents did not uniformly acknowledge the existence of a black market for ARVs, they felt that the risk for sharing, theft and selling of ARVs was present, and that this posed a certain amount of risk for improper distribution of drugs within the community, including for use as ingredients in illicit drugs. Second, community respondents recognized the key role of male partner involvement in the successful implementation of MTN-018, as their opinions will likely impact a woman's decision to enroll in the trial, and their involvement might decrease the risk of social harm to participants. Also critical will be study messaging that clearly explains why MTN-018 is being conducted, including the rationale for selection of study product(s), and the justification for research on effective products, known to be partially effective, but not yet available in the public sector. Reimbursement to study participants must realistically cover transportation costs, and consideration should be given to reimbursing participants equally, whether they are randomized to the Monthly or the Quarterly Arm of MTN-018. Community representatives were interested in the potential for a Non-VOICE cohort to contribute to the understanding of product preference and adherence. Lastly, while the respondents were in favor of including the option of quarterly study visits, they noted the need for effective adherence counseling strategies, and for consideration of challenges that participants may face in the storage of a three-month supply of products. The MTN-018 study team is committed to developing effective strategies to address these concerns, with the continued input of community representatives within and external to the study team.

2.2 Results of the VOICE Trial

Results of the VOICE Trial will be included here in a modification to this protocol.

2.3 Study Product Description: Tenofovir disoproxil fumarate

A modification to this protocol will indicate whether this product will be included in MTN-018.

2.3.1 Description

Tenofovir disoproxil fumarate (TDF) is approved under the trade name Viread[®] for treatment of HIV-1 infection in adults.^{6,7} 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.

2.3.2 Mechanism of Action

Once absorbed, TDF is rapidly converted by diester hydrolysis to tenofovir.⁷ 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 .

2.3.3 Strength of Study Product

The strength of the TDF tablets will be the dose approved by the US Food and Drug Administration (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.⁷

2.4 Study Product Description: Emtricitabine/Tenofovir Disoproxil Fumarate (FTC)

A modification to this protocol will indicate whether this product will be included in MTN-018.

2.4.1 Description

FTC is approved by the FDA for treatment of HIV-1 infection in adults.⁸ FTC is administered once-daily, either as a single drug formulation (Emtriva®) or in fixed-dose combination with TDF (as Truvada®).⁹ FTC/TDF is approved by the FDA 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.

2.4.2 Mechanism of Action

FTC is a synthetic nucleoside analogue of cytidine and is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate.⁸ 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 .

2.4.3 Strength of Study Product

Coformulation of FTC and TDF has been approved by the FDA. 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 pharmacokinetic (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

2.5 Study Product Description: 1% Tenofovir Gel

A modification to this protocol will indicate whether this product will be included in MTN-018.

2.5.1 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. Further information is available in the current version of the TFV gel investigator's brochure.¹¹

2.5.2 Mechanism of Action

Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate.¹² 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 .

2.5.3 Strength of Study Product

The strength of the TFV gel will be the strength (1%) previously tested in HIV Prevention Trials Network (HPTN) 050 (Investigational New Drug (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), MTN-002 (IND 55,690), VOICE (MTN-003) (IND 55,690), RMP-02/MTN-006 (IND 73,382), MTN-007 (IND 73,382) and CAPRISA 004 (non-IND). The 4 mL application in this study delivers 40 mg of tenofovir to the vaginal compartment.

2.6 *In vitro* Studies

Data from *in vitro* studies relevant to MTN-018 are summarized below. Further information is available in the VOICE protocol¹³ and the study product Investigator Brochure and package inserts.^{7,14, 15}

2.6.1 *In vitro* Studies of Tenofovir

In vitro studies of tenofovir have demonstrated antiviral activity against laboratory and clinical isolates of HIV-1, as assessed in lymphoblastoid cell lines, primary monocyte/macrophage cells and peripheral blood lymphocytes.⁷ The EC₅₀ (50% effective concentration) values for tenofovir were in the range of 0.04 µM - 8.5 µM. 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).

HIV-1 isolates with reduced susceptibility to tenofovir have been selected *in vitro*. These viruses expressed a K65R mutation in RT and showed a 2- to 4-fold reduction in susceptibility to tenofovir. Of note, this mutation also confers increased susceptibility to some other nucleoside reverse transcriptase inhibitors (NRTIs), and is associated with approximately 50% reduction in the replicative capacity of HIV-1 (potentially resulting in a “less fit” virus).¹⁶ Tenofovir-resistant isolates of HIV-1 have been recovered from some patients treated with Viread[®] in combination with certain ARV agents.

Cross-resistance among certain NRTIs has been recognized. 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 lamivudine (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

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.⁸ The EC₅₀ values for FTC were in the range of 0.0013-0.64 µM (0.0003 – 0.158 µg/mL). 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).

FTC-resistant isolates of HIV have been selected *in vitro*.⁸ 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.

FTC-resistance isolates (M184V/I) were cross-resistant to 3TC and zalcitabine but retained susceptibility *in vitro* to didanosine, stavudine (d4T), tenofovir, zidovudine (ZDV), and non-nucleoside reverse transcriptase inhibitor (NNRTIs) (delavirdine,

efavirenz (EFV), and nevirapine (NVP)).⁸ 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 1% Tenofovir Gel

An assessment of TFV gel formulation included osmolality, viscosity, *in vitro* release, and permeability testing.¹¹ Safety was evaluated by measuring the effect on the viability of vaginal flora, peripheral blood mononuclear cells (PBMCs), epithelial cells, and ectocervical and colorectal explant tissues. For efficacy testing, PBMCs were cultured with tenofovir or vehicle control gels and HIV-1 representing subtypes A, B, and C. Additionally, polarized ectocervical and colorectal explant cultures were treated apically with either gel. Tenofovir was added basolaterally to simulate systemic application. All tissues were challenged with HIV-1 applied apically. Infection was assessed by measuring p24 by enzyme-linked immunosorbent assay (ELISA) on collected supernatants and immunohistochemistry for ectocervical explants. Formulation testing showed the TFV and vehicle control gels were >10 times isosmolar. Permeability through ectocervical tissue was variable but in all cases the receptor compartment drug concentration reached levels that inhibit HIV-1 infection *in vitro*. The gels were non-toxic toward vaginal flora, PBMCs, or epithelial cells. A transient reduction in epithelial monolayer integrity and epithelial fracture for ectocervical and colorectal explants was noted and likely due to the hyperosmolar nature of the formulation. Tenofovir gel prevented HIV-1 infection of PBMCs regardless of HIV-1 subtype. Topical and systemic TFV were effective at preventing HIV-1 infection of explant cultures.

2.6.4 Condom Compatibility Studies of 1% Tenofovir Gel

The compatibility of 1% TFV gel was also tested with lubricated male latex condoms.¹² A matched placebo gel and hydroxyethylcellulose (HEC) placebo gel 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 two application treatments of 1% TFV gel and matched placebo gel increased airburst volumes by 5 – 6 L compared with the baseline, and decreased airburst pressures by 0.2 kPa, implying a physical change to a more elastic condom. This slight change in physical properties suggests an interaction of the 1% TFV gel with the silicone lubricant, but does not indicate that the condoms are unsuitable for use in clinical studies.

2.7 Animal Studies

2.7.1 Animal Studies of Tenofovir and Tenofovir Disoproxil Fumarate

A broad range of pharmacokinetic, toxicology, carcinogenesis, mutagenesis, reproductive toxicity, fertility impairment and effectiveness studies have been performed for multiple formulations of tenofovir in a range of species, including rodents, dogs, and non-human primates. Detailed information on these studies is available in the VOICE protocol¹⁷ and the Investigator Brochure and package inserts for the study products.^{7,12,14}

2.7.2 Animal Studies of Emtricitabine

A broad range of pharmacokinetic, toxicology, carcinogenesis, mutagenesis, reproductive toxicity, fertility impairment and effectiveness studies have been performed in a range of species, including rodents, dogs, and non-human primates.^{8, 18} Detailed information on these studies is available in the VOICE protocol¹⁷ and the Investigator Brochure and package inserts for the study products.^{7,12,14}

2.8 Clinical Studies of Tenofovir and Emtricitabine

2.8.1 Tenofovir Disoproxil Fumarate for Treatment of HIV

Pharmacokinetics

Tenofovir disoproxil fumarate PK have been evaluated in healthy volunteers and HIV-1 infected individuals.⁷ Tenofovir PK are similar between these populations and between male and female patients. Oral bioavailability of TFV from TDF in fasted patients is approximately 25%. *In vitro* binding of TFV 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 area under the curve (AUC) values are 296 ± 90 ng/mL and 2287 ± 685 ng·hr/mL, respectively. Approximately 70-80% of the intravenous dose of TFV 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 TFV is approximately 17 hours. The PK of individual doses of TFV are dose-proportional over a TDF dose range of 75 to 600 mg and are not affected by repeated dosing.

Gilead Study 903

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-infected 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, aspartate aminotransferase (AST) or alanine transaminase (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.¹⁹ 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,²⁰ especially in patients with other medical problems or pre-existing renal dysfunction,²¹ although observational prospective studies tend to accord with Gilead Study 903 in a finding of absence or low frequency of significant renal dysfunction; when renal dysfunction occurs, it is generally predictable based on identifiable risk criteria.²² One study that followed 27 HIV-infected children treated with TDF for 96 weeks found no evidence of impaired glomerular or tubular renal function.²³

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 hepatitis B virus (HBV) and HIV and have discontinued TDF. Both TDF and FTC are highly active against HBV and are recommended as part of the ART regimens in HIV/HBV co-infected individuals.^{24,25} 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.^{26,27} Flares have typically been self-limited, but more serious liver decompensation has been reported.²⁸ 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 for at least several months with both clinical and laboratory follow-up among patients coinfecting with HIV and HBV after TDF and/or FTC are discontinued.

Pregnancy Outcomes

The Antiretroviral Pregnancy Registry (APR) 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 07/31/2010 show 25 defects among 981 first trimester TDF exposures.²⁹ This rate (2.5%) is not elevated compared to 13/584 (2.2%) after second/third trimester exposure, the 2.72% background rate of defects reported by the Centers for Disease Control Metropolitan Atlanta Congenital Defect Program³⁰, or the generally accepted background rate for birth defects in the US population (approximately 3 – 4%). The APR estimates that it captures data on about 15% of HIV-infected women giving birth each year in the US and a small fraction of those from other countries. Based on that estimate, over 10,000 pregnant women have likely used oral tenofovir in the US alone. In addition, the APR conducts a specific review each reporting period of renal and bone abnormalities reported after in utero tenofovir exposure. No increased risk of these abnormalities has been detected.

The safety of oral tenofovir as treatment for HIV-infected pregnant women has been examined among 110 pregnant women and their infants in multiple studies. Of note, Habert and colleagues reported on data from all women who had received TDF in the Frankfurt HIV Cohort.³¹ From December 2002 until December 2007, 76 pregnant women received TDF-containing regimens. No TDF toxicity was observed in the children; two women stopped TDF, because of exanthema (1) and nausea (1). None of the observed malformations was associated with TDF.

In a retrospective case series, the charts of pregnant HIV-infected women who received highly active antiretroviral therapy (HAART) that included tenofovir were reviewed.³² Fifteen HIV-infected women with limited treatment options were prescribed HAART

containing tenofovir during 16 pregnancies. In utero tenofovir exposure was a median of 127 days (range 6-259). Tenofovir was well tolerated by all women throughout pregnancy. There were 15 successful deliveries occurring at a median (range) of 36 weeks (30-40), with a median birth weight of 3255 g (1135-3610). Complications, including 1 spontaneous abortion, occurred in 9 pregnancies and were not attributed to tenofovir. Eleven (73%) women had abnormal laboratory results, including 6 who experienced Grade 1 hemoglobin abnormalities; 4 of these women had preexisting anemia. Fourteen infants demonstrated normal growth and development for weight and height at birth, as well as during the 12-month follow-up period; no congenital malformations were documented.

2.8.2 Emtricitabine for Treatment of HIV

Pharmacokinetics

Following oral administration, FTC is rapidly absorbed with peak plasma concentrations occurring at 1-2 hours post-dose.⁸ *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.⁸ 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 study, FTC-301A, 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.³³ 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).³⁴ 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 has not been studied in controlled clinical trials; however, registry data to date are reassuring. 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.⁸ 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.

Pregnancy Outcomes

As of 7/31/10, 6 defects among 542 first-trimester exposures to FTC and 9 defects among 344 exposures during pregnancy after the first trimester had been reported.²⁹ This rate is not elevated compared to the 2.72% background rate of defects reported by the Centers for Disease Control Metropolitan Atlanta Congenital Defect Program³⁰, or the generally accepted background rate for birth defects (approximately 3 - 4%).

2.8.3 Emtricitabine and Tenofovir Disoproxil Fumarate in Combination (Truvada[®]) for Treatment of HIV

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. The steady state PK of FTC and tenofovir were unaffected when FTC and TDF were administered together versus each agent dosed alone.¹⁴

Truvada[®] may be administered with or without food.¹⁴ *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

Several studies have assessed the safety and efficacy of FTC with TDF.¹⁴ 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[®].

Gilead Study 934 is a Phase 3, randomized, open-label, non-inferiority, multi-center 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 Combivir[®]) + EFV QD in ARV-naïve, HIV-1-infected participants. 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. All participants with confirmed >400 copies/mL of HIV-1 ribonucleic acid (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. Usually symptoms are self-limiting; however, serious complications have been reported. Causal relationship to TDF or FTC discontinuation is unknown. Participants coinfecting with 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.

2.8.4 TDF and FTC/TDF for Treatment of HIV-infected Pregnant Women and as PMTCT

Data from PACTG/IMPAACT 394 support that single-dose TDF with and without FTC is safe and well-tolerated among mothers and infants.³⁵ The safety of this combination in a multi-dose regimen was also noted in TEmAA (Tenofovir/Emtricitabine for PMTCT in Africa and Asia) ANRS 12109.³⁶ Tenofovir has been deemed an acceptable drug during pregnancy according to US guidelines under certain circumstances, including intolerance or resistance to zidovudine and in the presence of HBV/HIV co-infection.³⁷

2.8.5 TDF and FTC/TDF for HIV Prevention in Healthy Adults

Additional safety information from clinical studies on the TDF 300 mg tablet is available in the Viread package insert.⁷

FHI TDF West African Trial

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. 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).³⁸ 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.

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).³⁸ 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 acquired HIV infection while on TDF revealed no drug-resistance mutations.

CDC 4323

CDC 4323 was a Phase 2 extended safety study of tenofovir-disoproxil fumarate (TDF) among HIV-negative men carried out at three US sites. This trial was designed to examine the safety of TDF for HIV prevention in HIV-negative men who have sex with

men. Preliminary data announced in July 2010 showed no serious safety concerns on the basis of the preliminary analysis.³⁹

iPrEx Study

The iPrEx study, a randomized, double-blind, Phase 3 clinical trial conducted in the United States, Brazil, Ecuador, Peru, South Africa and Thailand was designed to determine whether FTC/TDF 200 mg/300 mg tablets could safely and effectively prevent HIV infection among men who have sex with men (MSM) and transgendered women who have sex with men, when taken daily.² Participants were randomized to receive either oral FTC/TDF or placebo. All participants were routinely counseled about safe sex practices, provided condoms and treated for sexually transmitted infections. Study participants were followed for 3324 person-years (median, 1.2 years; maximum, 2.8 years). Participants who took the daily dose of oral FTC/TDF experienced an average of 44% fewer HIV infections than those who received a placebo pill (95% CI, 15 to 63; $P=0.005$). A total of 100 participants seroconverted while enrolled in the iPrEx study. Of those, 36 HIV infections occurred among the 1,251 participants randomized to receive FTC/TDF compared with 64 HIV infections among the 1,248 participants who were randomized to receive placebo. Oral FTC/TDF was found to be most effective among participants who were adherent to the daily drug regimen. Participants who took the drug on 50% or more days as measured by pill count, self-report, and dispensation records, experienced 50.2% fewer HIV infections (95% CI, 18 to 70; $P=0.006$). Those who took the drug on 90% or more days presented 73% fewer HIV infections (95% CI, 41 to 88; $P=0.001$). Overall, efficacy was greatest among participants who, at the time of enrollment, were at highest risk for HIV acquisition (58%), as captured by self-reports of unprotected receptive anal intercourse. Drug resistance mutations to FTC occurred in 3 participants, 2 of these from the FTC/TDF arm and one from the placebo arm, and all 3 of whom were infected at the time of enrollment. No resistance was observed in any participant with incident HIV infection.

FEM-PrEP Study

The FEM-PrEP Study is a Phase 3, randomized, placebo-controlled, trial of the effectiveness of daily oral FTC/TDF for HIV prevention among HIV-uninfected women in Kenya, South Africa and Tanzania. The FEM-PrEP study enrolled HIV-negative women between the ages of 18 and 35 who were at higher risk for HIV. Higher risk was defined as: 1) has had at least one vaginal sex act in the last two weeks, or 2) has had more than one sexual partner in the last month. Only women who used study-approved contraception at enrollment were eligible for participation. The study was conducted at four sites in three countries (Bondo, Kenya; Bloemfontein and Pretoria, South Africa; and Arusha, Tanzania). All participants in the study were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for sexually transmitted infections. This trial was designed to close at 72 HIV endpoints; however, during a scheduled review by the trial's Independent Data Monitoring Committee (IDMC) on April 7, 2011, the trial had accumulated 56 endpoints, with 28 endpoints in the FTC/TDF arm and 28 endpoints in the placebo arm, leaving 16 endpoints until the trial was complete.⁴² The trial was stopped early due to futility. No significant safety concerns were noted.

Pregnancy rates were noted to be higher in women taking hormonal contraceptives (at the onset of participation) and FTC/TDF compared with those taking hormonal contraceptives and the placebo. Final study results are expected to be available in late 2011 or early 2012.

TDF2

The TDF2 Study is a Phase 2B study that assessed the safety, adherence and efficacy of daily oral FTC/TDF in 1,200 HIV-uninfected heterosexual male and female participants aged 18-39.⁴⁰ The trial, originally known as the Botswana PrEP Study, began in 2005 as a Phase III trial of TDF. In 2007, the study product was changed to FTC/TDF. In 2009, the completed enrollment of 1,200 participants, but due to lower than expected HIV incidence and suboptimal retention, it was determined that the study would not be able to answer its primary objective of efficacy. The trial continued, but with intent to evaluate safety and adherence. Of the 1,200 participants in the TDF2 Study, 45% of whom were women, 601 were randomly assigned to FTC/TDF, and 599 were assigned to placebo. All participants were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for sexually transmitted infections. During the study, 33 of 1,200 participants acquired HIV (nine of the 601 participants on the FTC/TDF arm and 24 participants of the 599 on the placebo arm), corresponding to a 62.6% reduction in HIV acquisition for those assigned to FTC/TDF, compared to placebo (HR 0.37, CI 21.5-83.4, P = 0.013). Among 21 total HIV endpoints in women in the trial, 7 were in the FTC/TDF arm and 14 were in the placebo arm. While results for the subset of women in the trial did not meet statistical significance (HR 0.51, CI -0.217-80.8, P = 0.107), a non-ITT analysis among women thought to have a supply of study drug (3 HIV endpoints in the FTC/TDF arm and 13 in the placebo arm) found an estimated efficacy of 75.5%, P = 0.021. No significant safety concerns were noted, though participants randomized to the FTC/TDF arm did experience more nausea, vomiting, and dizziness than those randomized to placebo.

Partners PrEP Study

The Partners PrEP Study is a double-blind, placebo-controlled, Phase 3 clinical trial to assess the safety and efficacy of daily oral PrEP for the prevention of HIV infection within heterosexual African HIV serodiscordant couples, using TDF alone or in the fixed dose combination of FTC/TDF.⁴¹ The Partners PrEP Study enrolled 4,758 HIV serodiscordant couples from 9 clinical trial sites in Kenya and Uganda. HIV-uninfected partners were randomly assigned in equal numbers to one of three study groups (TDF tablet, FTC/TDF tablet, and placebo tablet). Of the HIV-uninfected partners, 38% were women. The study began in July 2008 and enrollment was completed in November 2010. All study participants received a comprehensive package of HIV prevention services, which included intensive safer sex counseling (both individually and as a couple), HIV testing, free condoms, testing and treatment for sexually transmitted infections, and monitoring and care for HIV infection. The Partners PrEP Study DSMB at its 10 July 2011 meeting reviewed data collected through 31 May 2011. Through that date, a total of 78 HIV infections occurred in the study: 18 among those assigned TDF, 13 among those assigned FTC/TDF, and 47 among those assigned placebo. Those

who received TDF had an average of 62% fewer HIV infections (95% CI 34 to 78, P = 0.0003) and those who received FTC/TDF had 73% fewer HIV infections (95% CI 49 - 85, P <0.0001) than those who received placebo. Subgroup analysis by gender showed that both TDF and FTC/TDF significantly reduced HIV risk in both men and women within serodiscordant partnerships. For TDF, the HIV risk reduction was 68% for women (CI 29-85%, P = 0.01) and 55% for men (CI 4-79%, P = 0.04). For FTC/TDF, the HIV risk reduction was 62% for women (CI 19-82%, P = 0.01) and 83% for men (CI 49-94%, P = 0.001). Among 42 total HIV infections in women, 8 were in the TDF arm, 9 were in the FTC/TDF arm, and 25 were in the placebo arm. The rate of serious medical events was similar for those assigned to TDF, FTC/TDF, and placebo. Adherence to study drug was very high, with greater than 97% of dispensed doses of study drugs taken, according to self-report and pill counts. More than 95% of participants were retained in follow-up. Given the efficacy results, the Partners PrEP DSMB recommended that administration of placebo be suspended; participants initially randomized to TDF and FTC/TDF will remain on those medications, and those initially randomized to placebo will start receiving TDF or FTC/TDF via random assignment.

Bangkok Tenofovir Study

The Bangkok CDC Tenofovir study is a Phase 3 randomized, placebo-controlled study of daily TDF among injection drug users (IDUs) that is assessing the safety and efficacy of daily tenofovir to prevent HIV infection among IDUs. Assessment of changes in HIV-associated risk behaviors, adherence to study drug, and, among IDU who become HIV-infected during the trial, evaluation of HIV viral load set point, CD4 counts, genetic characterization of infecting HIV viruses, and antiretroviral resistance will also be done. Results are anticipated in 2012.

2.8.6 Clinical Studies of 1% Tenofovir Gel

Pharmacokinetics

A Phase 1 Safety and Acceptability Study of the Vaginal Microbicide Agent PMPA Gel (HPTN 050) is a completed study of tenofovir vaginal gel with published data.⁴³ 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. Pharmacokinetic evaluations were performed in 25 women. Systemic absorption was limited (maximum serum levels 3.0-25.8 ng/mL) and levels were below the limit of detection in 11/25 participants.

A study of the pharmacokinetics of tenofovir gel was conducted among 49 sexually-abstinent women in the USA and Dominican Republic (CONRAD A04-095, IND 73,382).⁴⁴ The following are results from a subset (n=21) who completed the single-dose phase. Following an intravaginal dose (4 g) of TFV gel, blood samples were obtained at 0.5, 1, 2, 4, 6, 8, and 24 hr(s) from all participants. Participants were randomized to one of seven time-points [0.5, 1, 2, 4, 6, 8, and 24 hr(s)] for vaginal fluid collection and vaginal biopsies. Total TFV was measured in blood plasma, fluid, and biopsies. Most blood plasma TFV concentrations were below 5 ng/mL. Four had higher values (up to 19.5 ng/mL) which were not sustained. Vaginal fluid concentrations were high, generally $1.5-5.0 \times 10^6$ ng/mL through 8 hrs and $4.5-47.1 \times 10^4$ ng/mL at 24 hrs.

The mean concentration in vaginal tissue at 0.5, 1, 2, 4, 6, 8 and 24 hr(s) were 275×10^3 , 450×10^3 , 186×10^3 , 89×10^3 , 69×10^3 , 24×10^3 and 15×10^3 ng/g of tissue, respectively, (lower limit of quantitation = 1 ng/mL) with a peak at 1-4 hrs. Vaginal fluid elimination appeared linear. Tissue elimination appeared to follow a multi-compartment model. Total TFV was detectable in vaginal tissue and fluid up to 24 hrs post single-dose exposure.

MTN-001 was a Phase 2 study of adherence to, and pharmacokinetics of, oral and vaginal preparations of tenofovir among 144 sexually active HIV-negative women at sites in Uganda, South Africa and the United States.⁴⁵ Each participant received 6 weeks of oral, 6 weeks of vaginal, and 6 weeks of dual (vaginal and oral) tenofovir; the sequence of the dosing periods was randomly assigned and the periods were separated with one week of no study product. Concentrations of tenofovir in vaginal tissue and blood were found to be 2,352 femtomols (fmol) of TFV-PP per mg of vaginal tissue after tenofovir gel use, whereas, with daily TDF tablet, the concentration in tissue was less than 17 fmol/mg. The concentration of TDF-PP in PBMC associated with oral TDF use was 52 fmol/million cells and less than 5 fmol/million cells with the vaginal gel. The combined use of oral and vaginal tenofovir did not significantly impact the tissue or blood concentrations.

Safety

In HPTN 050 the 1% tenofovir gel formulation was well tolerated in both HIV-uninfected and infected women.⁴³ 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.

In MTN-001, all three daily regimens (vaginal gel, oral tablet and the two combined) were found to be safe and well-tolerated. Nausea occurred in 15 percent of the women when using the tablet and 14 percent when the gel and tablet were used together. Vaginal itching and irritation were the most common side effects with the gel.

In a male tolerance study (CONRAD A04-099/IND 73,382), 1% tenofovir gel was well tolerated in men following seven days of once-daily penile exposure.⁴⁶ 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.

HPTN 059 was a Phase 2 four-arm, three-site, randomized, controlled trial comparing 1% tenofovir gel used once-daily and gel used prior to intercourse, to placebo gel, with 6 months gel exposure and follow-up.⁴⁷ 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 a once-daily or coitally-dependent group, and received either tenofovir or placebo gel.

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.⁴⁷ 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.

Pregnancy Outcomes

MTN-002 was a Phase 1, single-dose study of 1% tenofovir gel in term pregnancy. Sixteen HIV-negative healthy pregnant women undergoing planned cesarean delivery received a single dose of 1% tenofovir gel prior to delivery. In this study, no adverse pregnancy outcomes related to study product were noted.

Within CAPRISA 004, the overall pregnancy rate was 4.0 per 100 woman-years; 3.2 per 100 woman-years in the tenofovir arm and 4.7 per 100 woman-years in the placebo arm ($P = 0.183$).¹ At the time of CAPRISA 004 analysis, there were six ongoing pregnancies while 58.3% of the remaining 48 pregnancies had resulted in a full-term live birth. There were no significant differences in pregnancy outcomes by study arm and there were no congenital anomalies. A total of 20.9 woman-years of follow-up occurred while women were not using gel due to pregnancy.

Pregnancy registry (MTN-016) data for VOICE participants with first trimester exposure to study gel (TFV and placebo gel) are reviewed at least annually by the MTN Study Monitoring Committee. Outcomes from MTN-016 will be unblinded when VOICE is unblinded (projected late 2012).

Resistance

In HPTN 050, no new resistance mutations evolved in plasma or cervicovaginal lavage after 14 days of tenofovir gel use among 22 HIV-positive women, although 3 women had plasma mutations associated with low level tenofovir resistance identified at both Days 0 and 14 (M41L, L210M, \pm T215I/Y).⁴³

Effectiveness

The CAPRISA 004 trial was a Phase 2B trial which was designed to assess the effectiveness and safety of a 1% tenofovir vaginal gel, for the prevention of HIV acquisition in women.¹ A double-blind, randomized controlled trial was conducted

comparing TFV gel ($n = 445$) with placebo gel ($n = 444$) when used in a pericoital regimen, in sexually active, HIV-uninfected 18 to 40-year-old women in urban and rural KwaZulu-Natal, South Africa. HIV serostatus, safety, sexual behavior and gel and condom use were assessed at monthly follow-up visits for 30 months. HIV incidence in the TFV gel arm was 5.6 per 100 women-years, compared to 9.1 per 100 women-years in the placebo gel arm (incidence rate ratio = 0.61; $P = 0.017$). Tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence. No differences in the overall adverse event rates were observed. Additionally, the use of TFV gel was associated with 51% protection against HSV-2 (CI: 22% - 70%).

2.9 Rationale

2.9.1 Study Design

The safety and effectiveness profile for VOICE study products is still unknown. However, based on evidence from other clinical trials of the same products, it is prudent to be prepared for the possibility that at least one or more VOICE study products will be found to be safe and effective as prophylaxis for HIV.^{1,2} It has also been noted that regulatory entities will require additional safety data on the use of these products in healthy, HIV-uninfected women before licensure is granted. Therefore, the primary focus of MTN-018 is the collection of additional safety data and the examination of multiple approaches to safety monitoring.

While there are many facets of the future roll-out of ARV-based prevention that are worthy of study, including potential impacts on behavior, optimizing drug adherence, and implementation strategies for the public sector, all future approaches must be grounded in an evidence base for safe management of these drugs in healthy populations. MTN-018 will contribute to this evidence base by describing the safety outcomes associated with both monthly and quarterly monitoring schedules for women using ARVs for HIV prevention. Roll-out of ARV-based prevention in the public sector in resource-limited environments will likely require a pharmacovigilance strategy that is less costly and time-consuming than the options described here. However, MTN-018 will provide valuable information that will help guide the formulation of those strategies, which may eventually rely heavily on the clinical judgment of local providers of care.

2.9.2 Inclusion of Non-VOICE Cohort

The VOICE Cohort is selective in ways that could potentially limit understanding of issues that might arise in real world roll out of microbicide and PrEP products.

- No women < 20 years of age will likely be represented in the VOICE Cohort because 18 years of age was the minimum for VOICE; those eligible for MTN-018 will have completed 12-36 months enrollment in VOICE, plus the months until unblinding, making them at least age 20, presuming their reported age in VOICE was true and correct.

- They may be lower risk than the general population of women, because those on placebo, eligible for MTN-018, did not acquire HIV in VOICE.
- They are likely to be more adherent than the general population of women because those eligible for MTN-018 did not acquire HIV if on active product.
- The intensive counseling that they have been exposed to during VOICE has likely impacted on their risk behavior and adherence to product.

The MTN-018 objectives are strengthened by the addition of the Non-VOICE Cohort for several reasons. The MTN-018 research questions about adherence in different visit schedules and determinants of product choice are best addressed with trial naïve participants. The MTN-018 VOICE Cohort will have adhered to the VOICE schedule of monthly visits for at least a year, making it difficult to assess adherence, given their history of adhering to the more conservative strategy for follow-up. Additionally, with former VOICE participants, “choice” of product represents continuation of VOICE-assigned product or switching to a new product from a VOICE assigned product. Better insight into real-world study product adherence will be gained by assessing an HIV prevention trial-naïve cohort, as well as former VOICE participants, who already have experience adhering to a daily regimen. However, women within the VOICE Cohort represent long-term users and their participation in the trial represents measurement of long-term adherence/study continuation, a critically important area for understanding the feasibility of long-term use of chemoprevention. Within both the VOICE and Non-VOICE Cohorts we will be able to compare “real world” adherence and to assess whether it varies by risk perceptions, product choice, and timing of follow-up visits, quarterly vs. monthly.

With a Non-VOICE Cohort, we will be able to examine distribution of initial product choice and the determinants of that choice, which is very critical information for roll out in the real world. As noted above, former VOICE participants only allow for analysis of product switching and continuation. Moreover, if limited to former VOICE participants, we will have to analyze the data separately by VOICE study arm, as those who were in the placebo arm may experience side effects differently than those in the active arms; these participants did not face any side effects related to active study product while in VOICE. Additionally, the inclusion of a Non-VOICE Cohort will allow examination of whether participants and their partners are more likely to engage in risky behavior after initiating product use (behavioral disinhibition) and whether this varies by product choice. (With former VOICE participants we do not have baseline behavioral measures “untainted” by trial participation so we are unable to compare risk behavior prior to active product use with behavior after initiation of product use).

As with the former VOICE participants, at the Enrollment Visit, each Non-VOICE Cohort participant will select the MTN-018 study product that she prefers to use for the next month. At the Month 1 Visit, each study participant will have the opportunity to switch to the other product. The participant will then enter into approximately 11 additional months of scheduled follow-up on study product. As with former VOICE participants, the adherence counseling will be streamlined to more closely resemble counseling that would be followed in real world settings.

As with VOICE participants, Non-VOICE Cohort participants will be randomized to one of two types of follow-up:

- Monthly
- Quarterly

Behavioral data collection will be the same for Non-VOICE participants as it is for former VOICE participants. The trial is also anticipated to incorporate at least one objective measure of adherence.

2.9.3 Contraception and Pregnancy Intention

A range of studies supports the assertion that acquisition of HIV among pregnant women is common in many parts of the world, and equals or exceeds rates in non-pregnant women. Of note, in a prospective study, Gray et al described HIV incidence rates of 2.3 per 100 person years during pregnancy, 1.3 per 100 person years during breastfeeding, and 1.1 per 100 person years in non-pregnant and non-lactating women.⁴⁸ The adjusted incidence rate ratios were 2.16 (95% CI 1.39-3.37) during pregnancy and 1.16 (0.82-1.63) during breastfeeding. In the United States, 11% of 54 women with positive HIV rapid tests at delivery had primary infection in pregnancy.⁴⁹ A retrospective study of women previously identified as HIV seronegative during antenatal care in Kenya found early postpartum testing consistent with an estimated HIV-1 incidence of 6.8 (95% CI: 5.1-8.8) per 100 woman-years.⁹ In addition, HIV seroconversion during pregnancy results in higher risk of mother-to-child-transmission of HIV.^{15,50} Thus, the need to do study interventions for prevention of maternal HIV during pregnancy is high.

As previously noted in this protocol, reassuring pregnancy outcome data are available for oral TDF and oral FTC/TDF in the context of HIV treatment and PMTCT, and further accumulation of pregnancy data for TFV gel are in progress. With this reassuring data in mind, as well as the critical need to better understand the safety of HIV chemoprevention in pregnancy, the MTN-018 protocol removes several barriers related to contraceptive use and pregnancy intention. There are ample data to support the idea that this shift in eligibility criteria does not pose undue risk to pregnant women or their infants

To be eligible for MTN-003, women must be willing to use an effective method of contraception and must agree to delay childbearing while enrolled in the study. These inclusion criteria have been removed from MTN-018 for both individual and study-related reasons. From the perspective of an individual participant, requiring a woman to delay her childbearing yet another 14 months in addition to 24 months required by MTN-003 is unrealistic. In the countries in which this study will be conducted, the average number of children per woman ranges from 2.8 to 6.75. An important aspect of MTN-018 is to provide effective protection from sexually transmitted HIV to past participants. Being more inclusive at screening and recognizing that women have different fertility

intentions facilitates that goal. Furthermore, from a study perspective, imposing these requirements at screening would move MTN-018 one step further from mimicking real world conditions, an important aspiration of the study, in some respects. As plans for rolling out effective prevention agents are developed, restricting access to these products to women who vow not to become pregnant and who demonstrate that they are on effective contraception is unrealistic.

In MTN-018, contraceptive counseling will be provided at every visit as needed and, as in MTN-003, the provision of contraception will take place at the site level, facilitating participants' access to effective methods. In addition, pregnancy tests will be performed at every scheduled visit. Participants will be counseled to return to the clinic for a pregnancy test should they miss a menses and are known to be at risk of pregnancy.

2.9.4 Behavioral Research

VOICE is unique in that women participating are randomized to two different drug delivery systems – oral pill or vaginal gel. CHOICE will correspondingly be a unique open-label study in that it has potential to include more than one type of delivery system for chemoprevention, and moreover, will permit women to choose, providing an opportunity to answer behavioral research questions about preferences between types of products. This will enable the study to assess which product is preferred and to investigate the determinants of product choice, specifically whether there are differences by age, educational level, partnership status, sexual behavior, parity, and locale, information that will contribute to program planning for future HIV chemoprevention rollout.

Beyond the question of product preference, another important issue for HIV prevention concerns behavior change among those who know they have protection from the product. Little data exist on risk behavior while on HIV chemoprevention. One study from Ghana did not report an increase among women in the trial.⁵¹ Moreover, data from male circumcision trials in Africa found little evidence of behavioral disinhibition.^{52,53, 54} While such findings are encouraging, there are reasons to be concerned about the likelihood of increased risk outside clinical trial settings where counseling on partner reduction and condom use and follow-up are much less intensive. Indeed, in a recent survey, over one-third of men who have sex with men, who indicated an intention to use PrEP if effective, reported they would be likely to decrease condom use while on PrEP⁶. Until there is evidence from open-label studies on HIV chemoprevention, the level of behavioral disinhibition or risk compensation will be unknown. A comparison of the pattern of behaviors of the women in CHOICE will allow for an assessment of behavioral disinhibition and/or risk compensation.

2.9.5 Safety Monitoring Strategy

The decision to assess baseline renal, hepatic, and hematologic function and limit enrollment to healthy women stems from the protocol team's desire to minimize participant risk in this study of an agent intended for use in healthy women. The team

acknowledges that the risk benefit ratio for participation in a trial is dramatically influenced by the indication for therapy.

The current WHO guideline for antiretroviral use in HIV-positive individuals suggests that laboratory monitoring should not be a barrier to initiating antiretroviral therapy. Once on therapy, the guideline suggests monitoring creatinine clearance in patients with underlying renal disease every 6 months, if feasible, for patients on a tenofovir-based treatment; otherwise, drug toxicity laboratory monitoring should be symptom-directed. For TDF-containing regimens, creatinine clearance calculation is recommended, if feasible, before initiation of drug and every 6 months. Creatinine clearance monitoring is recommended in those with underlying renal disease, of older age groups, and with low body weight or other renal risk factors such as diabetes or hypertension.

Due to the potentially significant although rare possibility of tubular dysfunction with use of tenofovir, all MTN-018 participants will have their renal function checked regularly via clinical evaluation and creatinine monitoring throughout study follow-up. However, minimizing the complexity of laboratory evaluation is imperative if these products are expected to be rolled out in resource-limited settings. While creatinine clearance, which accounts for weight and gender, may be more sensitive than creatinine in detecting renal dysfunction in a high-risk population, in a population of healthy young women, there is no evidence that it is more useful. Finally, serum phosphate was not a reliable marker for safety in MTN-001. High-grade phosphate abnormalities were rarely confirmed and were subject to natural variation, thus making interpretation difficult.

While the WHO guidelines for ARV use do not endorse checking transaminases in an asymptomatic participant, the MTN-018 protocol does include this evaluation, periodically. While clinically significant elevated transaminases are usually associated with symptomatology, in a research study assessing the safety of different monitoring strategies, checking for abnormalities in asymptomatic participants and monitoring trends has value.

2.9.6 Management of Signs of Acute Seroconversion

Previous studies of oral and topical ARVs for HIV prevention have demonstrated partial efficacy, and HIV seroconversions are expected to occur in MTN-018, as they would during rollout of either or both ARV products. It is also expected that the prescription of ARV-based chemoprevention would include advice on seroconversion symptoms and signs to facilitate its recognition and decrease the time during which microbicides and PrEP are administered to HIV infected individuals, so reducing the risk of developing ARV resistance.

Approximately 75% of individuals who become infected with HIV develop signs and symptoms of primary HIV infection that typically appear a few days to a few weeks after HIV exposure. The DHHS reports fever (96%), lymphadenopathy (74%), pharyngitis (70%), rash (79%), diarrhea (32%), headache (32%), myalgia/arthralgia (54%), nausea (27%), hepatomegaly (14%), weight loss (13%), and neurological signs (12%) at HIV

seroconversion.⁵⁵ These signs and symptoms are similar to those of many other illnesses including other viral syndromes and as a result, acute HIV seroconversion is frequently unrecognized by both at-risk individuals and by clinicians in acute care settings.

There is no guidance available as to the frequency of primary HIV infection signs and symptoms in African populations. In MTN-018 the clinical algorithm for detection of possible HIV seroconversion is based on participant reported 'hard' signs of rash and fever only, excluding more non-specific symptoms that commonly occur in association with other etiologies. This strategy aims to focus resources on those individuals most likely to have a seroconversion illness based on the presence of high-frequency signs, to prevent individuals taking product for more than one month (after which ARV resistance becomes more likely)⁵⁶, and to reduce the time off effective product in participants at risk of HIV infection.

3 OBJECTIVES

3.1 Primary Objective

1. **Safety.** To compare the safety profiles associated with two different strategies of follow-up for participants taking daily study product
2. **Amount of Time Off Study Product.** To compare total amount of time off product associated with two different strategies of follow-up for participants taking daily study product

3.2 Secondary Objectives

1. **Drug Resistance.** To assess the frequency of HIV-1 drug resistance in women who acquire HIV-1 infection while using study product who are monitored for HIV seroconversion monthly and quarterly
2. **Product Choice (if more than one product is selected to move forward in MTN-018).** To identify the determinants of product choice and product switching within the VOICE and Non-VOICE Cohorts
3. **Adherence.** To compare study product adherence between the VOICE cohort and the Non-VOICE cohort
4. **HIV Seroconversion Outcomes.** To describe participant HIV seroconversion outcomes associated with each study group

3.3 Exploratory Objectives

1. **Pharmacokinetics.** To evaluate the potential relationship between plasma drug concentrations and study outcomes
2. **Product Choice.** To compare product choice by VOICE arm (active vs. placebo)
3. **Study Product Diversion.** To describe product sharing, selling, and theft and to assess whether these vary by visit schedule (Monthly vs. Quarterly Arms) and among Quarterly Arm by timing of study product resupply
4. **Adherence.** To compare adherence by follow-up interval (Monthly vs. Quarterly)
5. **Perceptions of Efficacy.** To determine if understanding of partial efficacy affects product choice, adherence and risk behavior
6. **Product Use Patterns.** To determine if use of product is linked to timing of sex and if this differs by product
7. **Condom Use.** To measure differences in condom use by product
8. **Acute Seroconversion.** To establish the predictive value of participant-identified clinical signs to predict HIV seroconversion in a population of women at risk of HIV

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-018 is a Phase 3B, open-label, multi-site, randomized trial. Following the release of VOICE results, and sponsor approval for implementation, eligible VOICE participants and a Non-VOICE cohort will have the option to enroll in MTN-018.

At the Enrollment Visit, and provided that more than one product is selected to move forward in MTN-018, each participant will select the MTN-018 study product that she prefers to use for the first month. For example, a woman randomized to vaginal gel in VOICE would have the option to select either gel or tablet in MTN-018, provided both are study products in MTN-018.

At the Month 1 Visit, and provided that more than one product is selected to move forward in MTN-018, each study participant identifies which product she would like to use (through Month 12). She will be asked about the reason(s) for her study product selection. The participant will then be randomized to Monthly or Quarterly follow-up, and enter into approximately 11 additional months of scheduled follow-up on study product.

However, participants who enroll more than six months after the onset of the study site's accrual period will have a contracted period of follow-up on product. Participants go off study product at follow-up Month 12 and return next at follow-up Month 14 for a Termination Visit, at which point participants will undergo HIV testing to assess for possible masked HIV infection.

4.2 Summary of Major Endpoints

For the primary objectives, endpoints will include Grade 3 and higher clinical AEs; Grade 2 and higher laboratory AEs in the categories of AST, ALT, and creatinine; and days off study product.

For the secondary objectives on drug-resistance mutations and HIV-1 seroconversion, endpoints will include, respectively, HIV drug-resistance mutations among participants who acquire HIV-1, as measured by genotypic methods; study product choice based upon study product selection and product switch; adherence based upon study product counts, participant self-report, study drug levels and/or remote data collection (at sites with capacity; and, HIV-1 seroconversion according to the algorithm specified in the protocol.

4.3 Description of Study Population

The MTN-018 study population will consist of the following two cohorts:

- 1) **VOICE Cohort.** Former VOICE participants who are healthy, HIV-uninfected, and meet other MTN-018 eligibility criteria; and
- 2) **Non-VOICE Cohort.** Healthy, HIV-uninfected women who are not pregnant or breastfeeding and meet MTN-018 eligibility criteria, but with no previous history of participation in VOICE or any other HIV prevention trial.

4.4 Time to Complete Accrual

The time to complete accrual in MTN-018 is anticipated to be approximately 6 to 9 months.

4.5 Study Groups

Study arms include Monthly and Quarterly Arms. Individual study groups depend upon selection of study product(s) for MTN-018. Groups may include:

- 1% TFV vaginal gel: monthly follow-up (Monthly Gel)
- 1% TFV vaginal gel: quarterly follow-up (Quarterly Gel)
- TDF 300 mg tablet, monthly follow-up (Monthly TDF)
- TDF 300 mg tablet, quarterly follow-up (Quarterly TDF)
- FTC/TDF 200 mg/300 mg tablet, monthly follow-up (Monthly Truvada)

- FTC/TDF 200 mg/300 mg tablet, quarterly follow-up (Quarterly Truvada)

4.6 Expected Duration of Participation

The expected duration of participation for an individual participant enrolled in MTN-018 is approximately 14 months, including the 2 months post product use follow-up. Participants who enroll more than 6 months after the onset of the study site's accrual period may have a shortened follow-up period.

4.7 Sites

Study sites will be former VOICE sites.

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 study site cohorts of VOICE participants as well as other recruitment populations (for the Non-VOICE Cohort). Efforts will be made by study sites to maintain contact with VOICE participants between the end of follow-up in VOICE and the initiation of MTN-018, to provide VOICE study results to VOICE participants and information regarding MTN-018. 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. Group educational sessions may be utilized as part of site strategies for participant education during the recruitment process.

5.1.2 Retention

Once a participant is enrolled in MTN-018, the study site will attempt 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. An average retention rate of 95 percent per year is targeted at each study site, and across all sites. All study sites are responsible for developing and implementing local SOPs to achieve this. Should a participant decide to terminate her follow-up prior to the scheduled end of study participation, this will not be counted as lost to follow-up for the purposes of calculating retention.

Study sites may use a participant tracking database to facilitate visit scheduling and timely identification and follow-up on missed visits. The MTN Statistical Data Management Center (SDMC) will generate 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) will 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 – VOICE Cohort

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

- 1) Previously enrolled in VOICE
- 2) Less than or equal to 50 years old (inclusive) at screening, verified per site SOPs
- 3) Able and willing to provide the following:
 - a) written informed consent to be screened for and to take part in the study
 - b) 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 protocol appendices)
- 5) At screening and enrollment, agrees not to participate in other research studies involving drugs, vaccines, medical devices, or vaginal products for the next 14 months

5.3 Exclusion Criteria – VOICE Cohort

- 1) Participant reported any of the following:
 - a) Known allergy to any of the study products (ever)
 - b) Post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to enrollment
 - c) Participation in any research study (other than VOICE) involving drugs, medical devices, or vaginal products 30 days or less prior to enrollment
 - d) Currently using medication(s) with significant nephrotoxic potential, including but not limited to amphotericin B, aminoglycosides, cidofovir, foscarnet and systemic chemotherapy or medication(s) that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid)
- 2) Currently pregnant

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

Note: At participating sites, pregnant women should be referred to MTN-016 and MTN-018C, the Pregnancy Sub-study.

3) Currently breastfeeding

Note: At participating sites, breastfeeding women should be referred to MTN-018B, the Breastfeeding Sub-study.

4) Weight less than 35 kg at Screening

5) 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, or medication use that would make study participation unsafe

6) Has any of the following laboratory abnormalities:

- a) AST or ALT greater than 1.5 x site laboratory ULN
- b) Serum creatinine greater than the site laboratory ULN for women
- c) Positive for HBsAg
- d) Urine dipstick positive for protein $\geq 2+$
- e) Urine dipstick positive for glucose $\geq 2+$

Note: Otherwise eligible participants with an exclusionary test result (other than HIV or HBsAg) may be re-tested during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 42 days of providing informed consent for screening, the participant may be enrolled.

Note: Creatinine levels below site LLN will be retested prior to Enrollment.

7) 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 Inclusion Criteria – Non-VOICE Cohort

- 1) Age 18 through 50 years (inclusive) at screening, verified per site SOPs
- 2) Per participant report, sexually active, defined as having vaginal intercourse at least once in the 3 months prior to screening
- 3) Able and willing to provide the following:

- a. written informed consent to be screened for and to take part in the study
 - b. 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 protocol appendices)
 - 5) At screening and enrollment, agrees not to participate in other research studies involving drugs, vaccines, medical devices, or vaginal products for the next 14 months

5.5 Exclusion Criteria – Non-VOICE Cohort

- 1) Participant reported any of the following:
 - a) Enrollment in any HIV prevention trial, including VOICE
 - b) Enrollment in any research study involving drugs, medical devices, or vaginal products 30 days or less prior to enrollment
 - c) History of or current residence with an enrolled participant in VOICE
- 2) Participant reported any of the following:
 - a) Known allergy to any of the study products (ever)
 - b) Post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to enrollment
 - c) Currently using medication(s) with significant nephrotoxic potential, including but not limited to amphotericin B, aminoglycosides, cidofovir, foscarnet and systemic chemotherapy or medication(s) that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid)
- 3) Currently pregnant

Note: Self-reported pregnancy is adequate for exclusion from the study. A documented negative pregnancy test performed by study staff at Enrollment is required for inclusion.
- 4) Currently breastfeeding
- 5) Weight less than 35 kg at Screening
- 6) 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, or medication use that would make study participation unsafe
- 7) Has any of the following laboratory abnormalities:

- a) AST or ALT greater than 1.5 x site laboratory ULN
- b) Serum creatinine greater than the site laboratory ULN for women
- c) Positive for HbsAg
- d) Urine dipstick positive for protein $\geq 2+$
- e) Urine dipstick positive for glucose $\geq 2+$

Note: Otherwise eligible participants with an exclusionary test result (other than HIV or HBsAg) may be re-tested during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 42 days of providing informed consent for screening, the participant may be enrolled.

Note: Creatinine levels below site LLN will be retested prior to Enrollment.

- 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

5.6 Co-enrollment Guidelines

In general, participants should not take part in other research studies involving drugs, vaccines, medical devices, or vaginal products while taking part in MTN-018. Participants will be discouraged from taking part in other studies, except for the following:

- Participants may take part in ancillary studies approved by MTN-018 Protocol Chairs
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-infected persons (MTN-015, for example)
- Participants who become pregnant may take part in registries (e.g., MTN-016) and/or MTN-018C, the planned pregnancy sub-study to MTN-018

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-018, the IoR/designee will consult the Protocol Safety Review Team (PSRT) regarding ongoing product use and other potential safety considerations associated with co-enrollment.

6 STUDY PRODUCT

6.1 Regimen

At the Enrollment Visit, each participant will indicate their choice of one of the following regimens (pending selection of study product(s) for MTN-018) for use during the first month following Enrollment:

- One TDF 300 mg tablet by mouth (PO) every day
- One FTC/TDF 200 mg/300 mg tablet PO every day
- One applicator of 1% tenofovir gel applied vaginally every day

At the Month 1 Visit, participants will identify their chosen study product for the duration of the trial. Thereafter, one participant-initiated change to a different MTN-018 study product will be allowable, with a corresponding prescription from an authorized prescriber. This guidance does not restrict study product changes advised by the IoR/designee for other reasons (e.g., participant safety or significant personal reasons).

6.2 Administration

Study staff will instruct participants in proper methods of administering and storing their study product. 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 tablet by mouth, once each day without regard to meals or sexual activity. They will be instructed to take their tablets as close to the same time each day as possible.

6.2.2 1% Tenofovir Gel

Study participants will be instructed to insert one dose (the entire contents of one applicator) of product into the vagina once each day without regard to sexual activity. 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.

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.

1% Tenofovir 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. Each dose administered will be 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.

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 (Viread[®]) tablets and FTC/TDF (Truvada[®]) tablets will be supplied by Gilead Sciences, Inc. (Foster City, CA, USA).

Vaginal Gel

Tenofovir 1% vaginal 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*.

At the Month 1 visit, participants will return all unused study product, regardless of intent to continue or discontinue use of that study product. Participants who switch study products during the trial are required to return any previously dispensed study product to the study site.

6.5 Study Product Dispensing

Participants will be randomized at the Month 1 Visit to either monthly or quarterly scheduled study follow-up visits. Participants randomized to monthly follow-up visits will return to the study clinic and the pharmacy each month. Participants randomized to quarterly follow-up visits will return to the study clinic and the pharmacy at the Month 1

visit and then quarterly (Month 3, Month 6, Month 9, and Month 12). However, participants randomized to quarterly study visits will have the option to receive study product on a monthly basis. Where possible, participants randomized to the Quarterly Arm who choose to receive product monthly will not be seen in the clinic, and will go directly to the pharmacy to pick up study product. Prescriptions and dispensing will be customized for those participants who enroll close to the end of a study site's accrual period.

Study products will be dispensed only to enrolled participants, for which there is receipt of a written prescription signed by an authorized prescriber. Products will be dispensed in quantities sufficient until the next scheduled study or pharmacy visit. Dispensing will take place on the day of enrollment and at each scheduled follow-up visit, except at the Month 12 and Termination Visits.

6.6 Retrieval of Unused Study Products

As per Section 9, study product use for a participant may be temporarily held or permanently discontinued. Study product must be retrieved (optimally within 24 hours) and returned to the study site pharmacy when study product use is permanently discontinued for HIV seroconversion. For temporary hold due to pregnancy study product should be retrieved within 5 working days if a participant declines participation into MTN-018C. For temporary hold for reasons other than pregnancy with expected duration of at least 7 days, study staff should make every effort to retrieve study product within 7 working days. It is not necessary to retrieve products from participants for whom study product use is temporarily being held for less than 7 days. Study products may be retrieved from these participants if there is a safety concern regarding the participant's ability to comply with duration of the temporary product hold. For each participant, all other unused supplies remaining in the participant's possession should be retrieved at the Month 12 Visit or the last study visit if earlier than 12 months. If the participant does not bring her remaining supplies to the Month 12/last Visit, study staff must arrange to retrieve the supplies within 3 business days. If the study product(s) are not retrieved within that time frame, the MTN-018 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 the following approaches:

- Participant self-report
- Study product counts by pharmacy staff at follow-up visits
- Study drug levels

Study product adherence counseling will be provided to all study participants. 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 expected use of study products, visit schedule, and reminders to contact study staff with questions about study product use and requests for additional supplies. Participants who choose to receive study gel also will be counseled to only use the study gel vaginally. All participants will be counseled not to use other participants' study products, and not to distribute their study products to other people. Appropriate guidance based on evidence of the connection between adherence and study product effectiveness will be provided to participants.

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. Reasons for study product choice and discontinuation will be captured in the study database.

6.8 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation, with the exception of those listed in Section 5.3 (VOICE Cohort) of this protocol. 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 Enrollment, will be recorded on case report forms (CRFs) designated for that purpose. Should a participant report use of a medication for which concomitant use poses significant risk to the participant, according to the clinical judgment of the IoR/designee, the IoR/designee will institute a temporary product hold, for as long as the participant is taking the medication. Study product will be held for participants who report taking PEP for HIV exposure. 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 the protocol for HIV testing during follow-up. 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.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendices I and II. 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-018 Study Specific Procedures (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

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

The window for screening procedures will be 42 days. Screening procedures may be completed over multiple visits, if necessary.

7.2.1 Administrative, Behavioral and Regulatory

- Co-enrollment assessment (site-specific)
- Informed consent for screening
- Assignment of participant identification number (PTID)
- Locator information
- Demographic information
- Eligibility assessment (behavioral eligibility information, including clinical trial history)
- Behavioral assessment
- HIV pre- and post-test counseling, including risk reduction counseling
- Offer HIV/STI counseling, testing, and referral for partner(s), as indicated
- Provision of condoms
- Reimbursement
- Schedule next visit (if applicable)

7.2.2 Clinical Procedures

- Concomitant medications
- Medical and menstrual history (including exclusionary medical conditions)
- Blood collection
- Urine collection
- Full physical exam, including weight, height and vital signs (VS)

- Pelvic exam to include the following:
 - visual inspection per guidelines for naked eye inspection only, without colposcopy (described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at <http://www.conrad.org/publications-13.html>) and bimanual exam
 - pelvic swab collection, if indicated by signs or symptoms of vaginitis or sexually transmitted infection (STI)
- Disclosure of available test results
- Treatment or referral of conditions identified at Screening, according to local standard of care
- Ascertainment of current contraceptive method (if any) and contraceptive counseling
- Provision of contraception, if indicated

7.2.3 Laboratory Procedures

- HIV serology
- HBsAg/HBsAb (may be omitted for VOICE Cohort participants who completed HBV vaccination series, or who have documented evidence of HBV immunity)
- Creatinine
- AST/ALT
- Urine pregnancy test
- Urine dipstick for protein and glucose
- If indicated, appropriate laboratory testing may be performed to establish vaginitis and/or STI diagnosis

7.2.4 Final Screening Procedures and Confirmation of Eligibility

Before proceeding with the enrollment procedures described in this section or “on study” procedures described in Section 7.3, the following procedures will be performed to confirm participant eligibility:

- Review of all prior screening documentation
- Update medical history and/or current medications, if applicable
- Re-confirmation (by participant self-report) of medical eligibility information assessed at Screening
- Re-confirmation (by participant self-report) of behavioral eligibility, specifically that the participant:
 - has not taken PEP for HIV exposure within the six months prior to enrollment
 - has not participated in any other research study (other than VOICE) involving drugs, medical devices, or vaginal products within 30 days prior to enrollment
 - is not currently breastfeeding
- Physical and/or pelvic examination may be performed on the day of enrollment, if relevant for the confirmation of eligibility
- Urine collection and pregnancy test

- Blood collection and HIV serology, HIV pre- and post-test counseling
- Any other clinically indicated behavioral, clinical, or laboratory assessments

7.3 Enrollment

7.3.1 Administrative, Behavioral and Regulatory

- Informed consent for Enrollment
- Informed consent for specimen storage and possible future research testing (not required for enrollment, may be deferred to later visit, up to 3 months following enrollment)
- Locator information
- Eligibility assessment (See Section 7.2.6)
- Baseline behavioral assessment
- HIV/STI risk reduction counseling
- Offer HIV/STI counseling, testing, and referral for partner(s), as indicated
- Initial participant study product selection
- Adherence counseling
- Provision of condoms
- Provision of study product, instructions
- Reimbursement
- Schedule next visit

7.3.2 Clinical Procedures

- Concomitant medications
- Update medical and menstrual history
- Blood collection
- Urine collection
- Pelvic exam, if indicated, to include the following:
 - visual inspection per guidelines for naked eye inspection only, without colposcopy (described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at <http://www.conrad.org/publications-13.html>) and bimanual exam, if indicated
 - pelvic swab collection, if indicated by signs or symptoms of vaginitis or sexually transmitted infection (STI)
- Treatment or referral of conditions according to local standard of care
- Disclosure of available test results
- Education on possible signs of acute HIV seroconversion
- Contraceptive counseling
- Provision of contraception, if indicated

Note: HBV-susceptible participants will be given information and offered the HBV vaccine series starting at their MTN-018 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 MTN-018.

7.3.3 Laboratory Procedures

- Plasma archive
- Urine pregnancy test
- If indicated, appropriate laboratory testing may be performed to establish vaginitis or STI diagnosis

Note, plasma archive is collected on all participants on the day of Enrollment, and may be collected during the blood draw used for testing related to final confirmation of eligibility, provided informed consent has been documented for this specimen collection.

7.4 Follow-up Visits

Target dates are set based on the enrollment date (Day 0), 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 follow-up visits on the targeted dates, monthly and quarterly 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 a visit window, the visit will be considered “missed” and relevant CRFs will be completed to document the missed visit. When participants miss visits at which creatinine, AST/ALT, and/or plasma archive are required, these procedures must be conducted at the participants’ next visit. See Section 7.5 for further procedural modifications that may be required during follow-up.

The last two scheduled visits for each participant are referred to as the Month 12 and the Termination Visit (Month 14), respectively. The Month 12 Visit will serve as all participants’ last routine follow-up visit. The Termination Visit will take place approximately eight weeks after the Month 12 Visit (i.e., eight weeks after the participant is expected to have completed product use). Visit windows for the Month 12 and Termination Visit are specified in the MTN-018 SSP Manual (www.mtnstopshiv.org).

7.4.1 Administrative, Behavioral and Regulatory Procedures

Unless otherwise specified, requirements apply to participants in both arms (Monthly and Quarterly Arms).

- Review/Update locator information
 - At all visits
- Randomization
 - Month 1
- Behavioral assessment

- Month 1
- Month 6
- Month 12
- Month 14/Termination Visit

- Adherence assessment
 - Month 1
 - Month 3
 - Month 6
 - Month 9
 - Month 12

- Social harms assessment
 - Month 3
 - Month 6
 - Month 9
 - Month 12

- Study product-sharing assessment
 - Month 12

- HIV pre- and post-test counseling
 - Whenever HIV testing is performed

- HIV/STI risk reduction counseling
 - At all visits

- Offer HIV/STI counseling, testing, and referral for partner(s)
 - When clinically indicated

- Provision of condoms
 - At all visits

- Study product selection/ confirmation
 - Month 1

- Study product supplies and instructions
 - Monthly Arm
 - Monthly prior to Month 12
 - Quarterly Arm
 - At all scheduled visits prior to Month 12

- Study product adherence counseling
 - Monthly Arm
 - Monthly prior to Month 12
 - Quarterly Arm

- At all scheduled visits prior to Month 12
- Reimbursement
 - At scheduled visits and per site SOP
- Schedule next visit
 - At all scheduled visits except the Termination Visit (at Termination Visit, next (off-study) visit is scheduled only if needed, i.e., to provide test results and counseling, follow-up on AEs, etc.)

7.4.2 Clinical Procedures

Unless otherwise specified, requirements apply to participants in both arms (Monthly and Quarterly Arms).

- Medical and menstrual history and concomitant medication review/update interval (i.e., since last visit)
 - At all scheduled visits
 - Additionally at unscheduled visits in response to intercurrent symptoms/illnesses/ongoing AEs
- Blood collection
 - At all scheduled visits
 - When needed to perform confirmatory HIV testing per Appendix IV
 - Additionally when clinically indicated
- Urine collection
 - At all scheduled visits
 - Additionally when clinically indicated
- Physical exam, plus weight, height, VS
 - Month 6
 - Month 12
 - Additionally when clinically indicated
- Evaluation for suspected HIV acute seroconversion
 - When clinically indicated
- Pelvic exam to include the following:
 - Visual inspection per guidelines for naked eye inspection (without colposcopy) described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004 and bimanual exam:
 - Month 12
 - When clinically indicated
- Labs for vaginitis and/or STI testing/diagnosis

- When indicated by local standard of care

Note: If a participant is menstruating at a study visit during which a pelvic exam is clinically indicated, all other visit procedures will be conducted, and the participant may be scheduled to return to the clinic optimally within 48 hours after end of menses to complete her pelvic exam.

- Education on possible signs of acute HIV seroconversion
 - Month 3
 - Month 6
 - Month 9
 - Month 12
- Treatment or referral of conditions according to local standard of care
 - At all scheduled visits
- Hepatitis B vaccination (as indicated for consenting HBV susceptible participants)
 - At visits corresponding with recommended time points for hepatitis B vaccine series
- Contraceptive counseling, if indicated by site SOP
 - If needed at all visits
- Provision of contraception, if indicated by site SOP
 - As needed at all visits
- Disclosure of available test results
 - At all scheduled visits
 - Additionally when clinically indicated

7.4.3 Laboratory Procedures

- Plasma archive
 - Month 6
 - Month 12
 - At Termination Visit
 - If indicated
 - Within algorithm for HIV testing during follow-up
 - Within algorithm for detection of acute HIV infection
 - At other time points if instructed by MTN NL
- HIV serology
 - Monthly Arm
 - Monthly until Month 12
 - Termination Visit
 - Additionally when clinically indicated

- Quarterly Arm
 - Month 1
 - Month 3
 - Month 6
 - Month 9
 - Month 12
 - Termination Visit
 - Additionally when clinically indicated
- HIV-1 RNA polymerase chain reaction (PCR)
 - If indicated (within algorithm for HIV testing during follow-up)
 - At other time points if instructed by MTN NL
- CD4+ T cell count
 - If indicated (within algorithm for HIV testing during follow-up)
 - At other time points if instructed by MTN NL
- Hepatitis B surface antigen/antibody (HBsAg/HBsAb)
 - When clinically indicated
- Creatinine
 - For those most recently using oral product
 - Month 6
 - Month 12
 - Additionally when indicated by Section 9 or clinical judgment of IoR/designee
- AST/ALT
 - Month 6
 - Month 12
 - Additionally when indicated by Section 9 or clinical judgment of IoR/designee
- Urine pregnancy test
 - At all scheduled visits
 - Additionally at unscheduled visits when a participant reports a missed menstrual period
- Urine dipstick for protein and glucose
 - Monthly and Quarterly Arms for those most recently using oral product
 - Month 6
 - Month 12
- Study drug levels
 - Month 6
 - Month 12

- Labs for vaginitis and/or STI testing/diagnosis
 - When indicated by local standard of care

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

7.5.1 Participants Who Become Infected with HIV

All participants who become HIV infected on study will be referred for HIV care and treatment. All participants who become infected with HIV-1 will be encouraged to enroll into MTN-015 (www.mtnstopshiv.org) at the visit when seroconversion confirmation test results are discussed with the participant. Women who are enrolled in MTN-015 will be terminated from MTN-018. If enrollment into MTN-015 is declined or delayed, participants will be offered the option of continued follow-up per the schedule described below. Participants randomized to monthly follow-up will have a modified follow-up schedule (quarterly visits).

For participants who delay or decline enrollment in MTN-015, the following procedures are completed as part of the MTN-018 study:

- Plasma archive
- CD4+ T cell count
- HIV-1 RNA PCR

The aforementioned procedures will be performed at the following MTN-018 visits:

- The visit (scheduled or interim) at which the participant is given her Western Blot or HIV RNA/DNA test results confirming her HIV-infection. This visit is expected to occur, in most cases, no later than one month after the date of HIV seroconversion (i.e., date of Sample 1 positive HIV rapid test result).
- The MTN-018 visits that occur 3 months and 6 months after the date of HIV seroconversion. If the participant exits the study prior to the visits that occur 3-months and 6-months post-seroconversion, these visits and associated procedures will be omitted.

Please reference the SSP for additional details.

7.5.2 Participants Who Become Pregnant

Former VOICE participants who are pregnant at MTN-018 screening or enrollment will be offered screening for MTN-018C.

Participants who become pregnant following enrollment in MTN-018 will be offered screening for MTN-018C, and if enrolled, they will not continue to be followed in MTN-018.

Participants who choose not to enroll in or who are ineligible for MTN-018C will continue follow-up in MTN-018. All protocol-specified study procedures will continue except the following:

- Provision of study product and procedures related to continued use of study product, e.g., study product instructions, product adherence counseling, product adherence assessment, study product sharing assessment.

All participants who test positive for pregnancy following enrollment in MTN-018 will be offered co-enrollment in MTN-016.

7.5.3 Participants Who Temporarily Hold or Permanently Discontinue Study Product Use

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

- Provision of study product and procedures related to continued use of study product, e.g., study product instructions, product adherence counseling, product adherence assessment, study product sharing assessment

Participants who permanently discontinue study product will have final safety and HIV status assessments before terminating study participation. Reason(s) for discontinuation will be captured on applicable CRFs and entered in the study database.

7.6 Interim Visits

Interim visits may be performed at any time during the study, in response to participant concerns or other reasons, and/or to perform additional evaluations/procedures, as needed. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

7.7 Final Contact

Since participants' Termination Visit includes laboratory testing for HIV, a final contact may be required to provide additional study test results, and post-test counseling. 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, as specified in site SOPs, depending on site capacities and site and participant preferences. All final contacts will be documented in participant study records.

7.8 Clinical Evaluations and Procedures

Physical Exams will include the following assessments:

- Vital signs
 - Oral temperature

- Blood pressure
- Pulse
- Respirations
- Measurement of height and weight
- Clinical assessments of
 - Head, eyes, ears, nose, and throat (HEENT)
 - Neck
 - Lymph nodes
 - Heart
 - Lungs
 - Abdomen
 - Extremities
 - Neurological
 - Skin
 - Breasts

Targeted physical exams will be done if clinically indicated according to the judgment of the IoR/designee, and will include clinically indicated components of the Physical Exam. 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 without colposcopy, described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at <http://www.conrad.org/publications-13.html>.

7.9 Laboratory Evaluations

The location of laboratory evaluations will depend on laboratory capacity.

- Urine pregnancy test
- Urine dipstick for protein and glucose
- Creatinine
- ALT and AST
- HBsAg/HBsAb
- HIV serology
- Plasma archive
- HIV-1 RNA PCR
- CD4+ T Cell Count
- Standardized and specialized HIV-1 resistance tests
- Blood tenofovir level
- Blood emtricitabine level, if applicable for MTN-018
- Vaginitis testing
- STI testing

7.10 Specimen Collection and Processing

Each study site will adhere to the standards of good clinical laboratory practice, the HPTN-MTN Network Laboratory (NL) Manual (www.mtnstopshiv.org), in accordance with current DAIDS Laboratory Requirements, MTN-018 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.

7.11 Specimen Handling

Specimens will be handled in accordance with Requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials (<http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/labpolicy.pdf>).

7.12 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 Centers for Disease Control (CDC) and NIH. All biological specimens will be transported using packaging mandated by the US Code of Federal Regulations (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, CONRAD Medical Officer (if 1% TFV gel is selected as a study product) and SCHARP Clinical Affairs Safety Associate will serve as the PSRT. The MTN SDMC will prepare routine AE and clinical data reports for review by the PSRT,

which will meet 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.

8.2 Adverse Events Definitions and Reporting Requirements

An AE is defined as any untoward medical occurrence in a clinical research participant, starting from the time she is enrolled through when she terminates from the study. An AE 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 applies to all study groups. The term “investigational product” for this study refers to all study products, as well as the study gel applicator, if applicable.

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 events reported by or observed in enrolled participants:

- All AEs of severity Grade 3 or higher
- All laboratory values
- All serious AEs, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
- All AEs that result in product hold or permanent discontinuation of study product use by the IoR or designee

AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification, August 2009) and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004), except that asymptomatic bacterial vaginosis (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 (Clarification, August 2009). 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.

8.3 Expedited Adverse Event Reporting Requirements

8.3.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the Regulatory Support Center (RSC) website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

At sites where it is implemented, the DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

8.3.2 Reporting Requirements for this Study

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

The study agents for which expedited reporting are required are:

Oral

- Tenofovir disoproxil fumarate (TDF) 300 mg tablet
- Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) 200 mg/300 mg tablet

Vaginal

- 1% TFV gel

8.3.3 Grading Severity of Events

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 (Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 is used and is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

8.3.4 Expedited AE Reporting Period

The expedited AE reporting period for this study is as per the DAIDS EAE manual. After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the DAIDS EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8.4 Regulatory Requirements

Information on all reported AEs will be included in reports to the US FDA and other applicable government and regulatory authorities. Site IoRs/designees will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. Site IoRs/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

Social harms will be assessed on a quarterly basis for all participants.

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. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs. The PSRT is available for consultation as needed per site IoR.

It is expected that the IoR/designee will manage observed toxicities consistently among participants at the site allowing for individual alterations, as needed. Management plans may be outlined in site SOPs to facilitate this. The PSRT will review all Adverse Events, including abnormal labs, and product holds on a monthly basis. Serious Adverse Events and a subset of more severe Adverse Events will be reviewed at a minimum on a weekly basis. Should the PSRT note a concern with a site's management plan, the PSRT will query the sites for more information. All specific PSRT recommendations will be followed. The PSRT is available for consultation as needed per site IoR/designee.

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 temporarily held from study product for any of the following reasons:

- A positive rapid HIV test result. Study product should be held beginning immediately upon recognition of the first positive rapid HIV test result. If the participant is determined to be HIV-uninfected per the algorithm in Appendix IV, she may resume product use.
- Pregnancy (does not apply within pregnancy substudy). A participant who becomes pregnant while participating in MTN-018 will be referred to appropriate MTN pregnancy protocols and continue in follow-up for MTN-018 until pregnancy outcome. The participant may resume product use after a pregnancy outcome, as evidenced by a negative pregnancy test performed by study staff, provided that she is not breastfeeding. For participants using the gel, a pelvic exam must be performed prior to product resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.
- Breastfeeding (does not apply within breastfeeding substudy). Product use may resume when the participant reports complete cessation of breastfeeding.
- Report of use of PEP for HIV exposure. 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 IV.
- Clinical suspicion of acute HIV infection.⁵⁵
- 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. If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee can restart product at his or her discretion.

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

- Acquisition of HIV-1 infection, confirmed per the algorithm in Appendix IV; such participants will not resume product use at any time.

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

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

In general, study product need not be held in response to AEs determined to be already resolved at the time of report/discovery, according to the judgment of the IoR/designee.

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 not specifically addressed below and judged by the IoR/designee to be not related to study product may continue product use. Participants who develop a Grade 3 AE not specifically addressed below and judged by the IoR/designee to be related to study product may have a temporary product hold initiated at the discretion of the IoR.

Grade 4

A participant who develops a Grade 4 AE not specifically addressed below (regardless of relationship to study product) should have the study product held. The IoR/designee must notify the PSRT of the site's management plan.

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 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 B infection is confirmed, product use must be permanently discontinued.

ORAL STUDY PRODUCT

Grade 1 and Grade 2

Study product may continue at the discretion of the IoR/designee. A management plan will be devised by the site IoR/designee.

Grade 3

The IoR/designee must temporarily hold study product and repeat the ALT and AST as soon as possible (at most within 2 weeks). The participant should then be followed at an interval determined by the site IoR/designee until levels are Grade ≤ 1 , at which point, study product may be resumed per discretion of the site IoR/designee. The PSRT should be notified of the decision to restart product.

Grade 4

Study product should be temporarily held and AST and ALT repeated as soon as possible (at most within 2 weeks). The PSRT should be notified of the event as well as the site's management plan.

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 notify the PSRT.

9.5.2 Creatinine

ORAL STUDY PRODUCT

The IoR/designee should temporarily hold oral study product for any creatinine \geq Grade 2. The creatinine should be repeated as soon as possible (at most within 2 weeks). The frequency of follow-up testing is left to the discretion of the site IoR/designee. Product use may be resumed when the creatinine level returns to less than Grade 1.

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, the PSRT should be notified.

9.6 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. Study products need not be held in the event of genital STI/RTI requiring treatment, unless other product hold/permanent discontinuation requirements apply.

9.7 HIV Infection

Suspected Acute HIV Seroconversion

All participants will be counseled about the importance of detecting HIV infection as quickly as possible to avoid continued product exposure. Detection of potential acute HIV infection will be performed following the algorithm in Appendix V. Participants will be instructed to contact the study clinic any time they have a rash and a fever. The participant will be scheduled for an interim visit as soon as possible for evaluation for potential acute seroconversion. At the interim visit, the clinician will review the history of fever and rash with the participant and perform an examination for generalized lymphadenopathy. If the clinician cannot confirm at least 1 of the 3 signs of potential acute seroconversion (fever, rash, lymphadenopathy), the participant will have a blood sample obtained for plasma archive and will resume her routine schedule for follow-up and HIV testing. If 1 or more signs are confirmed by the clinician without an alternative clinical diagnosis, two rapid HIV tests will be performed. If both rapid tests are positive, the participant will proceed to product hold and follow the algorithm for follow-up HIV testing (Appendix IV). If one or none of the rapid tests are positive, the participant will proceed to product hold and an HIV viral load test will be performed. If the HIV viral load test result is undetectable, the participant will resume study product use and resume her routine follow-up schedule including routine HIV testing. If the HIV viral load is detectable, the participant will continue product hold and have a Western blot performed in 4-8 weeks to confirm infection.

Positive HIV Tests

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 IV, 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 will receive results of resistance testing performed in MTN-018. 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. Participants will be referred for HIV-1 care and treatment, according to local guidelines. Participants enrolled in MTN-015 will discontinue follow up in MTN-018.

The 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.

9.8 Hepatitis B Infection

If symptoms or signs of clinical hepatitis are present, the IoR/designee must temporarily hold study product and test the participant for hepatitis (including HBsAg, plus any other testing indicated by the local standard of care). If hepatitis B infection is confirmed, product use must be permanently discontinued, but participants will continue MTN-018 follow-up visits. Participants identified as infected with hepatitis B (acute or chronic active infection) will be managed or referred for management according to the local standard of care.

9.9 Pregnancy

Study participants will be offered, or referred to, contraceptive counseling and contraceptive methods during the course of the study. In addition, study staff will also provide participants with condoms and counseling on use of condoms ideally during every sex act during study participation. Participants will be instructed to come to the clinic for pregnancy testing in the event that delayed menses is noted. 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 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 enrolled in MTN-018 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).

A participant who becomes pregnant during the course of the study will have study product held as per Section 9.3, but may resume study product after delivery, or spontaneous or elective termination of the pregnancy, provided she is not breastfeeding. However, pregnant participants who co-enroll in MTN-018B or MTN-018C may be provided study product in that context. 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.

9.10 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. The IoR should notify the PSRT. Participants also may be withdrawn if 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 3B, open-label, multi-site, randomized trial. The three main goals of the trial are:

- 1) to provide access to the VOICE participants to safe and effective product(s) identified in VOICE for preventing HIV acquisition in women;
- 2) to provide additional safety data for potentially supporting further pre-, peri-, and/or post- registration requirements and/or a change of label; and
- 3) to compare the safety profiles associated with two different strategies for follow-up, monthly versus quarterly, for participants taking daily study product(s).

Of the 5,000 women expected to enroll in VOICE, we anticipate that 80% will be eligible and reachable (i.e., not lost to follow-up between the time the VOICE trial will end and the time this trial will start). Therefore, we expect approximately 4,000 women will consent and enroll in this trial. In addition, approximately 300 women who did not participate in VOICE will be consented and enrolled.

10.2 Study Endpoints

Primary Safety Endpoints

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

- Grade 3 and higher clinical AEs
- Grade 2 and higher laboratory AEs for AST, ALT, or creatinine

Primary Product Use Endpoints

Consistent with the primary objective to evaluate total amount of **time off product**, days off study product over the entire on-product follow-up period due to AEs, investigator-initiated product hold/discontinuation, or participant-initiated product hold/discontinuation will be assessed.

Secondary Endpoints

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

Product Choice

Consistent with the objective to identify the determinants of **the choice of product and product switching** within the VOICE Cohort and the Non-VOICE Cohort, the following endpoints will be assessed:

- If more than one product is available, the choice of product at enrollment
- If more than one product is available, the switching of product during follow-up

Adherence

Consistent with the objective to **compare adherence between the VOICE Cohort and the Non-VOICE Cohort**, the following endpoints will be assessed:

- Adherence by self-report and/or remote data collection, study product counts, study drug levels

HIV-1 Seroconversion

Consistent with the secondary objective to assess the incidence of HIV-1 seroconversion across study products the following secondary endpoint will be assessed:

- HIV infection as defined by the protocol algorithm at the end of the study product use period (i.e., at the start of the additional 8 weeks of follow-up off product)

10.3 Study Hypotheses

Hypothesis: Primary Safety Endpoint

The protocol team hypothesizes that all active study products will be safe, well-tolerated, and acceptable for once-daily use among healthy sexually active women and that there are no missed or loss in the collection of major safety events associated with a less frequent visit schedule (i.e., quarterly) compared to a monthly visit schedule. Therefore, the null hypothesis is that there will be no difference in the safety profile between the two strategies of follow-up.

Hypothesis: Primary Product Use Endpoint

The protocol team hypothesizes that if the hypothesis for the primary safety endpoints holds, then there should be no difference in total amount of time off product use between the two strategies for follow-up. Therefore, the null hypothesis is that there will

be no difference in the days off study product during the on-product follow-up period between the two strategies for follow-up.

Hypothesis: Secondary Non-VOICE Cohort Endpoints

The protocol team hypothesizes that there is no difference in the product choice and switching if two products are available. Furthermore, if the hypothesis for the primary safety endpoints holds, then there should be no difference in adherence between the two cohorts. Therefore, the null hypothesis is that there will be no difference in the mean adherence between the two cohorts.

10.4 Sample Size and Power Calculations

From the VOICE trial, we anticipate that about 20% of women will not be eligible for this trial (e.g., will be HIV infected), or will not consent or be reached. Therefore, we expect approximately 4,000 women will consent and enroll in this trial. To this, we need to add the Non-VOICE Cohort of 300 for a total of 4,300. As designed, there are three major factors affecting the power of the study:

1. If the trial will offer the choice of one or two study products.
2. If two products are available in this trial, women are allowed to choose the product they want to use. Given that most of the analyses will be stratified by product, any substantial preference in the choice of one product over the other product will have an impact on the power of the study.
3. If two products are available in this trial, women are allowed to change product at the Month 1 visit and possibly thereafter.

Of these, (1) has the greatest impact on the power of the study, as the stratified (by product) analysis is essentially cutting the sample size in two parts (not necessarily equal). For (2), the potential imbalance resulting from the preference of one product over another must be extreme before having a substantial impact on power. As an example, if women are choosing product with a 1:1 preference ratio, then 2,150 women will be available for the comparison of the two strategies of follow-up. For each product, the power to detect an absolute difference in proportion of 4% (10% vs. 6%) is about 90% with 1,075 women per arm (with a 1:1 preference ratio), while the power drops to 83% if the preference ratio is 3:2 for the product selected less frequently by women (for the other product, the power will be higher). The power drops to 73% in the more extreme case where 7 out of 10 women choose one product over the other one (a 7:3 preference ratio). Similarly, the effect of switching product in (3) will only have a substantial impact on power if the switching of product is much greater in one direction than the other (i.e., switching from product A to product B or vice versa). Because the only data currently available on the study products is from randomized clinical trials in which product choice and switching are not allowed, we cannot predict what the preference ratio will be or whether there will be differential switching of product. However, for the purpose of power calculations, we will assume a 1:1 preference ratio in the event that two products are available in this trial, and we will assume that product switching is not differential, acknowledging that study power will differ depending on the actual preference ratio and product switching.

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 analyzed separately in the event that two products are available, a 5% significance level for a two-sided test (i.e., a 2.5 % false positive rate), 1,935 and 968 p-y of follow-up per arm if one or two products are available, respectively (see Section 10.5). As well, assuming a pooled (pooled across Monthly and Quarterly arms) 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 $\leq 72\%$ if only one product is available. This corresponds to safety and toxicity rates in the Quarterly and Monthly arms of 8.4 and 11.6 per 100 p-y, respectively. If two products are available, the detectable (hazard) rate ratio is $\leq 63\%$. This corresponds to safety and toxicity rates in the Quarterly and Monthly arms of 7.7 and 12.3 per 100 p-y, respectively. Table 2 displays the statistical power achieved for different safety and toxicity rates and (hazard) rate ratios.

Table 1: Power by Safety Rate and Hazard Rate Ratio if One Product is Available

Safety/Toxicity Rate (per 100 p-y) (pooled over both arms)	Hazard Rate Ratio (quarterly over monthly)								
	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80
2.5%	99.5%	97.7%	92.9%	84.1%	71.5%	56.8%	42.3%	29.6%	19.6%
5.0%	100.0%	100.0%	99.8%	98.6%	94.5%	85.1%	70.0%	51.7%	34.2%
7.5%	100.0%	100.0%	100.0%	99.9%	99.2%	95.7%	86.2%	69.1%	47.9%
10.0%	100.0%	100.0%	100.0%	100.0%	99.9%	98.9%	94.0%	80.9%	59.4%
12.5%	100.0%	100.0%	100.0%	100.0%	100.0%	99.7%	97.5%	88.6%	69.0%
15.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.9%	99.0%	93.4%	76.8%
17.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.6%	96.3%	82.8%
20.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.9%	97.9%	87.4%
22.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	98.9%	90.9%
25.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.4%	93.5%
27.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.7%	95.4%
30.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.8%	96.7%
32.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.9%	97.7%

Table 2: Power by Safety Rate and Hazard Ratio if Two Products are Available

Safety/Toxicity Rate (per 100 p-y) (pooled over both arms)	Hazard Rate Ratio (quarterly over monthly)								
	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80
2.5%	90.0%	80.6%	68.8%	56.1%	43.9%	33.1%	24.2%	17.3%	12.1%
5.0%	99.5%	97.7%	92.9%	84.1%	71.5%	56.8%	42.3%	29.6%	19.6%
7.5%	100.0%	99.8%	98.7%	95.1%	87.0%	74.0%	57.7%	41.2%	27.0%
10.0%	100.0%	100.0%	99.8%	98.6%	94.5%	85.1%	70.0%	51.7%	34.2%
12.5%	100.0%	100.0%	100.0%	99.6%	97.8%	91.8%	79.2%	60.9%	41.1%
15.0%	100.0%	100.0%	100.0%	99.9%	99.2%	95.7%	86.2%	69.1%	47.9%
17.5%	100.0%	100.0%	100.0%	100.0%	99.7%	97.8%	90.8%	75.6%	53.9%
20.0%	100.0%	100.0%	100.0%	100.0%	99.9%	98.9%	94.0%	80.9%	59.4%
22.5%	100.0%	100.0%	100.0%	100.0%	100.0%	99.4%	96.1%	85.2%	64.4%
25.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.7%	97.5%	88.6%	69.0%
27.5%	100.0%	100.0%	100.0%	100.0%	100.0%	99.9%	98.5%	91.4%	73.2%
30.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.9%	99.0%	93.4%	76.8%
32.5%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	99.4%	95.1%	80.0%

Assuming that no difference in safety profiles is observed between the two regimens of follow-up then the randomized arms can be pooled. Under the same assumptions as above this should provide 3,870 and 1,935 p-y of follow-up if one or two products are available, respectively. This represents a substantial amount of additional safety data. In comparison, the VOICE trial will be providing 1,800 p-y of on-product follow-up for each active product. Although there is sufficient power for a comparison of the safety profile between the two products (if two are available), interpretation from such comparisons have to be done with extreme caution as the allocation of women to product will not be randomized. It is highly conceivable that women’s choice of product will be associated with past-experience with product and socio-demographics, risk behavioral and other factors which could lead to the introduction of confounding biases.

Primary product use endpoint

Based on the current information on the time off product from the VOICE trial, we expect the proportion of total time off product to be between 5% and 10% with a standard deviation of approximately 22%. Note that although a proportion is computed for each woman, the mean of these proportions will be compared between the follow-up strategy arms using a two-sided t-test. Assuming a sample size per arm of 1,935 and 968 women if one or two products are available, respectively, a minimum detectable alternative between 2.3 and 3.2% can be detected with 90% power and a false-positive error rate of 2.5%. Assuming that no difference in time off product is observed between the two strategies of follow-up, then the randomized arms can be pooled. This should provide 3,870 and 1,935 women if one or two products are available, respectively. This can be used to provide more precise estimates of the time off product for each of the

products. However, the same cautions as mentioned for the safety endpoints in interpretation need to be exercised.

Secondary endpoints

As stated in Section 10.2, this trial will generate about 3,870 p-y of follow-up on product. Assuming a background HIV rate of 3.0 per 100 p-y with an effectiveness of 50% for all products, then the expected number of HIV seroconversions in this trial is about 58.

In terms of secondary objectives on HIV-1 resistance and HIV-1 seroconversion, the expected number of HIV endpoints is too small to make any formal statistical comparison. However, the additional HIV-1 resistance data will be combined with the HIV-1 resistance data obtained from other trials. No single study can provide sufficient data to provide more precision on the acquisition rate of an HIV-1 resistant virus, this can only be achieved by combining the resistance data of several studies.

In terms of the HIV-1 seroconversion rate, if the observed rate is 1.5 per 100 p-y, then the upper bound of the 95% CI will be 1.9 and 2.1, if one or two products are available, respectively, and the Monthly and Quarterly Arms are pooled. Comparisons with the rates observed in the placebo and active arms of the VOICE trial might be tempting; however, these comparisons are subject to several potential biases such that they are ill-advised.

Secondary Endpoints for the Non-VOICE Cohort

If two products are available in MTN-018, the sample size available for the comparison of product choice at enrollment between the VOICE Cohort and the Non-VOICE Cohort will be 4,000 and 300 women, respectively. To be conservative, we will assume that the VOICE Cohort women are selecting products with a 1:1 ratio. An absolute difference of 8.5% or more can be detected with 80% power with a two-sided alpha of 5%, i.e., 50.0% and 58.5% (or 41.5%) are selecting product A in the VOICE and Non-VOICE Cohorts, respectively. Power to detect the same absolute difference will be higher for comparing the proportion of women who are switching products during follow-up, as we expect these proportions to be lower than 50% (e.g., 10% to 30% of women will switch products during follow-up).

For each product, mean adherence will be compared where the expected sample sizes will be 1,800 and 135 (assuming that those lost to follow-up will have no adherence assessments). An effect size as small as 0.25 SD can be detected with 80% power and a two-sided alpha of 5%. An effect size less than 0.25 SD is usually considered very small. If only one product is available, the detectable effect size is 0.18 SD.

10.5 Participant Accrual, Follow-up and Retention

A total of about 4,300 women will be enrolled over an accrual period of 6 to 9 months. Each woman will be followed for 12 months with product use (unless she enrolls late in the accrual period) and an additional 2 months off product. Therefore, each woman will be followed for up to 14 months. The total duration of the trial (at each study site) will be

between 20 and 23 months, approximately. The protocol team will be targeting an average annual retention rate of 95 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. Each study site will establish participant retention procedures to target lost-to-follow-up rates to minimize potential bias associated with loss-to-follow-up. However, the assumed average retention rate 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, 3,870 p-y of follow-up on product is expected while 645 p-y of follow-up off product is expected. If only one product is available, then 1,935 p-y of follow-up is expected per follow-up strategy arm. If two products are available, then analysis will be conducted by product, and 968 p-y of follow-up per follow-up strategy arm for each product is expected with a 1:1 product preference ratio.

10.6 Randomization

At the Month 1 Visit, participants will be assigned at random to one of the two follow-up arms in a 1:1 ratio. The randomization scheme will be stratified by product choice and 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 numbers. One set of envelopes is stored and used in the study clinic. The other set is stored and used in the study pharmacy. 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 randomization.

10.7 Blinding

This is an open-label and unblinded trial.

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 SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, adherence, and completion of primary and secondary endpoint assessments. The SMC will review the frequency of antiretroviral resistance in HIV-infected participants enrolled in MTN-018. These reviews will take place approximately every 4-6 months, or as needed or required by the SMC. 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. The SMC may consider recommending termination of this study if recruitment is lower than targeted, or if study data quality is poor.

10.8.2 Data and Safety Monitoring Board (DSMB)

No Data and Safety Monitoring Board (DSMB) oversight is planned for this study.

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 and laboratory measurements using descriptive statistics.

Primary Safety Analysis

The primary analysis will be conducted separately for each of the products in this trial (if more than one is available), safety and toxicity data from participants in the Monthly Arm of the study will be compared to that from participants in the Quarterly Arm. Incidence rates of safety and toxicity endpoints will be compared using Andersen Gill Proportional Hazards Models stratified by site and robust variance estimates.⁵⁷ 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. This analysis will exclude the last 2 months of follow-up without product. Therefore, all the follow-up of women will be censored at the Month 12 visit. Since Grade 2 or higher AEs for AST, ALT, or creatinine could be transient and recurrent and are a part of this combined safety endpoint, it is important to also assess differences in the point prevalence of the safety events. Thus, in addition to the Andersen Gill Proportional Hazards analysis, a point prevalence per visit will be calculated for safety outcomes and averaged within each arm for the common quarterly visits to assess differences in point prevalence of these safety events at the common visits. In addition, the above analyses will be repeated where the primary safety endpoints are not combined (i.e., Grade 3 and higher clinical AEs alone, Grade 2 and higher AEs for AST, ALT, or creatinine). In the case two products are available, women are allowed to switch products during follow-up at the Month 1 visit and potentially other times during follow-up. The portion of follow-up using a different product from the one selected at enrollment will be excluded, but will be added in the analysis of the other product. The reverse will also be done (i.e., adding the follow-up of women that have selected a different product at enrollment but switch to the other product during follow-up).

Adverse events 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 available products, all AEs will be grouped by body system and a p-value and confidence interval for the relative risk (Monthly Arm: Quarterly Arm) of each AE will be calculated, as well as the difference in rates between treatment groups (Monthly Arm – Quarterly Arm) 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. 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. 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 Product Use Analysis

The primary analysis will be conducted separately for each of the available products in this trial (if more than one is available), product use data from participants in the Monthly Arm of the study will be compared to that from participants in the Quarterly Arm. For each woman, the proportion of time off product will be computed where the numerator is the number of days off product divided by the total number of days of follow-up. As for the primary safety analysis, portion of follow-up will be added or excluded in order to take into account the women who are switching products. For the Monthly and Quarterly Arms, the mean of these proportions will be obtained and compared between follow-up arms using a t-test (if the distribution allows the use of the t-test). Note that the above analysis will be conducted under the intention-to-treat (ITT) principle.

Non-VOICE Cohort Analysis

The analysis on product choice and switching can only be carried out if two products are available. If it is the case, the extension of the Mantel-Haenszel procedures will be used to compare the proportions between the two cohorts taken into account the stratification by site. All women that will be randomized will be included in this analysis in accordance with the ITT principle.

For adherence, each product will be analyzed separately. The number of days with product use will be divided by the number of days of follow-up so to obtain a measure of adherence for each woman. The cohort means of these proportions will be compared using a Student t-test for independent samples. Power can be gained if the stratification by site is taken into account; this can be achieved by performing an ANCOVA. For these analyses, the portion of follow-up using a different product from the one selected at enrollment will be excluded, but will be added in the analysis of the other product. The reverse will also be done (i.e., adding the follow-up of women that have selected a different product at enrollment but switch to the other product during follow-up).

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. CRF 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 current DAIDS policies. Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with US regulations, for each of the 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 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 current DAIDS policies.

12 CLINICAL SITE MONITORING

Study monitoring will be carried out by Pharmaceutical Product Development (PPD) (Wilmington, NC) in accordance with current DAIDS policies. Study monitors will visit the site to do the following:

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (GCP) guidelines, and applicable regulatory requirements (US and non-US), including US 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

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 Coordinating and Operations Center (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, MTN, the FDA, OHRP or any of their appointed agents, CONRAD, and Gilead Sciences, Inc.

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 MTN-018 study, including but not limited to general research 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

Study sites will submit Version 1.0 of this protocol to their IRBs/ECs prior to the release of VOICE results and the selection of MTN-018 study products. Following the release of VOICE results, and pending the identification of effective products within VOICE, a modified version of this protocol will be distributed to study sites for submission to local IRBs/ECs. This modified version will incorporate all relevant findings from VOICE, including consideration for the safety and effectiveness profiles of study drugs, as well as the rationale for and identification of study products in MTN-018.

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. 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

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Initial site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *WILL NOT* be reviewed and

approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

13.3 Study Coordination

DAIDS holds the IND application 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 Trial 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.

13.4 Risk Benefit Statement

While risks of ARV use in HIV-infected women are generally outweighed by the benefits in terms of decreased morbidity and mortality, the risk-benefit ratio is necessarily altered in the context of ARV use (with rare although potentially significant adverse effects) among healthy HIV-uninfected women. However, in settings such as those surrounding VOICE sites, women are at significant risk for contracting HIV infection. Currently, equipoise still exists in VOICE; however, at the end of the VOICE trial, the identification of a safe and effective product may support the argument that risks associated with participation in MTN-018 are related to an intervention holding out the prospect of direct benefit to study participants.

13.4.1 Risks

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, bruising, and/or swelling. Pelvic examination may cause mild discomfort and/or vaginal bleeding or spotting. Learning 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. Continuing to use the study product after HIV infection has occurred could lead to the development of drug resistance.

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. In some communities, theft of ARVs has been reported.

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.

Tenofovir 1% Gel

Administration of TFV gel intravaginally at 1% concentration in the HPTN 050 Phase 1 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 TFV 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 Phase 1 study of TFV 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 TFV levels. Given that Phase 1 data demonstrate measurable plasma concentrations of TFV in some participants, participants with hepatitis B infection might be at risk for development of TFV-resistant hepatitis B. However, participants with known hepatitis B infection will not be eligible for enrollment. It is not known what effect TFV gel could have on the HIV virus or HIV disease progression in HIV-infected participants or their partners. There is a theoretical risk that TFV absorbed systemically from oral TDF or vaginal TFV 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 TFV gel use. No participant had high level TFV mutations (e.g., K65R).

In a male tolerance study of 1% tenofovir 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.

In CAPRISA 004, there were no serious adverse events deemed related to the use of study product. No renal disorders were observed in the study. Mild, self-limiting diarrhea was more common among women who used TFV gel (16.9 percent) compared to women who used the placebo gel (11.0 percent). No TFV resistance was observed among the women who became infected with HIV in the TFV group. No increase in hepatic flares was observed in participants infected with the hepatitis B virus. There were no safety concerns in the 54 pregnancies observed in the trial.

Emtricitabine

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

- Headache
- Dizziness
- Tiredness
- Inability to sleep, unusual dreams
- Loose or watery stools
- Upset stomach (nausea) or vomiting
- Abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Skin darkening of the palms and/or soles
- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage

Persons infected with both hepatitis B and HIV may have increases in transaminases, and symptoms associated with hepatitis may worsen if emtricitabine is stopped.

Tenofovir

The following side effects have been associated with the use of tenofovir (oral tablet):

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness

- Dizziness
- Depression
- Headache
- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver
- Shortness of breath
- Rash
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness

Persons infected with both hepatitis B and HIV may have increases in transaminases, and symptoms associated with hepatitis may worsen if tenofovir is stopped.

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.

13.4.2 Benefits

In a modification to this protocol, this section will describe the reduction in risk of HIV infection known for study products. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research.

Participants will receive HIV/STI risk reduction counseling, HIV testing, physical examination, pelvic examination, and routine laboratory testing related to 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.

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. 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 current DAIDS policies. 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 importance to this study:

- The importance of safer sex behaviors for reducing risk of HIV acquisition.
- The importance of participants in all 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 potential 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 of concepts identified by the protocol team as essential to the informed consent decision.

13.6 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:

- Study staff
- DAIDS, NICHD, OHRP, NIMH and/or its contractors, including study monitors
- Representatives of Gilead Sciences, Inc. and CONRAD
- The US FDA and/or other government and regulatory authorities
- Site IRBs/ECs

13.7 Special Populations

13.7.1 Pregnant Women

TDF and FTC/TDF are designated as FDA use-in-pregnancy Category B. Participants in MTN-018 will be counseled regarding the potential risks of drug exposure in pregnancy. Additionally, they will be offered contraception by the study site and referred to settings where contraception may be accessed in the community, if desired. Women who become pregnant during trial participation will have study drug held and will be offered participation in MTN-016. At applicable sites, participants will be offered participation in MTN-018C.

13.7.2 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.” This study does not plan to enroll participants under 18 years old.

13.8 Compensation

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

13.9 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.

13.10 Access to HIV-related Care

13.10.1 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 this protocol. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site. 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.

13.10.2 Care for Participants Identified as HIV-Infected

Care for participants identified as HIV-infected is described in Section 9.

13.11 Study Discontinuation

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

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 VISITS AND EVALUATIONS – MONTHLY

	SCR	ENR	MLY	QRTLY	M6	M12	TER/ M14	INT
ADMINISTRATIVE, BEHAVIORAL and REGULATORY								
Co-enrollment assessment	X							
Informed consent(s)	X	X						
Assignment of PTID	X							
Locator information	ALL VISITS							
Demographic info.	X							
Eligibility assessment	X	X						
Randomization			M1					
Behavioral assessment	X	X	M1		X	X	X	◆
Adherence assessment			M1	X	X	X		◆
Social harms assessment				X	X	X		◆
Study product selection		X	M1					
Adherence counseling		X	X	X	X	X		◆
Sharing assessment						X		
HIV pre-/post-test counseling	X		X	X	X	X	X	◆
HIV/STI risk reduction counseling	X	X	X	X	X	X	X	◆
Offer HIV/STI couns./test/referral partners	◆	◆	◆	◆	◆	◆	◆	◆
Reimbursement	X	X	X	X	X	X	X	◆
Schedule next visit	◆	X	X	X	X	X	◆	◆
CLINICAL								
Concomitant meds.	X	X	X	X	X	X	X	◆
Collect/Update medical/menstrual history	X	X	X	X	X	X	X	◆
Blood collection	X	X	X	X	X	X	X	◆
Urine collection	X	X	X	X	X	X	X	◆
Physical exam	X		◆	◆	X	X	◆	◆
Eval. for acute HIV seroconversion			◆	◆	◆	◆	◆	◆
Pelvic examination	X	◆	◆	◆	◆	X	◆	◆
Pelvic swab for STI/vaginitis testing	◆	◆	◆	◆	◆	◆	◆	◆
Collect AEs			X	X	X	X	X	◆
Treatment/referral	◆	◆	◆	◆	◆	◆	◆	◆
Test result disclosure	X	X	X	X	X	X	X	◆
Acute HIV seroconv. educ.		X		X	X	X		
Assess/counsel contraception	X	X	◆	◆	◆	◆	◆	◆
Provision - contraception	◆	◆	◆	◆	◆	◆	◆	◆
Hepatitis B vaccination	As indicated, to be performed at the recommended time points for Hepatitis B vaccine series.							
LABORATORY								
Plasma archive		X			X	X	X	◆
HIV serology	X		X	X	X	X	X	◆
HIV-1 RNA PCR			◆	◆	◆	◆	◆	◆
CD4+ T cell count			◆	◆	◆	◆	◆	◆
HBsAg*	X	◆	◆	◆	◆	X+	◆	◆
HBsAb*	X	◆	◆	◆	◆	◆	◆	◆
Creatinine	X		◆	◆	X-oral	X-oral		◆
AST/ALT	X		◆	◆	X	X	◆	◆
Drug level					X	X		◆
Urine HCG	X	X	X	X	X	X	X	◆
Dip. UA (protein, glucose)	X				X-oral	X-oral		◆
Labs for vaginitis or STI diagnosis	◆	◆	◆	◆	◆	◆	◆	◆
STUDY SUPPLIES								
Provision - condoms	X	X	X	X	X	X	X	◆
Provision - study product		X	X	X	X			◆

X=scheduled, M1=Month 1, ◆=as indicated, *HBsAg/HBsAb required for Non-VOICE Cohort, but may be omitted for VOICE Cohort with evidence of immunity (within VOICE documentation) or completed HBV vaccine series, +=for all susceptible participants not vaccinated against HBV. INT= Interim Visits, *Informed consent for specimen storage can be obtained up to 3 months after ENR. Additional procedures (e.g., HIV and pregnancy testing) are performed on the day of enrollment as part of final screening procedures and confirmation of eligibility (Section 7.2.4). HBV vaccine occurs at visits corresponding with recommended time points for vaccine series.*

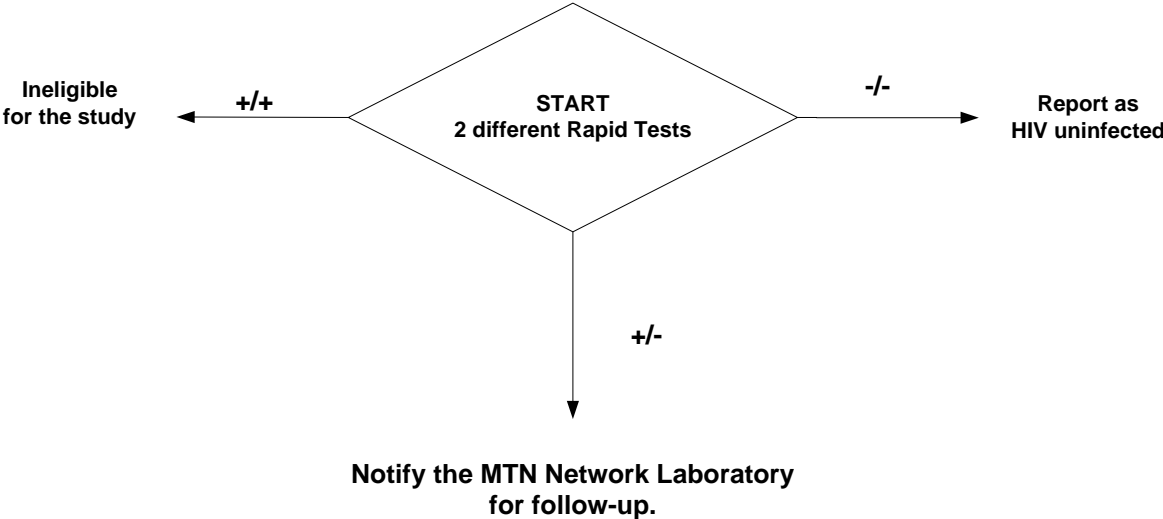
APPENDIX II: SCHEDULE OF VISITS AND EVALUATIONS – QUARTERLY ARM

	SCR	ENR	M1	QRTL	M6	M12	TER/ M14	INT
ADMINISTRATIVE, REGULATORY, and BEHAVIORAL PROCEDURES								
Co-enrollment assessment	X							
Informed consent(s)	X	X						
Assignment of PTID	X							
Locator information	ALL VISITS							
Demographic information	X							
Eligibility assessment	X	X						
Randomization			X					
Behavioral assessment	X	X	X		X	X	X	◆
Adherence assessment			X	X	X	X		◆
Social harms assessment				X	X	X		◆
Study product selection		X	X					
Adherence counseling		X	X	X	X	X		◆
Sharing assessment						X		
HIV pre/post-test counseling	X		X	X	X	X	X	◆
HIV/STI risk reduction counseling	X	X	X	X	X	X	X	◆
Offer HIV/STI couns./test/referral partners	◆	◆	◆	◆	◆	◆	◆	◆
Reimbursement	X	X	X	X	X	X	X	◆
Schedule next visit	◆	X	X	X	X	X	◆	◆
CLINICAL								
Concomitant meds.	X	X	X	X	X	X	X	◆
Collect/Update medical/menstrual history	X	X	X	X	X	X	X	◆
Blood collection	X	X	X	X	X	X	X	◆
Urine collection	X	X	X	X	X	X	X	◆
Physical exam	X		◆	◆	X	X	◆	◆
Eval. for acute HIV seroconversion			◆	◆	◆	◆	◆	◆
Pelvic examination	X	◆	◆	◆	◆	X	◆	◆
Pelvic swab for STI/vaginitis testing	◆	◆	◆	◆	◆	◆	◆	◆
Collect AEs			X	X	X	X	X	◆
Treatment/referral	◆	◆	◆	◆	◆	◆	◆	◆
Test result disclosure	X	X	X	X	X	X	X	◆
Acute HIV seroconv. educ.		X		X	X	X		
Assess/counsel contraception	X	X	◆	◆	◆	◆	◆	◆
Provision - contraception	◆	◆	◆	◆	◆	◆	◆	◆
Hepatitis B vaccination	As indicated, to be performed at the recommended time points for Hepatitis B vaccine series.							
LABORATORY								
Plasma archive		X			X	X	X	◆
HIV serology	X		X	X	X	X	X	◆
HIV-1 RNA PCR			◆	◆	◆	◆	◆	◆
CD4+ T cell count			◆	◆	◆	◆	◆	◆
HBsAg*	X	◆	◆	◆	◆	X+	◆	◆
HBsAb*	X	◆	◆	◆	◆	◆	◆	◆
Creatinine	X		◆	◆	X-oral	X-oral		◆
AST/ALT	X		◆	◆	X	X	◆	◆
Drug level					X	X		◆
Urine HCG	X	X	X	X	X	X	X	◆
Dip. UA (protein, glucose)	X				X-oral	X-oral		◆
Labs for vaginitis or STI diagnosis	◆	◆	◆	◆	◆	◆	◆	◆
STUDY SUPPLIES								
Provision - condoms	X	X	X	X	X	X	X	◆

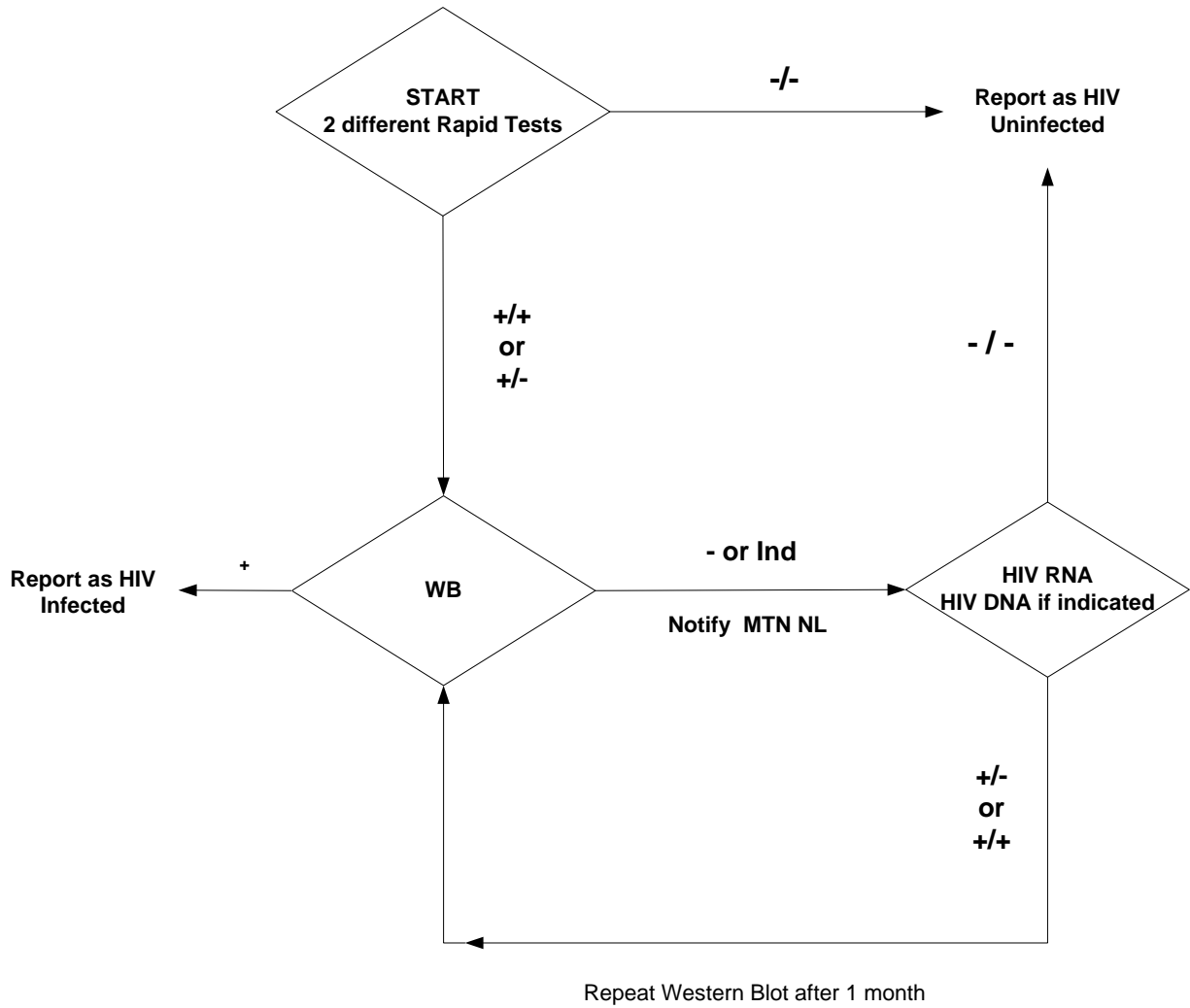
Provision - study product		X	X	X	X			◆
---------------------------	--	---	---	---	---	--	--	---

X=scheduled, M1=Month 1, ◆=as indicated, *HBsAg/HBsAb required for Non-VOICE Cohort, but may be omitted for VOICE Cohort with evidence of immunity (within VOICE documentation) or completed HBV vaccine series, +=for all susceptible participants not vaccinated against HBV. INT= Interim Visits, *Note: Informed consent for specimen storage can be obtained up to 3 months after ENR. Additional procedures (e.g., HIV and pregnancy testing) are performed on the day of enrollment as part of final screening procedures and confirmation of eligibility (Section 7.2.4). HBV vaccine occurs at visits corresponding with recommended time points for vaccine series.*

**APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING –
SCREENING/ENROLLMENT**

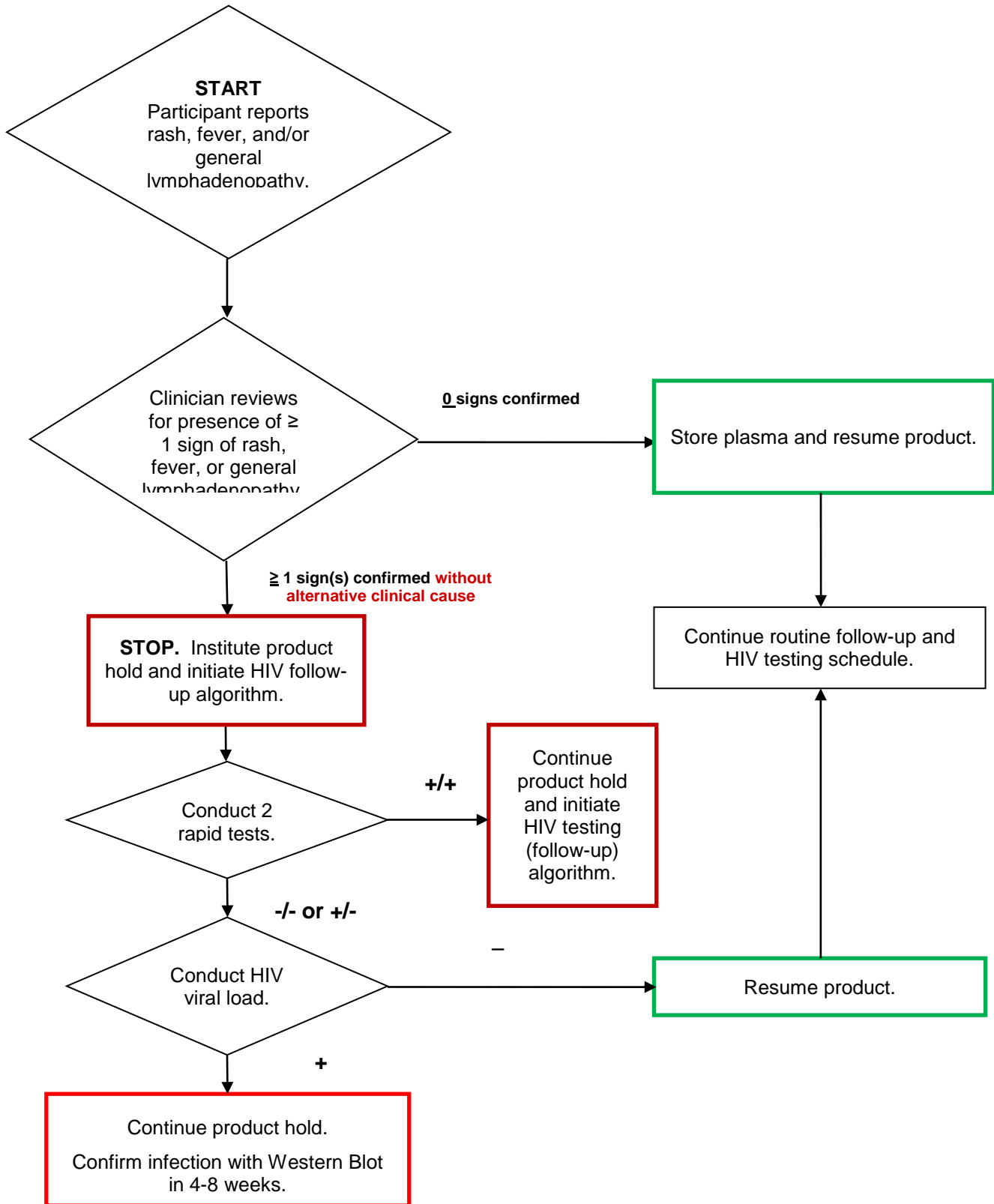


APPENDIX IV: ALGORITHM FOR HIV TESTING – FOLLOW-UP

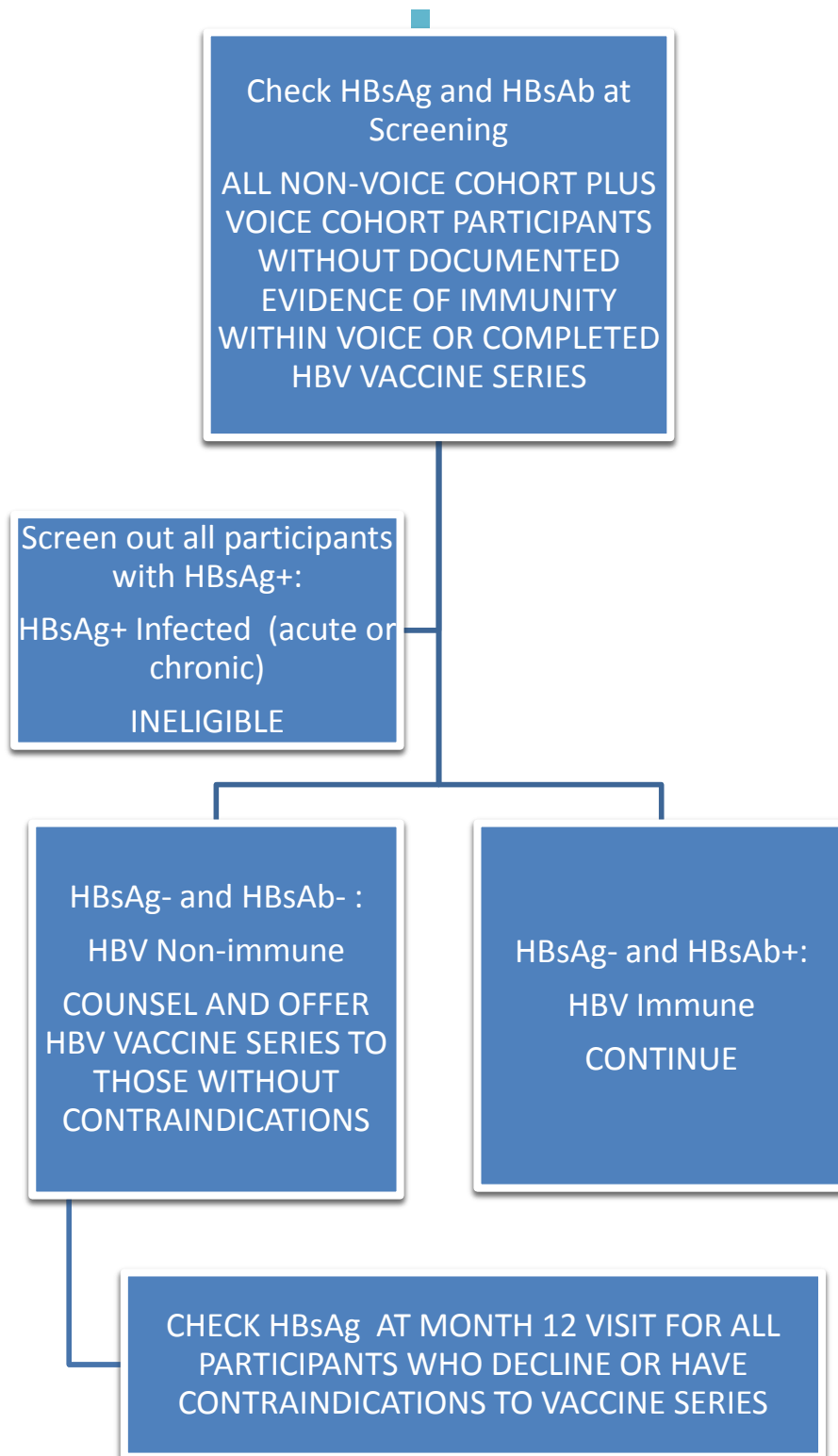


Ind: Indeterminate test results

APPENDIX V: ALGORITHM FOR DETECTION OF HIV ACUTE INFECTION



APPENDIX VI: ALGORITHM FOR HBV TESTING



APPENDIX VII: SAMPLE INFORMED CONSENT FORM (SCREENING – VOICE COHORT)

DIVISION OF AIDS, NIAID, US National Institutes of Health (US NIH)

MTN-018

**Committed to Having Options for Interventions to Control the Epidemic (CHOICE):
A Follow-up Study to MTN-003**

Version 1.0

September 6, 2011

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

INFORMED CONSENT

You are being asked to volunteer for screening tests to find out if you are eligible for a research study known as CHOICE. CHOICE is for women who were in the VOICE study and a smaller group of women who have never been in an HIV prevention study. CHOICE's main purpose is to collect more information about the safety of [*insert study products*]. CHOICE is also testing different schedules of follow-up (monthly check-ups compared to check-ups every three months). Screening for this research study includes questions, blood tests, a physical exam, and genital exam. The United States National Institutes of Health (US NIH) is funding the study. About 4,000 women from VOICE and about 300 women who were not in VOICE will join CHOICE at different locations in Africa. Here we will explain the purpose of screening, risks and benefits to you, and what is expected of you. This form may have unfamiliar words. 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 screening tests in CHOICE. Once you understand this form, 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 to keep. Before you learn about the screening tests, it is important that you know that 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 at any time after signing this form, without losing your regular medical care. Even if you agree to do screening tests, you do not have to join CHOICE. If you decide not to have the screening tests, you can join another study later, if one is available and you qualify. However, you cannot join CHOICE if you are in another study of drugs, medical devices or vaginal products. Please tell us about any other studies you are in, or thinking of taking part in. This is very important for your safety.

PURPOSE OF THE SCREENING TESTS

The purpose of the screening tests is to find out if you are eligible for CHOICE. Some people may not be able to join CHOICE because of results of screening tests. You will receive test results even if you are not eligible to join CHOICE. The study doctors will also review your records from VOICE.

PROCEDURES

For you to join CHOICE, all screening tests must be completed within 6 weeks after you sign this form. If all tests are not done within 6 weeks, and you want to join CHOICE, you will have to do all screening tests again. Screening will begin after you discuss, understand and sign or make your mark on this form. We will answer your questions before you sign or mark this form. Procedures at this visit take about [*insert time*].

- We will ask where you live and other questions about you and your health.
- You will give urine for a pregnancy test and to test the health of your kidneys. If you are pregnant, you are not eligible for CHOICE. We will refer you to sources of medical care and other available services. If CHOICE is still open after your pregnancy, you may return to find out if you are eligible.
- You will talk with staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex. You will give blood (XX mL) for HIV testing. You will be told your result as soon as it is available on the same day (results take [*insert estimate*] minutes). You will talk with us about your results and how you feel about them. Sometimes HIV tests are not clearly positive or negative. In that case, we do more tests until we know your status for sure. You must receive your HIV test results to be in CHOICE. If you have HIV, you are not eligible for CHOICE. We will tell you about other studies you may be eligible for, if any. We will refer you to sources of medical care and other available services.
- If the tests show that you do not have HIV, the study staff will test your blood for:
 - The health of your liver and kidneys.
 - Hepatitis B, if a study doctor thinks this is necessary based on your blood tests from VOICE. This is a liver infection that can pass from mother to baby, through sex or through body fluids infected with hepatitis B. If tests show you have hepatitis B active in your liver, you are not eligible for CHOICE.
- You will have a physical exam including measurements of your height and weight .
- You will have an exam of your genital area and inside your vagina. Study staff may collect fluid from your vagina with a swab to test for infections if necessary.
- You will get condoms.
- You will get treated for infections passed through sex, if needed.
- You will get referrals for other available services if you or your partner(s) need them.

You will return for a visit when your test results are available [*insert estimate*]. If results show that you may have some health problems, you may be ineligible for CHOICE. Study staff will refer you to available sources of medical care and other available services. If these problems resolve, you can come back to find out if you are eligible.

Final Screening Procedures/Confirmation of Eligibility:

The screening tests done at this visit will take about *[insert estimate]*. We will:

- Tell you your test results and what they mean.
- Ask questions to update the information from your earlier visits.
- Test your urine for pregnancy. If you are not pregnant, study staff will talk with you about contraception and provide it if you need it.
- You will have testing for HIV with the same procedures as above. If tests show you have HIV, you are not eligible for CHOICE. We will tell you about other studies you may be eligible for, if any, and refer you to medical care and other services.

We then will review all of your screening test results. If results show you are eligible for CHOICE, we will fully explain the study to you and answer any questions you have. If you decide to take part in CHOICE, you will be asked to sign another consent form. *[For applicable sites: You may sign the consent form for further participation in CHOICE before you finish the screening tests. This gives us permission to do final blood tests for screening and the first set of blood tests for women who enroll in CHOICE using one blood draw instead of two. We will talk with you more about this if you request it.]*

Alternatives: What other choices are there besides screening for this study?

You are free to choose not to be in this research. There may be other research in the area that you can be in. HIV testing is available free at *[to be completed by sites]*. Other tests and care are available at *[to be completed by sites]*.

RISKS AND/OR DISCOMFORTS

Some people feel pain, dizziness, or faintness when blood is drawn. You may have more than expected bleeding, a bruise, swelling, small clot, or infection where the needle goes into your finger or arm. You may feel discomfort or embarrassment during a genital exam. You may have a small amount of vaginal bleeding which will stop shortly after the exam. You may become embarrassed or worried when discussing sex, HIV, and your test results. You may feel worried while waiting for results or if you learn that you have HIV or other infections. Trained counselors will help you deal with any feelings or questions you have. We will make every effort to protect your privacy and confidentiality. Your visits will take place in private. However, it is possible that others may learn of your participation and, because of this, treat you unfairly. For example, you could have problems with your job, family or community. Finding out your HIV status could cause problems between you and your partner. If you have problems, 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, genital exam, and tests of your liver and kidneys. If tests show you might have health problems, you will be referred for medical care and other available services. You will get counseling and testing for HIV and free condoms. If you have HIV, you will be referred for care, counseling, and other available services. You will get counseling and testing for other infections passed through sex, and treatment, if needed. Your

partner(s) can come here for HIV counseling and testing and treatment for infections passed through sex. For other problems not treated here, we will refer you to places where you can get care.

If new information is learned about the study or study products, you will be told about this as soon as possible.

WHY YOU MAY BE WITHDRAWN FROM SCREENING TESTS WITHOUT CONSENT

You may be withdrawn from screening tests without your consent if:

- You are found to not be eligible for CHOICE, or if CHOICE 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, attend visits or complete screening.
- Other reasons, decided by the study staff.

COSTS TO YOU

There is no cost to you for screening tests. Treatments for you and/or your partner(s) for infections passed through sex (other than HIV and hepatitis B) are 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. We will use your personal information, if needed, to verify that you are not in other studies. Study publications will not use your name or identify you personally.

Your records may be reviewed by study staff, as well as:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH) or its study monitors and other representatives of NIH
- US Office of Human Research Protections (OHRP)
- *[insert applicable local authorities, e.g., Institutional Review Board (IRB), medicine control authority]*
- the organizations that supply the gel (CONRAD) and tablets (Gilead Sciences)

[Sites to include/amend the following if applicable:] *[Local/state/national]* regulations require us to report names of people who test positive for *[HIV and other infections]* passed during sex to *[local health authority]*. Outreach workers from *[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 *[health authority]*.

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you will be injured as a result of having screening tests. If you are injured, *[institution]* will give you immediate treatment for your injuries. You *[will/will not]* have to pay for this. You will be told where you can get additional treatment. There is no program to pay money or 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]* at *[insert contact information]*. If you have questions about your rights as a research participant, you should contact *[insert name or title of person on the IRB/Ethics Committee (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 Community Advisory Board (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
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

APPENDIX VIII: SAMPLE INFORMED CONSENT DOCUMENT (SCREENING – NON-VOICE COHORT)

DIVISION OF AIDS, NIAID, US National Institutes of Health (US NIH)

MTN-018

**Committed to Having Options for Interventions to Control the Epidemic (CHOICE):
A Follow-up Study to MTN-003**

Version 1.0

September 6, 2011

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

INFORMED CONSENT

You are being asked to volunteer for screening tests to find out if you are eligible for a research study known as CHOICE. CHOICE is for women who were in the VOICE study and a smaller group of women who were not in VOICE. VOICE was a research study that tested the safety and effectiveness of three different products (Truvada tablets, tenofovir tablets, and tenofovir gel) to prevent HIV infection in women. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome). The results of the VOICE study showed [to be updated in modification].

You are being asked to volunteer because you are between 18 and 50 years old and were not in VOICE or other research studies of HIV prevention. CHOICE's main purpose is to collect more information about the safety of [*insert study products*]. CHOICE is also testing different schedules of follow-up (monthly check-ups compared to check-ups every 3 months). Screening includes questions, blood tests, a physical exam, and genital exam. The United States National Institutes of Health (US NIH) is funding the study. About 4,000 women from VOICE and about 300 women who were not in VOICE will join CHOICE at different locations in Africa. Here we will explain the purpose of screening, risks and benefits to you, and what is expected of you. This form may have unfamiliar words. 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 in CHOICE. Once you understand this form, 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 to keep. Before you learn about the screening tests, it is important that you know that 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 at any time after signing this form, without losing your regular medical

care. Even if you agree to do screening tests, you do not have to join CHOICE. If you decide not to have the screening tests, you can join another study later, if one is available and you qualify. However, you cannot join CHOICE if you are in another study of drugs, medical devices or vaginal products. Please tell us about any other studies you are in, or thinking of taking part in. This is very important for your safety.

PURPOSE OF THE SCREENING TESTS

The purpose of the screening tests is to find out if you are eligible for CHOICE. Some people may not be able to join CHOICE because of results of the screening tests. You will receive your test results even if you are not eligible to join CHOICE.

PROCEDURES

For you to join CHOICE, all screening tests must be completed within 6 weeks after you sign this form. If all tests are not done within 6 weeks, and you want to join CHOICE, you will have to do all screening tests again. Screening will begin after you discuss, understand and sign or make your mark on this form. We will answer your questions before you sign or mark this form. Procedures at this visit take about [*insert estimate*].

- We will ask about where you live, past and present members of your household, and other questions about you and your health.
- We will ask about any research studies in which you have participated, and check to see if you have been in studies here or at other research clinics.
- You will give urine for a pregnancy test and to test the health of your kidneys. If you are pregnant, you are not eligible for CHOICE. We will refer you to sources of medical care and other available services. If CHOICE is still open after your pregnancy, you may return to find out if you are eligible.
- You will talk with staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex. You will give blood (XX mL) for HIV testing. You will be told your result as soon as it is available on the same day (results take [*insert estimate*] minutes). You will talk with us about your results and how you feel about them. Sometimes HIV tests are not clearly positive or negative. You will have HIV tests until we know your status for sure. You must receive your HIV test results to be in CHOICE. If you have HIV, you are not eligible for CHOICE. We will tell you about other studies you may be eligible for, if any. We will refer you to sources of medical care and other available services.
- If the tests show that you do not have HIV, the study staff will test your blood for:
 - The health of your liver and kidneys.
 - Hepatitis B. This is a liver infection that can pass from mother to baby, through sex or through body fluids infected with hepatitis B. If tests show you have hepatitis B active in your liver, you are not eligible for CHOICE.
- You will have a physical exam and measurements of your height and weight
- You will have an exam of your genital area and inside your vagina. Study staff may collect fluid from your vagina with a swab to test for infections if necessary.
- You will get condoms.
- You will get treated for infections passed through sex, if needed.
- You will get referrals for other services if you or your partner(s) need them.

You will come back for a visit when your test results are available [*insert estimate*]. If the results show that you might have some health problems, you may not be eligible for CHOICE. Study staff will refer you to available sources of medical care and other services. If these problems resolve, you can come back to find out if you are eligible.

Final Screening Procedures/Confirmation of Eligibility:

The screening tests done at this visit will take about [*insert estimate*] hours. We will:

- Tell you your test results and what they mean.
- Ask questions to update the information from your earlier visits.
- Test your urine for pregnancy. If you are not pregnant, study staff will talk with you about contraception and provide it if you need it.
- You will have testing for HIV, using the same procedures as above. If tests show you have HIV, you are not eligible for CHOICE. We will tell you about other studies you may be eligible for, if any, and refer you to medical care and other services.

We then will review all of your screening test results. If results show you are eligible for CHOICE, we will fully explain the study to you and answer any questions you have. If you decide to take part in CHOICE, you will be asked to sign another consent form. [*For applicable sites: You may sign the consent form for further participation in CHOICE before you finish the screening tests. This gives us permission to do final blood tests for screening and the first set of blood tests for women who enroll in CHOICE using one blood draw instead of two. We will talk with you more about this if you request it.*]

ALTERNATIVES: What other choices are there besides being in this research?

You are free to choose not to be in this research. There may be other research in the area that you can be in. HIV testing is available free at [*to be completed by sites*]. Other tests and care are available at [*to be completed by sites*].

RISKS AND/OR DISCOMFORTS

Some people feel pain, dizziness, or faintness when blood is drawn. You may have more than expected bleeding, a bruise, swelling, small clot, or infection where the needle goes into your finger or arm. You may feel discomfort during a genital exam. You may have a small amount of vaginal bleeding which will stop shortly after the exam. You may become embarrassed or worried when discussing sex, HIV, and your test results. You may feel worried while waiting for results or if you learn that you have HIV or other infections. Trained counselors will help you deal with any feelings or questions you have. We will make every effort to protect your privacy and confidentiality. Your visits will take place in private. However, it is possible that others may learn of your participation and, because of this, treat you unfairly. For example, you could have problems with your job, family or community. Finding out your HIV status could cause problems between you and your partner. If you have problems, 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, genital exam, and tests of your liver and kidneys. If tests show you might have health problems, you will be referred for medical care and other available services. You will get counseling and testing for HIV and free condoms. If you have HIV, you will be referred for care, counseling, and other available services. You will get counseling and testing for other infections passed through sex, and treatment, if needed. Your partner(s) can come here for HIV counseling and testing and treatment for infections passed through sex. For other problems not treated here, we will refer you to places where you can get care.

If new information is learned about the study or study products, you will be told about this as soon as possible.

WHY YOU MAY BE WITHDRAWN FROM SCREENING TESTS WITHOUT CONSENT

You may be withdrawn from screening tests without your consent if:

- You are found to not be eligible for CHOICE, or if CHOICE 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, attend visits or complete screening tests.
- Other reasons, decided by the study staff.

COSTS TO YOU

There is no cost to you for the screening tests. Treatments for you and/or your partner(s) for infections passed through sex (other than HIV and hepatitis B) are 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. We will use your personal information, if needed, to verify that you are not in other studies. Study publications will not use your name or identify you personally.

Your records may be reviewed by study staff, as well as:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH) or its study monitors and other representatives of NIH
- US Office of Human Research Protections (OHRP)
- [*insert applicable local authorities, e.g., Institutional Review Board (IRB), medicine control authority*]
- the organizations that supply the gel (CONRAD) and tablets (Gilead Sciences)

[Sites to include/amend the following if applicable:] [Local/state/national] regulations require us to report names of people who test positive for [HIV and other infections] passed during sex to [local health authority]. Outreach workers from [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 [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, [institution] will give you immediate treatment for your injuries. You [will/will not] have to pay for this. You will be told where you can get additional treatment. There is no program to pay money or 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]* at *[insert contact information]*. If you have questions about your rights as a research participant, you should contact *[insert name or title of person on the IRB/Ethics Committee (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 Community Advisory Board (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
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

APPENDIX IX: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT – VOICE COHORT)

DIVISION OF AIDS, NIAID, US National Institutes of Health (US NIH)

MTN-018

**Committed to Having Options for Interventions to Control the Epidemic (CHOICE):
A Follow-up Study to MTN-003**

Version 1.0

September 6, 2011

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

INFORMED CONSENT

You are being asked to take part in a research study known as CHOICE. CHOICE is for women who were in the VOICE study and a smaller group of women who were not in VOICE, or any other study of HIV prevention. The main purpose of CHOICE is to collect more information on the safety of [*insert study products*]. CHOICE is also testing different schedules of follow-up (monthly check-ups compared to check-ups every 3 months). The United States National Institutes of Health (US NIH) is funding the study. We expect that about 4,000 women from VOICE and 300 women who were not in VOICE will join CHOICE at different sites in Africa. You are being invited to be in CHOICE because you took part in the VOICE study. We will explain the purpose of the study, risks and benefits to you, and what is expected of you. This form may have unfamiliar words. Please ask questions about anything you do not understand or want to learn more about. 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.]

YOUR PARTICIPATION IS VOLUNTARY

This form gives information about joining CHOICE. Once you understand the study, and if you agree to join, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep. You do not have to join the study if you do not want to. You may decide not to join, or withdraw at anytime, without losing your regular medical care. If you decide not to join CHOICE, you can join another study later, if one is available and you qualify. However, you cannot join CHOICE if you are in another study of drugs, medical devices or vaginal products. Please tell us about any other studies you are in, or thinking of joining. This is very important for your safety.

PURPOSE OF THIS RESEARCH STUDY

[VOICE results to be inserted here]

The main purpose of CHOICE is to collect more information on the safety of [*insert study products*]. CHOICE is also testing different schedules of follow-up (monthly check-ups compared to check-ups every 3 months). The study is expected to be finished in [*insert*]. Each woman will be in the study for about a year, depending on when they join the CHOICE study.

CHOICE is testing [*insert number*] products.

- A gel that is put in the vagina called tenofovir gel.
- A tablet that is taken by mouth, called [*insert name*]

There is no placebo gel or placebo tablet in CHOICE. (a placebo contains no medication). We will ask you to choose a product to use during CHOICE. You can choose the gel or the tablet. You do not have to choose the same thing you used in VOICE.

STUDY GROUPS

There are two groups in CHOICE. In one group, most visits are monthly. In the other group, most visits are every three months. Your group will be chosen “by lot” [or other equivalent local term, for example, like flipping a coin]. You cannot choose your group, and we cannot choose for you. You have an equal chance of being placed in either of the two groups. Once you are in one group, you cannot change to another.

Both groups are very important to this study. All women will get condoms and counseling on how to avoid HIV and other infections passed during sex.

Regardless of your choice of study product:

- You will be given a supply of your study product at each scheduled study visit.
- You will be given instructions on how to use the product.
 - If you use 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 use the product once a day, at the same time.
- You will be asked to bring all unused product you have left from previous visits.
- You will be asked to return all unused product if you stop participating in this study or are asked to stop taking medication
- You will be asked not to share your product or use anyone else’s product.

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 join CHOICE, 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.

You will answer interview questions about your sexual practices. You will give [insert] teaspoons [or local equivalent] of blood that the study staff will keep here while you are in the study. If needed, they will test this blood later in the study to check on your health.

If your 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 get the hepatitis B vaccine, you will have this vaccine three times (usually today, in one month, and again in six months) [*insert local guidelines, if applicable*]. If you do not get the hepatitis B vaccine, you will be tested for hepatitis B at the end of the study. You may also be tested if you have signs or symptoms of hepatitis B during the study. If you are in the tablet group and become infected with hepatitis B, you may also have tests for the health of your liver, about 6 months after you finish taking the tablets.

If you join CHOICE, you will be in the study about one year or less, depending on when you join. The procedures done at these visits will take about [*insert estimate*].

At most visits, you will:

- Tell staff if you had any health problems since your last visit
- Tell staff about medications, herbal treatments and supplements you are taking
- Tell staff any new information on where you live and how to keep in contact with you. If you miss a visit, we will try to contact you by [site-specific methods]. We also may visit your home. We will try to reach you through the contact people that you list. If we talk to these people, we will not say why we want to reach you.
- Bring your unused gel or tablets and bottles to be counted by study staff
- Talk with staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex
- You will give [about X mL [or local equivalent] of blood from your arm or finger] for HIV testing. We first do two tests that give results during your visit. Sometimes more tests are needed to know your HIV status. You will have testing (which may require you to return) until we know your status for sure. You will talk with staff about your results and how you feel about them. If tests show you have HIV, the US NIH requires that we send a sample of your blood to the US to check the results again. You must receive your HIV test results to stay in the study.
- Give urine for a pregnancy test
- 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
- Get new supplies of gel or tablets

After 1 month, you will:

- Tell study staff if you would like to continue using the study product you chose
- Be allowed to change to a different CHOICE study product if you want
- Answer questions about your sexual practices, reproductive health, your participation in this study and use of gel or tablets. Some of these questions will be asked by computer, just like in VOICE

- You will find out if you will have most visits monthly or every three months.

If you are in the group that comes for monthly visits, you will:

- Have tests to check your HIV status every month for a year
- Have pregnancy test every month for a year
- Hear about possible signs of a new HIV infection (every three months), including rash and fever. If you have a rash and fever, you should come to the clinic for a check-up.

If you are in the group that comes for visits every three months, you will:

- Have tests to check your HIV status every three months for a year
- Have a pregnancy test every three months for a year
- Have the option of picking up your study product monthly from the pharmacy, instead of every three months, if you want [*insert if applicable: but you will not be reimbursed for these extra pick-up visits*]
- Hear about possible signs of a new HIV infection (every three months), including rash and fever. If you have a rash and fever, you should come to the clinic for a check-up.

About every six months, you will also:

- Have blood and urine tests of the health of your kidneys, if you have been using tablets most recently
- Have a blood test of the health of your liver
- Have a blood test for the amount of study drug in your blood

At your end of product visit, you will:

- Have a physical exam.
- Have 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

It will be necessary to ship some of your biological samples outside of the country, for example your blood will be shipped to the United States in order to assess how much of the study drug is absorbed by your body. If you are thought to be HIV-infected, this will be confirmed in a laboratory in the United States and additional testing related to the HIV infection will also be performed.

AT ANY TIME IN THE STUDY

If you want to change to a different study product, you will:

- Talk with a study doctor first to see if this is an option for you, based on your health and on the number of times you have already changed your study product. In general, only one change is allowed after your Month 1 visit.

If you have problems that may be caused by infections passed by sex, you will:

- Have an exam of your genital area and inside your vagina
- 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 a group that uses tablets
- Be given referrals for medical care and other services you may need

If you have a rash and fever:

- You will come in to get checked by a study doctor
- You may get tested for HIV, depending on the results of your check-up. (Some but not all people have these signs with a new HIV infection. These signs can also be due to side effects to medication or other medical problems.)

If you become infected with HIV:

If you may have been infected with HIV, you will have at least three tests to confirm your results. Each time blood is drawn for these tests, you will also give blood (XX mL) to test for the amount of HIV in your blood, whether any HIV in your blood is resistant to medications used to treat HIV, 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. Results of resistance tests will be given to you. If HIV tests confirm that you have HIV, you will stop using gel or tablets. If you do not have your study products with you, a staff person may go to your home to collect them.

We will counsel you and refer you for medical care and other available services. We also will refer you to another study called MTN-015. You will be asked to have additional blood drawn 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

POSSIBLE FUTURE TESTS

Some of the blood that you give during CHOICE may be left over after all the study tests are completed. The staff would like to keep your leftover blood. You will be asked to sign a separate form to give permission for that. Even if you do not give permission to store your blood after the study, you can still be in CHOICE.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may:

- Feel discomfort or pain when your blood is drawn
- Feel dizzy or faint, but most women do not have this reaction

- Have more than expected bleeding, 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 will be stored on a larger computer here at [study site] that can only be accessed by authorized staff. Your answers 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 uses gel, the gel could cause some bad effects. Some, but not all, women who used the gels in other studies have had:

- Dryness, itching, burning feeling, irritation or pain in the genital area
- Vaginal candidiasis (a kind of vaginal infection)
- Discharge from the vagina
- Diarrhea

You could have these effects or other effects that we do not know about.

Some, but not all women who used emtricitabine (one of the drugs in Truvada) have had these effects:

- Headache
- Dizziness
- Tiredness, inability to sleep, unusual dreams
- Loose or watery stools, upset stomach (nausea) or vomiting, abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Skin darkening of the palms and/or soles
- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage

Persons infected with both Hepatitis B and HIV may have increases in liver tests, and symptoms associated with hepatitis may worsen if emtricitabine is stopped.

Some, but not all women have had these effects while using tenofovir tablets:

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Headache
- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver
- Shortness of breath
- Rash
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness

Persons infected with both Hepatitis B and HIV may have increases in liver tests, and symptoms associated with hepatitis may worsen if tenofovir is stopped.

You could have these side effects or other side effects that we do not know about.

Both Gel and Tablet Groups

HIV infections are usually treated with three or more medications used together. If you become infected with HIV while using your study product, taking your study product would not properly treat HIV infection. Continuing to take study product after HIV infection occurs could cause drug resistance and limit your options for HIV treatment in the future. It is for this reason that you must stop using your study product if you get HIV. Study doctors are available to discuss this with you. If you do become infected with HIV during CHOICE, they can do blood tests to 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, such as pain at the injection site, 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 using gel or tablets. Please tell staff if you use any 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 HIV prevention studies have found an unexpected higher risk of getting HIV among participants. This could happen in any study, including CHOICE. Because of this, 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

Information on the effects of the study products on a developing fetus is limited. Studies have not shown bad effects on pregnancy, fetuses of women who use the gels or tablets when pregnant, or babies of women who use the gels or tablets when breastfeeding. However, pregnant women and women who are breastfeeding are not being included in this study. *[Insert if applicable: We can talk to you about other studies for pregnant and breastfeeding women.]*

Women who become pregnant during the study may be exposed to study product up to 3 months, if they are having pregnancy tests done every three months. 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. Participants who do not join the pregnancy substudy 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. 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 *[modify based on available substudies at the site]*. The study staff will talk more with you about this after your pregnancy.

BENEFITS

[insert VOICE effectiveness results]

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 and genital exams. You will have tests to check the health of your 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, you may benefit from getting the 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 or hepatitis B, 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 receive results of your resistance tests, be referred for medical care, counseling, and other services available to you.

NEW INFORMATION

You will be told any new information that might affect your willingness to stay in CHOICE, when study results may be ready, and how to learn them.

WHY YOU MAY HAVE TO STOP TAKING THE STUDY DRUG EARLY

You will have to stop using gel or tablets if you become infected with HIV, become infected with hepatitis B, are taking medication called PEP for possible recent exposure to HIV infection, are unwilling to follow study procedures or instructions, or could be harmed by continuing to take gel or tablets. Pregnant and breastfeeding women who are not enrolled in MTN-018 pregnancy and breastfeeding substudies must stop taking their gel or tablets. Even if you stop using gel or tablets, you will stay in the study and have your monthly visits as planned (unless you are HIV-infected and join MTN-015).

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

[*Sites to include/amend the following if applicable:* There may be other studies here or in the community. If you wish, we will tell you about other studies that we know about. There are 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 to be in CHOICE. Treatments available to you and/or your partner(s) for infections passed through sex other than HIV and hepatitis B will be provided free.

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. 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 study staff, as well as:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH) or its study monitors
- [insert applicable local authorities, e.g., IRB, medicine control authority]
- the organizations that supply the gel (CONRAD) and 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 confidentiality guidelines of [*health authority*].

RESEARCH-RELATED INJURY

[*Sites to specify institutional policy:*] If you are injured, [*institution*] will give you immediate treatment for your injuries. You [*will/will not*] have to pay for this. You will be told where you can get additional treatment. There is no program to pay money or 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*] at [*insert contact information*].

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 X: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT – NON-VOICE COHORT)

DIVISION OF AIDS, NIAID, US National Institutes of Health (US NIH)

MTN-018

Committed to Having Options for Interventions to Control the Epidemic (CHOICE):
A Follow-up Study to MTN-003

Version 1.0

September 6, 2011

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

INFORMED CONSENT

You are being asked to take part in a research study known as CHOICE. CHOICE is for women who were in VOICE and a smaller group of women who were not in VOICE or any other study of HIV prevention. VOICE was a study that tested the safety and effectiveness of three different products (Truvada tablets, tenofovir tablets, and tenofovir gel) to prevent HIV infection in women. HIV is the virus that causes AIDS (Acquired Immune Deficiency Syndrome).

The main purpose of CHOICE is to collect more information on the safety of [insert study products]. CHOICE is also testing different schedules of follow-up (monthly check-ups compared to check-ups every 3 months). The United States National Institutes of Health (US NIH) is funding the study. We expect about 4,000 women from VOICE and 300 women who were not in VOICE to join CHOICE at different locations in Africa. You are being invited to join CHOICE because you are between 18 and 50 years old and were not in VOICE or any other HIV prevention study. We will explain the purpose of CHOICE, risks and benefits to you, and what is expected of you. This form may have unfamiliar words. Please ask questions about anything you do not understand or want to learn more about.

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.]

YOUR PARTICIPATION IS VOLUNTARY

This form gives information about joining CHOICE. Once you understand the study, and if you agree to join, you will be asked to sign your name or make your mark on this form. You will be offered a copy to keep. You do not have to join the study if you do not want to. You may decide not to join, or withdraw at any time, without losing your regular

medical care. If you decide not to join CHOICE, you can join another study later, if one is available and you qualify. However, you cannot join CHOICE if you are in another study of drugs, medical devices or vaginal products. Please tell us about any other studies you are in, or thinking of joining. This is very important for your safety.

PURPOSE OF THIS RESEARCH STUDY

The main purpose of CHOICE is to collect more information on the safety of [*insert study products*]. CHOICE is also testing different schedules of follow-up (monthly check-ups compared to check-ups every 3 months). The study is expected to be finished in [*insert*]. Each woman will be in the study for about a year, depending on when they join CHOICE.

CHOICE is testing [*insert number*] products.

- A gel that is put in the vagina called tenofovir gel.
- A tablet that is taken by mouth, called [*insert name*]

There is no placebo gel or placebo tablet in CHOICE. (a placebo contains no medication). We will ask you to choose a product to use during CHOICE. You can choose the gel or the tablet.

STUDY GROUPS

There are two groups in CHOICE. In one group, most visits are monthly. In the other group, most visits are every three months. Your group will be chosen “by lot” [or other equivalent local term, for example, like flipping a coin]. You cannot choose your group, and we cannot choose for you. You have an equal chance of being placed in either of the two groups. Once you are in one group, you cannot change to another.

Both groups are very important to this study. All women will get condoms and counseling on how to avoid HIV and other infections passed during sex.

Regardless of your choice of study product:

- You will be given study product at each scheduled study visit.
- You will be given instructions on how to use your study product.
 - If you choose 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 use the product once a day, at the same time.
- You will be asked to bring all unused product you have left from previous visits.
- You will be asked to return all unused product if you stop participating in this study or are asked to stop taking medication
- You will be asked not to share your product or use anyone else’s product.

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 join CHOICE, 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.

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 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 (usually today, in one month, and again in six months) [*insert local guidelines, if applicable*]. If you choose not to get the hepatitis B vaccine, you will be tested for hepatitis B at the end of the study. You may also be tested if you have signs or symptoms of hepatitis B during the study. If you are in the tablet group and become infected with hepatitis B, you may also have tests for the health of your liver, about 6 months after you finish taking tablets.

If you join CHOICE, you will be in the study about one year or less, depending on when you join. The procedures done at these visits will take about [*insert estimate*].

At most visits, you will:

- Tell staff if you had any health problems since your last visit
- Tell staff about medications, herbal treatments and supplements you are taking
- Tell staff any new information on where you live and how to keep in contact with you. If you miss a visit, we will try to contact you by [*site-specific methods*]. We also may visit your home. We will try to reach you through the contact people that you list. If we talk to these people, we will not say why we want to reach you.
- Bring your unused gel or tablets and bottles to be counted by study staff
- Talk with staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex
 - You will give [about X mL [or local equivalent] of blood from your arm or finger] for HIV testing. We first do two tests that give results during your visit. Sometimes more tests are needed to know your HIV status. You will have testing (which may require you to return) until we know your status for sure. You will talk with staff about your results and how you feel about them. If tests show you have HIV, the US NIH requires that we send a sample of your blood to the US to check the results again. You must receive your HIV test results to stay in the study.
- Give urine for a pregnancy test
- 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

- Get new supplies of gel or tablets

After 1 month, you will:

- Tell study staff if you would like to continue using the study product you chose
- Be allowed to change to a different CHOICE study product if you want
- Answer questions about your sexual practices, reproductive health, your participation in this study and use of gel or tablets. Some of these questions will be asked by computer. We will help you learn how to answer questions on a computer
- You will find out if you will have most visits monthly or every three months.

If you are in the group that comes for monthly visits, you will:

- Have tests to check your HIV status every month for a year
- Have pregnancy test every month for a year
- Hear about possible signs of a new HIV infection (every three months), including rash and fever. If you have rash and fever, you should come here for a check-up.

If you are in the group that comes for visits every three months, you will:

- Have tests to check your HIV status every three months for a year
- Have a pregnancy test every three months for a year
- Have the option of picking up your study product monthly from the pharmacy, instead of every three months, if you want [*insert if applicable: but you will not be reimbursed for these extra pick-up visits*]
- Hear about possible signs of a new HIV infection (every three months), including rash and fever. If you have rash and fever, you should come here for a check-up.

About every six months, you will also:

- Have blood and urine tests of the health of your kidneys, if you have been using tablets most recently
- Have a blood test of the health of your liver
- Have a blood test for the amount of study drug in your blood

At your end of product visit, you will:

- Have a physical exam.
- Have 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

It will be necessary to ship some of your biological samples outside of the country, for example your blood will be shipped to the United States in order to assess how much of the study drug is absorbed by your body. If you are thought to be HIV-infected, this will

be confirmed in a laboratory in the United States and additional testing related to the HIV infection will also be performed.

AT ANY TIME IN THE STUDY

If you want to change to a different study product, you will:

- Talk with a study doctor first to see if this is an option for you, based on your health and on the number of times you have already changed your study product. In general, only one change is allowed after your Month 1 visit.

If you have problems that may be caused by infections passed by sex, you will:

- Have an exam of your genital area and inside your vagina
- 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 a group that uses tablets
- Be given referrals for medical care and other services you may need

If you have a rash and fever:

- You will come in to get checked by a study doctor
- You may get tested for HIV, depending on the results of your check-up. (Some but not all people have these signs with a new HIV infection. These signs can also be due to side effects to medication or other medical problems.)

If you become infected with HIV:

If you may have been infected with HIV, you will have at least three tests to confirm your results. Each time blood is drawn for these tests, you will also give blood (XX mL) to test for the amount of HIV in your blood, whether any HIV in your blood is resistant to medications used to treat HIV, 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. Results of resistance tests will be given to you. If HIV tests confirm that you have HIV, you will stop using gel or tablets. If you do not have your study products with you, a staff person may go to your home to collect them.

We will counsel you and refer you for medical care and other available services. We also will refer you to another study called MTN-015. You will be asked to have additional blood drawn 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

POSSIBLE FUTURE TESTS

Some of the blood that you give during CHOICE may be left over after all the study tests are completed. The staff would like to keep your leftover blood. You will be asked to sign a separate form to give permission for that. Even if you do not give permission to store your blood after the study, you can still be in CHOICE.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may:

- Feel discomfort or pain when your blood is drawn.
- Feel dizzy or faint, but most women do not have this reaction.
- Have more than expected bleeding, 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 will be stored on a larger computer here at [study site] that can only be accessed by authorized staff. Your answers 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 uses gel, the gel could cause some bad effects. Some, but not all, women who used the gels in other studies have had:

- Dryness, itching, burning feeling, irritation or pain in the genital area
- Vaginal candidiasis (a kind of vaginal infection)
- Discharge from the vagina
- Diarrhea

You could have these effects or other effects that we do not know about.

Some, but not all women used emtricitabine (one of the drugs in Truvada) have had these effects:

- Headache
- Dizziness
- Tiredness, inability to sleep, unusual dreams
- Loose or watery stools, upset stomach (nausea) or vomiting, abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Skin darkening of the palms and/or soles

- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage

Persons infected with both Hepatitis B and HIV may have increases in liver tests, and symptoms associated with hepatitis may worsen if emtricitabine is stopped.

Some, but not all women have had these effects while using tenofovir tablets:

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Headache
- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver
- Shortness of breath
- Rash
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness

Persons infected with both Hepatitis B and HIV may have increases in liver tests, and symptoms associated with hepatitis may worsen if tenofovir is stopped.

You could have these side effects or other side effects that we do not know about.

Both Gel and Tablet Groups

HIV infections are usually treated with three or more medications used together. If you become infected with HIV while using study product, taking your study product would not properly treat the HIV infection. Continuing to take study product after an HIV infection has occurred could cause drug resistance and limit your options for HIV treatment in the future. It is for this reason that you must stop using your study product if you get HIV. Study doctors are available to discuss this with you. If you do become infected with HIV during CHOICE, they can do blood tests to 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, such as pain at the injection site, 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 using gel or tablets. Please tell staff if you use any 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 HIV prevention studies have found an unexpected higher risk of getting HIV among participants. This could happen in any study, including CHOICE. Because of this, 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

Information on the effects of the study products on a developing fetus is limited. Studies have not shown bad effects on pregnancy, fetuses of women who use the gels or tablets when pregnant, or babies of women who use the gels or tablets when breastfeeding. However, pregnant women and women who are breastfeeding are not being included in MTN-018. *[insert if applicable at site: Only women previously enrolled in VOICE may be included in substudies for pregnant and breastfeeding women that include staying on study drug.]* We will tell you about another study for pregnant women and their infants called MTN-016.

Women who become pregnant during the study may be exposed to study product up to 3 months, if they are having pregnancy tests done every three months. 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. 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

[insert VOICE effectiveness results]

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 and genital exams. You will have tests to check on the health of your 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, you may benefit from getting the 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, testing, referral and testing for other infections passed through sex. If you or your partner(s) have infections passed through sex, other than HIV and hepatitis B, 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 receive results of your resistance tests, be referred for medical care, counseling, and other services available to you.

NEW INFORMATION

You will be told any new information that might affect your willingness to stay in CHOICE, when study results may be ready, and how to learn of them.

WHY YOU MAY HAVE TO STOP TAKING THE STUDY DRUG EARLY

You will have to stop using gel or tablets if you become infected with HIV, become infected with hepatitis B, become pregnant, are breastfeeding, are taking medication called PEP for possible recent exposure to HIV infection, are unwilling to follow study procedures or instructions, or 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 (unless you are HIV-infected and join MTN-015).

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

[Sites to include/amend the following if applicable: There may be other studies here or in the community. If you wish, we will tell you about other studies that we know about. There are also 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 to be in CHOICE. Treatments available to you and/or your partner(s) for infections passed through sex other than HIV and hepatitis B will be provided free.

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. 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 study staff, as well as:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH) or its study monitors and other representatives of NIH
- [insert applicable local authorities, e.g., IRB, medicine control authority]
- the organizations that supply the gel (CONRAD) and 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 confidentiality guidelines of [health authority].

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] If you are injured, [institution] will give you immediate treatment for your injuries. You [will/will not] have to pay for this. You will be told where you can get additional treatment. There is no program to pay money or 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*] at [*insert contact information*].

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 Community Advisory Board (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 XI: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS – BOTH COHORTS)

SAMPLE INFORMED CONSENT FORM DIVISION OF AIDS, NIAID, NIH

MTN-018

**Committed to Having Options for Interventions to Control the Epidemic (CHOICE):
A Follow-up Study to MTN-003**

Version 1.0

September 6, 2011

PRINCIPAL INVESTIGATOR: [insert name]

PHONE: [insert number]

Short Title for the Study: CHOICE

INTRODUCTION

You have decided to take part in the CHOICE study, funded by the United States National Institutes of Health (NIH). While you are in CHOICE, there may be blood taken from you that might be useful for future research. You are being asked to agree to storage of this blood. This consent form tells you about the collection, storage, and use of your blood. 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 stored and tested in the future. You will be offered a copy of this form to keep.

HOW WILL YOU GET THE BLOOD FROM ME?

You have agreed to have blood collected and tested as part of CHOICE. During CHOICE, your blood will be tested to check on your health and to see if you have HIV. The study staff would like to keep any leftover blood, after the CHOICE study is done, to use for future testing. If you agree to this, no additional blood will be taken from you. Only leftover blood will be kept and used for future testing.

HOW WILL YOU USE MY BLOOD?

Your blood 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 become 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. 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 will not be sold or used directly to produce commercial products. Research studies wishing to use your blood will be reviewed by the NIH 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 AND HOW WILL MY BLOOD BE STORED?

There is no time limit on how long your blood will be stored. Your blood will be stored at 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.

DOES STORAGE OF MY BLOOD BENEFIT ME?

There are no direct benefits to you. The benefits of doing research on stored blood include learning more about HIV infection.

WHAT ARE THE RISKS?

There are few risks related to storing your blood. When tests are done on the stored blood, 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 will be labeled with a code that can only be traced to your research clinic. Your name and other personal information will be protected by the research clinic. When researchers are given your stored blood 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 study staff, as well as:

- the United States Food and Drug Administration (FDA)
- the United States NIH or its study monitors and other representatives
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs]
- the organizations that supply the gel (CONRAD) and tablets (Gilead Sciences)

WHAT ARE MY RIGHTS?

Allowing your blood to be stored is completely voluntary. If you decide not to have any blood stored other than what is needed to complete CHOICE, you can still remain in CHOICE, and your leftover blood will be destroyed. If you decide now that your blood 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 will 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, 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 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 MTN-018 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 my leftover samples to be stored for future testing.

OR

_____ I do not agree to allow my leftover samples 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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