

**MTN-018C**

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

**Pregnancy Sub-study**

**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**

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

**DAIDS Protocol #: 11847**

**IND# 55,690**

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**Final Version 1.0**

**DAIDS RAB REVIEW VERSION**

**September 10, 2012**

# MTN-018C

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

### TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND ACRONYMS.....	1
PROTOCOL TEAM ROSTER .....	3
INVESTIGATOR SIGNATURE FORM .....	14
PROTOCOL SUMMARY .....	15
1 KEY ROLES.....	22
1.1 Protocol Identification.....	22
1.2 Sponsor and Monitor Identification.....	22
1.3 Medical Officer .....	22
1.4 Network Laboratory .....	23
1.5 Data Center .....	23
1.6 Study Operations .....	23
2 INTRODUCTION .....	23
2.1 HIV Prevention among Pregnant Women .....	23
2.2 Pregnancy Exposures by Trimester for MTN-018 Study Products .....	24
2.3 Results of the VOICE Trial .....	27
2.4 Results of CAPRISA 004 .....	27
2.5 Study Product Description: Tenofovir Disoproxil Fumarate .....	27
2.6 Study Product Description: Emtricitabine/Tenofovir Disoproxil Fumarate.....	28
2.7 Study Product Description: 1% Tenofovir Gel.....	29
2.8 <i>In vitro</i> Studies .....	29
2.9 Animal Studies .....	29
2.10 Studies of Oral Tenofovir and Emtricitabine in Pregnant Women.....	30
2.11 Rationale .....	35
3 OBJECTIVES.....	37
3.1 Primary Objectives .....	37
3.2 Secondary Objectives .....	37
4 STUDY DESIGN .....	38
4.1 Identification of Study Design.....	38
4.2 Summary of Major Endpoints .....	38
4.3 Description of Study Population .....	39
4.4 Time to Complete Accrual.....	39
4.5 Study Groups .....	40
4.6 Expected Duration of Participation .....	40
4.7 Sites .....	40
5 STUDY POPULATION.....	40
5.1 Selection of the Study Population .....	40
5.2 Inclusion Criteria – MOTHERS .....	41
5.3 Exclusion Criteria – MOTHERS .....	41
5.4 Co-enrollment Guidelines.....	42

6	STUDY PRODUCT .....	43
6.1	Regimen .....	43
6.2	Administration .....	43
6.3	Study Product Formulation.....	44
6.4	Study Product Supply and Accountability .....	44
6.5	Study Product Dispensing.....	45
6.6	Retrieval of Unused Study Products .....	45
6.7	Study Product Adherence Assessment and Counseling.....	46
6.8	Concomitant Medications .....	46
7	STUDY PROCEDURES .....	47
7.1	Pre-Screening .....	47
7.2	Screening .....	47
7.3	Enrollment .....	49
7.4	Follow-up Visits .....	50
7.5	Pregnancy Outcome Visit.....	55
7.6	Follow-up after Pregnancy Outcome.....	56
7.7	Follow-up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product .....	57
7.8	Interim Visits.....	57
7.9	Final Contact .....	58
7.10	Clinical Evaluations and Procedures.....	58
7.11	Laboratory Evaluations .....	59
7.12	Specimen Collection and Processing.....	59
7.13	Specimen Handling .....	59
7.14	Biohazard Containment.....	59
7.15	Calculation of Gestational Age .....	60
8	ASSESSMENT OF SAFETY .....	60
8.1	Safety Monitoring and Review .....	60
8.2	Adverse Events Definitions and Reporting Requirements .....	60
8.3	Expedited Adverse Event Reporting Requirements.....	62
8.4	Regulatory Requirements .....	63
8.5	Social Harms Reporting .....	63
9	CLINICAL MANAGEMENT .....	63
9.1	Grading System .....	64
9.2	Dose Modification Instructions .....	64
9.3	General Criteria for Temporary Hold and Permanent Discontinuation of Study Product.....	64
9.4	Temporary Product Hold/Permanent Discontinuation in Response to Observed Adverse Events.....	65
9.5	Management of Specific Adverse Events .....	65
9.6	HIV Infection.....	67
9.7	Antenatal Care .....	68
9.8	Signs/Symptoms of Labor .....	68
9.9	Criteria for Early Termination of Study Participation .....	68
10	STATISTICAL CONSIDERATIONS.....	68
10.1	Overview and Summary of Design.....	68

10.2 Study Endpoints .....	69
10.3 Sample Size .....	70
10.4 Participant Accrual, Follow-up and Retention .....	72
10.5 Blinding .....	72
10.6 Data and Safety Monitoring and Analysis .....	72
11 DATA HANDLING AND RECORDKEEPING.....	74
11.1 Data Management Responsibilities.....	74
11.2 Source Documents and Access to Source Data/Documents.....	74
11.3 Quality Control and Quality Assurance .....	74
12 CLINICAL SITE MONITORING .....	74
13 HUMAN SUBJECTS PROTECTIONS.....	75
13.1 Institutional Review Boards/Ethics Committees.....	75
13.2 Protocol Registration.....	76
13.3 Study Coordination.....	77
13.4 Risk Benefit Statement.....	77
13.5 Informed Consent Process.....	80
13.6 Participant Confidentiality.....	81
13.7 Special Populations.....	82
13.8 Compensation .....	84
13.9 Communicable Disease Reporting.....	84
13.10 Access to HIV-related Care .....	84
13.11 Study Discontinuation.....	84
14 PUBLICATION POLICY.....	84
15 APPENDICES.....	86
APPENDIX I: SCHEDULE OF VISITS AND EVALUATIONS .....	87
APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING FOR SCREENING/ENROLLMENT.....	88
APPENDIX III: ALGORITHM FOR HIV TESTING FOR FOLLOW-UP.....	89
APPENDIX IV: ALGORITHM FOR HBV TESTING.....	90
APPENDIX V: SAMPLE INFORMED CONSENT FORM (SCREENING).....	91
APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT).....	96
APPENDIX VII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS).....	106
REFERENCES.....	110

## FIGURES

Figure 1: MTN-018 and Sub-studies .....	17
Figure 2: Referral Patterns for VOICE and Pregnancy-related Studies .....	18

## TABLES

Table 1: Summary of Safety Data on 1% Tenofovir Gel in Pregnancy .....	25
Table 2: TDF and FTC/TDF PrEP Trials with Unscheduled Exposure in Pregnancy.....	26
Table 3: Oral TDF and FTC/TDF for Treatment and/or PMTCT during Pregnancy by Trimester .....	26
Table 4: Median (range) of Maternal Tenofovir Levels in HPTN 057 (Cohort 1).....	31

Table 5: Tenofovir Concentrations in Breast Milk in HPTN 057 (Cohort 1).....	31
Table 6: Median (range) Tenofovir Concentrations in Infants (Cohort 2).....	32
Table 7: Follow-up after Pregnancy Outcome.....	56

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#### LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
AOR	adjusted odds ratio
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
BV	bacterial vaginosis
CDC	Centers for Disease Control
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
DAIDS	Division of AIDS
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EC	ethics committee
EFV	efavirenz
FDA	Food and Drug Administration
FHCRC	Fred Hutchison Cancer Research Center
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practices
HAART	highly active antiretroviral therapy
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HC	head circumference
HEC	hydroxyethylcellulose
HELLP	hemolysis, elevated liver enzymes, low platelet count
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
hr	hour
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board

LBW	low birth weight
LDMS	Laboratory Data Management System
µg	microgram
MAA	multi-assay algorithm
mg	milligram
MTN	Microbicide Trials Network
NIAID	National Institute of Allergy and Infectious Disease
NICHD	National Institute of Child Health and Human Development
NIMH	National Institute of Mental Health
NIH	(United States) National Institutes of Health
NL	network laboratory
NVP	nevirapine
OHRP	Office of Human Research Protections
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PHACS	Pediatric HIV/AIDS Cohort Study
PK	pharmacokinetic(s)
PMPA	9-R-2-phosphonomethoxypropyl adenine
PMPApp	tenofovir diphosphate
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development
PrEP	pre-exposure prophylaxis
PROMISE	Promoting Maternal-Infant Survival Everywhere
PSRT	Protocol Safety Review Team
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
sdNVP	single-dose nevirapine
SMARTT	Surveillance Monitoring of Antiretroviral Toxicity
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
URAI	unprotected receptive anal intercourse
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-018C**

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

**INVESTIGATOR SIGNATURE FORM**

**Version 1.0**

**September 10, 2012**

**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-018C

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

#### PROTOCOL SUMMARY

- Short Title:** CHOICE-C Follow-up Study to MTN-003 (VOICE)
- IND Sponsor:** Division of AIDS, NIAID, US NIH
- MTN-018C Chair:** Felix Muhlana, MBChB, MMED, Obs and Gyn
- Sample Size:** Up to approximately 300 pregnant women, without upper limit, and based on site investigator estimates for expected % of former VOICE participants pregnant during implementation of MTN-018.
- Study Population:** Healthy, HIV-uninfected pregnant women formerly enrolled in VOICE. Infants are not considered research participants separately from the mother in MTN-018C.
- Study Sites:** CHOICE sites
- Study Duration:** Total study duration will be for the duration of MTN-018, plus additional time to follow pregnancies enrolled into MTN-018C.
- Study Products:** Unless emerging evidence at the time of implementation supports a different approach, MTN-018C study products are anticipated to be the same as MTN-018 study products.
- MTN-018C study products will include one or more of the following:
- tenofovir disoproxil fumarate (TDF) 300 mg tablet
  - emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) 200 mg/300 mg tablet
  - 1% tenofovir 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 versions of MTN-018 and MTN-018C 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 the parent protocol, MTN-018.

**Study Design:** MTN-018C is an open-label, multi-site sub-study to MTN-018. Following the release of VOICE results, 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 the parent protocol, MTN-018. Figure 1 illustrates the relationships among the parent protocol and pregnancy and breastfeeding substudies for MTN-018.

If only one product is selected to move forward in the parent protocol, MTN-018, all MTN-018C participant mothers would receive that product. If more than one product is selected to move forward in MTN-018C, MTN-018C participant mothers will select a study product at the MTN-018C Enrollment Visit, even if they were previously enrolled in MTN-018, for the following reasons:

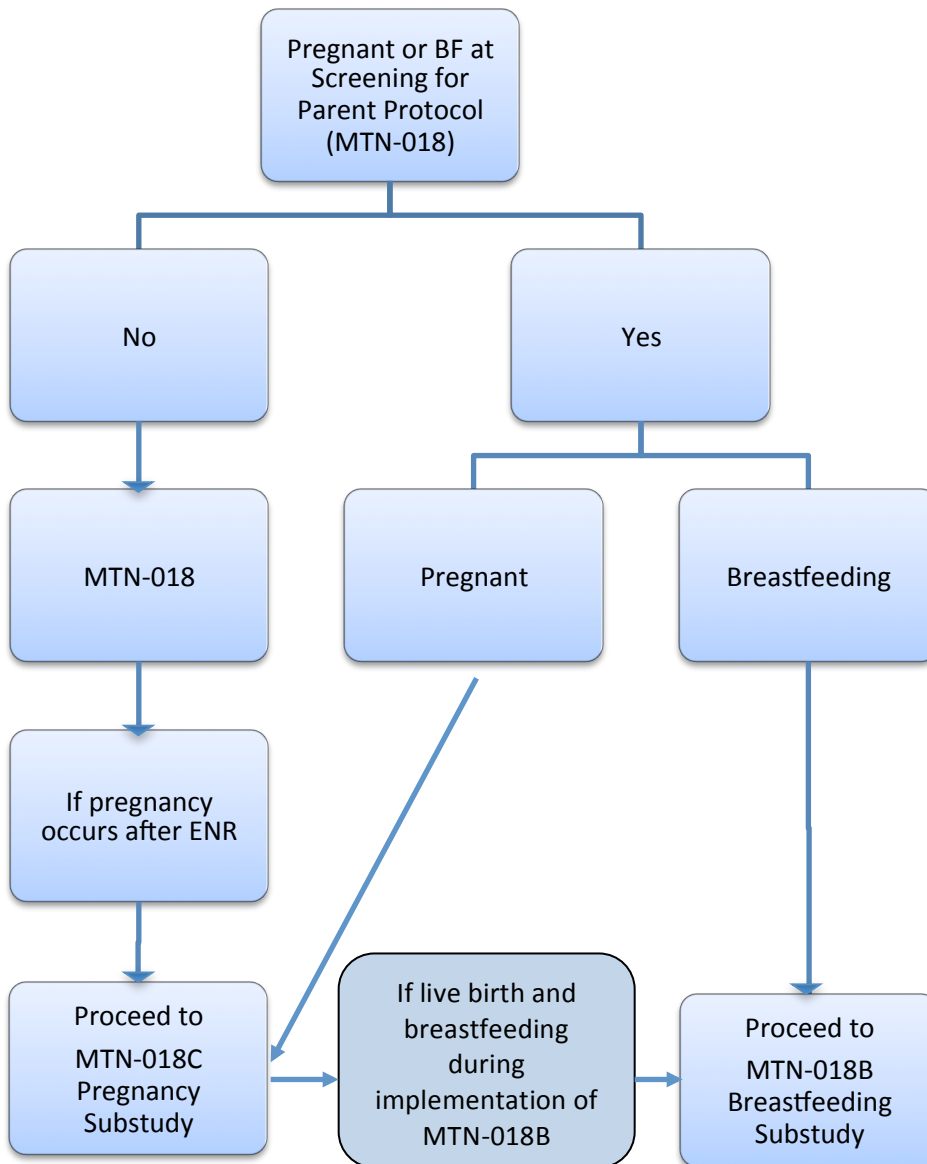
- Depending upon emerging data, the study products in MTN-018 and MTN-018C could differ.
- The overall risk/benefit profile in pregnancy may differ from that in the non-pregnant state
- Women's preferences regarding study product may change in the setting of pregnancy.

At Month 1, participant mothers will confirm their desire to continue with the study product chosen at the MTN-018C 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).

Participant mothers will not be randomized but will be followed monthly for the duration of follow-up. At a minimum, participant mothers have scheduled follow-up on study drug until pregnancy outcome, with additional follow-up on study drug after pregnancy outcome permitted as follows (see additional detail in Figure 1:

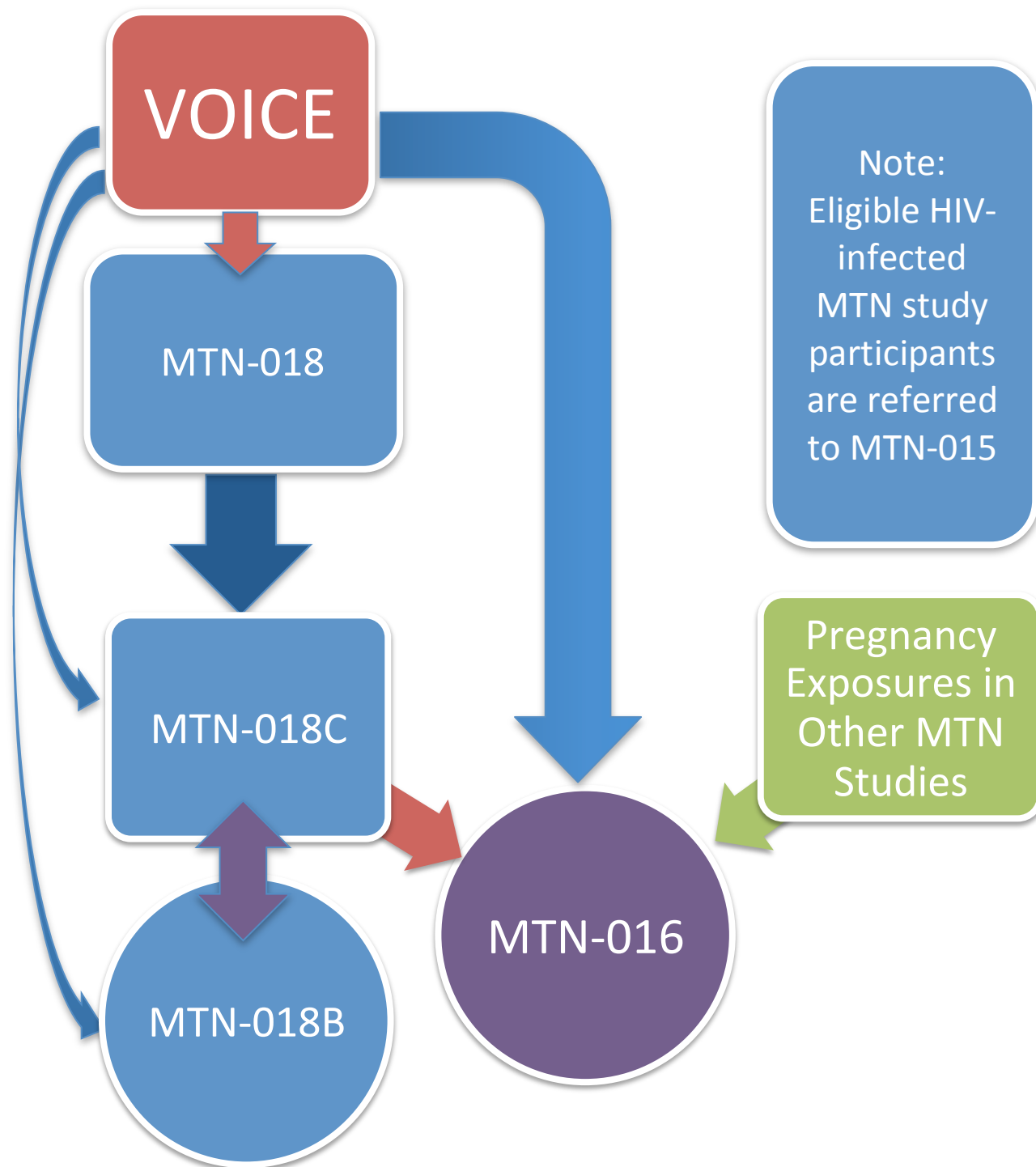
- Up until 12 months following original enrollment in MTN-018, if the participant was previously enrolled in MTN-018
- Up until 12 months following enrollment into MTN-018C, if the participant was not previously enrolled in MTN-018

Approximately two months after the Month 12 Visit, participant mothers will return for final HIV testing to assess for potential delayed seroconversion (Termination Visit).



**Figure 1: MTN-018 and Sub-studies**

Note: MTN-018B and MTN-018C participants must previously have been enrolled in VOICE. Simultaneous co-enrollment in MTN-018B and MTN-018C may be allowed with permission of the MTN-018 PSRT. Participants will not co-enroll into MTN-018B or MTN-018C with the parent protocol, MTN-018; rather, their participation in the parent protocol will be terminated.



**Figure 2: Referral Patterns for VOICE and Pregnancy-related Studies**

**Study Regimen:** Daily use of study product with monthly follow-up on study drug for up to 12 months

**Study Groups:** Final study groups will depend on selection of study product(s). Participant mother preferences for study product will impact the size of study groups.

1. 1% tenofovir gel
2. TDF 300 mg tablet
3. FTC 200mg / TDF 300 mg tablet

**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 and related sub-studies will be implemented
- Selection of MTN-018 (and sub-study) 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
- Modification of Version 1.0 of sub-study protocols

## **STUDY OBJECTIVES**

### **Primary Objectives**

- To compare pregnancy outcomes from MTN-018C participants to those of VOICE participants who became pregnant during VOICE
- To compare health outcomes for infants born to MTN-018C participants to those of MTN-016 infants of VOICE mothers in the first 30 days of life

### **Primary Endpoints**

- **Pregnancy outcomes**
  - Any of the following reported by participant mothers or obtained from medical records
    - Full-term live birth
    - Premature live birth



- Stillbirth/intrauterine fetal demise
  - Spontaneous abortion
  - Ectopic pregnancy
  - Other pregnancy outcomes
- **Infant Outcomes**
    - Any of the following reported by participant mothers or obtained from medical records for the first 30 days of infant's life
      - Life-threatening event
      - Persistent or significant disability/incapacity
      - Hospitalization/prolongation of hospitalization
      - Death

### Secondary Objectives

- **Pregnancy Morbidities.** To compare pregnancy morbidities among MTN-018C participants to those of MTN-016 participant (VOICE) mothers
- **Extended Safety Profile.** To describe the extended safety profile of study products among MTN-018C participants
- **Adherence.** To evaluate adherence to daily regimens of MTN-018C study products

### Secondary Endpoints:

- **Pregnancy morbidities**
  - Intrapartum hemorrhage
  - Postpartum hemorrhage
  - Chorioamnionitis
  - Hypertensive disorders of pregnancy
  - Gestational diabetes
  - Placenta previa
  - Placenta accreta
  - Placental abruption
  - Preterm premature rupture of membranes
  - Premature rupture of membranes at term ( $\geq 37$  weeks gestational age)
  - Sepsis during pregnancy or first 42 days following pregnancy outcome
- **Extended Safety Profile**
  - Grade 2 or higher adverse events (AEs) (laboratory)
    - AST/ALT
    - Creatinine
  - Grade 2 or higher AEs (clinical)

- **Adherence**
  - Self-report
  - Product counts
  - Drug levels

# 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 – Pregnancy Sub-study

Short Title: CHOICE-C

Protocol Number: MTN-018C

Date: September 10, 2012

## 1.2 Sponsor and Monitor Identification

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Bethesda, MD 20892 USA

Sponsor: US NICHD  
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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.  
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Wilmington, NC 28401-3331 USA

## 1.3 Medical Officer

Medical Officer: Jeanna Piper, MD  
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## 1.4 Network Laboratory

Laboratory: MTN Network Laboratory  
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## 1.5 Data Center

Data Center: Statistical Center for HIV/AIDS Research & Prevention (SCHARP)  
Fred Hutchison Cancer Research Center (FHCRC)  
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## 1.6 Study Operations

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# 2 INTRODUCTION

## 2.1 HIV Prevention among Pregnant Women

It is well-known that Africa bears the greatest burden of the HIV/AIDS epidemic. Among the countries in the world with the highest parity, the majority is in Africa. While the VOICE study has managed to date to keep the rate of pregnancy in the trial relatively low, this is likely related to the concerted efforts of site counseling staff and the availability of contraception within the trial. If one or more of the VOICE study products is found to be safe and effective, it will potentially be introduced into a setting with low uptake of contraception and high rates of desired fertility and parity. Thus, following VOICE, the study of the safety of candidate chemoprevention agents in pregnancy remains a high priority for the MTN.

Recent findings from the PEPI-Malawi demonstrate the association between recent HIV infection and the likelihood of *in utero* HIV transmission.<sup>1</sup> The PEPI-Malawi trial used a multi-assay algorithm (MAA) to identify recent HIV infection and to evaluate the association between recent maternal HIV infection and *in utero* transmission of HIV. Plasma samples were collected at delivery from 2,561 HIV-infected women and logistic regression models assessed association between recent HIV infection and *in utero* HIV transmission (defined as a positive infant HIV deoxyribonucleic acid (DNA) test at birth). Seventy-three women were identified as recently infected using the MAA. Those women were younger and had lower parity than women who were identified as not recently infected using the MAA ( $P < 0.0001$  for age and parity). The frequency of *in utero* HIV transmission was 17.8% among women identified as recently infected, compared to

6.7% among women identified as not recently infected (13/73 vs. 166/2488,  $P = 0.001$ ). In a multivariate model, three factors were independently associated with *in utero* HIV transmission: recent infection (adjusted odds ratio [AOR]: 2.49, 95% CI: 1.30-4.78,  $P = 0.006$ ),  $\log_{10}$  HIV viral load at delivery (AOR: 2.01, 95% CI: 1.60-2.51,  $P < 0.0001$ ), and younger age (per 10 year increase, AOR: 0.66, 95% CI: 0.43-0.93,  $P = 0.02$ ). Results obtained using a MAA suggest that recent maternal HIV acquisition is strongly associated with *in utero* HIV transmission, independent of HIV viral load at delivery. These findings reinforce the case made by previous analyses pointing to pregnancy as a high-risk time for incident HIV infection.<sup>2-3</sup> Thus, recent data support the special importance of pregnancy as a time for primary HIV prevention.

It is clear that long-term pregnancy safety data is critical for the safe introduction of ARV-based prevention targeted to reproductive-age women. However, without sufficient safety and pharmacokinetic data among pregnant women and their infants, regulatory approval and public sector roll-out of effective PrEP and microbicides may exclude pregnant women. This approach would effectively lead to unregulated use of antiretroviral-based prevention strategies during both undiagnosed and known pregnancies, with unknown consequences for public health impact. As reporting of pregnancy outcomes in the post-marketing phase is typically provider-driven, the possibilities of under-reporting and restrictions or warnings based on limited data are very real.

Following VOICE, pregnancy among the VOICE Cohort is likely to be common, according to estimates by VOICE investigators. The period of contraception required by an effectiveness trial may be followed by a significant number of participants attempting pregnancy; the influence of partners and family on participants to become pregnant following a longer than average interval between children may be substantial. A more real-world approach to contraception within the parent protocol, MTN-018, may be associated with higher rates of pregnancy than were seen during the implementation of VOICE. Thus, it is possible that we will see both significant rates of pregnant women at screening for MTN-018, and more substantial rates of incident pregnancy during the implementation of MTN-018.

This sub-study to MTN-018 provides the opportunity to obtain these valuable safety data in the context of a carefully regulated clinical trial, during all three trimesters of pregnancy. As described in further detail below, it is anticipated that sufficient safety data throughout pregnancy will have been obtained for all potential study products before the initiation of MTN-018, to allow this pregnancy sub-study to move forward.

## **2.2 Pregnancy Exposures by Trimester for MTN-018 Study Products**

The tables below summarize studies contributing safety data to the study of tenofovir in pregnancy. Table 1 includes available and expected data for tenofovir gel, while Table 2 includes completed and ongoing trials of tenofovir-based PrEP for HIV prevention among reproductive aged women. Table 3 includes a summary of exposures occurring in the context of HIV/AIDS treatment and the prevention of mother-to-child transmission

of HIV. More detailed information on study products and related studies in preclinical and clinical studies (both non-pregnant and pregnant states) follows this section.

**Table 1: Summary of Safety Data on 1% Tenofovir Gel in Pregnancy**

	<b>Status</b>	<b>First Trimester</b>	<b>Second Trimester</b>	<b>Third Trimester</b>
<b>MTN-002</b> <b>IND 55,690</b>	Analysis completed N = 16	None	None	Planned single dose, open-label TFV gel at term among healthy HIV-uninfected women, prior to cesarean delivery
<b>CAPRISA 004</b> <b>Non-IND</b>	Reported 2010 N = 889 (54 study gel exposures in pregnancy)	Unscheduled multi-dose exposure, placebo controlled, with product hold at diagnosis of pregnancy	None	None
<b>MTN-016</b> <b>Registry Study</b>	Enrolling N=268 women and 186 infants, as of 5/31/12	Registry data obtained from VOICE participants, including infant f/u to one year	PENDING registry data from MTN-019 participants, including infant f/u to one year	Registry data from MTN-002, MTN-008, and anticipated to include MTN-019, with infant f/u to one year
<b>MTN-003 (VOICE)</b> <b>IND 55,690</b>	Enrollment Completed N=5,029	Unscheduled multi-dose exposure, placebo-controlled, with product hold at diagnosis of pregnancy	None	None
<b>MTN-008</b> <b>IND 55,690</b>	Enrolling N = 90	None	None	7-day exposure, placebo-controlled, at term and near term
<b>MTN-019</b> <b>IND 55,690</b>	Pending, anticipated implementation in 2012 N=TBD	None	28-day exposure, placebo controlled	28-day exposure, placebo-controlled
<b>MTN-018C</b> <b>IND 55,690</b>	In development, anticipated implementation in 2013 N = ~300	Planned exposure of multi-dose, open-label TFV gel, pending VOICE results	Planned exposure of multi-dose, open-label TFV gel, pending VOICE results	Planned exposure of multi-dose, open-label TFV gel, pending VOICE results

The current portfolio of studies where tenofovir gel exposure has occurred during pregnancy (both scheduled and unscheduled) includes exposure during all trimesters. More detailed information on MTN studies is available later in this Section and at [www.mtnstopshiv.org](http://www.mtnstopshiv.org).

**Table 2: TDF and FTC/TDF PrEP Trials with Unscheduled Exposure in Pregnancy**

	<b>Product</b>	<b>Status</b>
<b>FHI TDF</b>	TDF	Reported
<b>FEM-PrEP</b>	FTC/TDF	Closed to enrollment, stopped for fertility
<b>Partners PrEP</b>	TDF and FTC/TDF	Reported
<b>MTN-003</b>	TDF and FTC/TDF	Completed enrollment, in follow-up
<b>CDC Bangkok</b>	TDF	Closed to enrollment, in follow-up
<b>CDC Botswana TDF2</b>	FTC/TDF	Reported

In the context of trials of PrEP for prevention of HIV infection in women, unscheduled exposure to oral TDF and FTC/TDF has occurred, even in the setting of regular, comprehensive family planning counseling and direct provision of contraception services on site. Thus, PrEP trials enrolling women have included unscheduled multi-dose exposure to TDF or FTC/TDF during the first trimester. To date, no PrEP trial has reported any difference between active drug and placebo with regard to pregnancy outcomes following first trimester exposure to TDF or FTC/TDF, although few PrEP trials have reached the stage of final analysis.

**Table 3: Oral TDF and FTC/TDF for Treatment and/or PMTCT during Pregnancy by Trimester**

	<b>N (mothers)</b>	<b>First</b>	<b>Second</b>	<b>Third</b>
<b>CDC 5877</b>	80	No	Yes	TDF-containing regimen for HIV/HBV co-infected mothers
<b>EGSA 19-02</b>	400	No	No	Single dose of FTC/TDF during labor
<b>IMPAACT 394</b>	22	No	No	Single dose of TDF or FTC/TDF during labor
<b>HPTN 057</b>	110	No	No	Single dose of TDF during labor
<b>Frankfurt HIV Cohort<sup>4</sup></b>	76	Yes, treatment	Yes, treatment	Yes, treatment
<b>Nurutdinova et al.<sup>5</sup></b>	127	TDF-based HAART during pregnancy		
<b>PHACS/SMARTT<sup>6</sup></b>		TDF-based HAART	TDF-based HAART	TDF-based HAART
<b>TEmAA ANRS<sup>7,8,9</sup></b>	36	No	No	Single dose of FTC/TDF during labor
<b>PACTG P1026s<sup>10</sup></b>	Estimated 800	No	No	TDF or TDF/FTC treatment regimen
<b>PROMISE – Antepartum<sup>11</sup></b>	Estimated 4,950	No	No	Antepartum triple ARV prophylaxis versus antepartum zidovudine (ZDV) + single dose nevirapine (sdNVP) + Truvada tail
<b>APR<sup>12</sup></b>	1,219	TDF and FTC/TDF treatment	TDF and FTC/TDF treatment	TDF and FTC/TDF treatment

Table 3 summarizes key planned, ongoing, and reported studies of pregnancy exposures to TDF and FTC/TDF by trimester in the context of treatment and regimens for prevention of mother-to-child transmission. More detailed information is available in Section 2.10.

### **2.3 Results of the VOICE Trial**

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

### **2.4 Results of CAPRISA 004**

To describe existing evidence for the prospect of direct benefit among pregnant women, the results of CAPRISA 004 are included here.<sup>13</sup> 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. A double-blind, randomized controlled trial was conducted comparing tenofovir 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 tenofovir 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. The use of tenofovir gel was associated with 51% protection against HSV-2 (CI: 22% - 70%).

### **2.5 Study Product Description: Tenofovir Disoproxil Fumarate**

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

#### **2.5.1 Description**

Tenofovir disoproxil fumarate is approved by the US Food and Drug Administration (US FDA) under the trade name Viread<sup>®</sup> for treatment of HIV-1 infection in adults.<sup>14</sup> 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<sup>®</sup> package insert.

#### **2.5.2 Mechanism of Action**

Once absorbed, TDF is rapidly converted by diester hydrolysis to tenofovir.<sup>14</sup> 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



DNA chain. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases  $\alpha$ ,  $\beta$ , and mitochondrial DNA polymerase  $\gamma$ .

### **2.5.3 Strength of Study Product**

The strength of the TDF tablets will be the dose approved by the US FDA for the indication of treatment of HIV-1 infection in adults (300 mg).<sup>14</sup> 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.

## **2.6 Study Product Description: Emtricitabine/Tenofovir Disoproxil Fumarate**

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

### **2.6.1 Description**

FTC is approved by the US FDA for treatment of HIV-1 infection in adults.<sup>15</sup> FTC is administered once daily, either as a single drug formulation (Emtriva<sup>®</sup>) or in fixed-dose combination with TDF (as Truvada<sup>®</sup>).<sup>16</sup> FTC/TDF is approved for treatment of HIV-1 infection in adults. The US FDA has recently approved Truvada<sup>®</sup> for pre-exposure prophylaxis to reduce the risk of sexually acquired HIV-1 in adults at high risk.<sup>16</sup> 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<sup>®</sup> is available in the current package insert.<sup>15</sup>

### **2.6.2 Mechanism of Action**

FTC is a synthetic nucleoside analogue of cytidine and is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate.<sup>15</sup> 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  $\alpha$  and  $\beta$ , and mitochondrial DNA polymerase  $\gamma$ .

### **2.6.3 Strength of Study Product**

Co-formulation of FTC and TDF has been approved by the US FDA.<sup>16</sup> 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<sup>®</sup> tablet was bioequivalent to one Emtriva<sup>®</sup> capsule (200 mg) plus one Viread<sup>®</sup> tablet (300 mg) following single-dose administration to healthy participants (n = 39). Further information on Truvada<sup>®</sup> is available in the current package insert.<sup>16</sup>

## **2.7 Study Product Description: 1% Tenofovir Gel**

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

### **2.7.1 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.<sup>17</sup> Further information is available in the current version of the tenofovir gel investigator's brochure.

### **2.7.2 Mechanism of Action**

Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate.<sup>17</sup> 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  $\alpha$ ,  $\beta$ , and mitochondrial DNA polymerase  $\gamma$ .

### **2.7.3 Strength of Study Product**

The strength of the tenofovir 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), MTN-008 (IND 55,690), MTN-011 (IND 73,382), and CAPRISA 004 (non-IND). The 4 mL application in this study delivers 40 mg of tenofovir to the vaginal compartment.

## **2.8 *In vitro* Studies**

Data from *in vitro* studies relevant to MTN-018C are included in the parent protocol, MTN-018.<sup>18</sup>

## **2.9 Animal Studies**

### **2.9.1 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 protocol and the Investigator Brochure for the study products.<sup>19,17</sup>

## 2.9.2 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.<sup>20</sup> Detailed information on these studies is available in the VOICE protocol and the package insert for the study product.<sup>15,19</sup>

## 2.10 Studies of Oral Tenofovir and Emtricitabine in Pregnant Women

Information regarding clinical studies of tenofovir and emtricitabine are included in the parent protocol, MTN-018. Key clinical studies with relevance to pregnancy are included here. The next version of this protocol will include updated findings from these trials.

### Tenofovir/Emtricitabine in Africa and Asia (TEmAA)

The TEmAA study investigated the use of TDF and FTC as a possible alternative or complement to single dose NVP for prevention of mother-to-child transmission.<sup>21</sup> The objectives of TEmAA were to study the pharmacokinetic properties, safety and viral resistance pattern of the combination of tenofovir disoproxil fumarate (600 mg) and emtricitabine (400 mg) in HIV-1-infected pregnant women and their newborns, with a view to prevention of mother-to-child transmission of HIV-1 in Africa and Asia. It is a Phase 2, multisite, open-label trial conducted in two steps with 30 mother-infant pairs per step and with a balanced allocation in Abidjan (Côte d'Ivoire), Soweto (South Africa) and Phnom Penh (Cambodia).

Step 1 of TEmAA was administration of TDF/FTC to the mother and Step 2 was administration of TDF/FTC to the mother and the newborn. In TEmAA Step 2, median tenofovir and emtricitabine breast milk doses represented 0.03% and 2% of the proposed oral infant doses. Neonatal simulated plasma concentrations were extremely low for tenofovir but between half maximal inhibitory concentration and adult minimal concentration for emtricitabine. It was noted that the rare children who will acquire HIV despite TDF/FTC therapy will need to be monitored for viral resistance acquisition. Clear and significant safety concerns were not identified among infants exposed *in utero*, although it was noted that some infants with adverse events had a higher intracellular concentration of emtricitabine.

### HPTN 057

The purpose of HPTN 057 is to evaluate the safety and pharmacokinetics of TDF when administered to HIV-infected pregnant women during labor and to their infants during the first week of life to determine the optimal regimen for a subsequent efficacy trial, if indicated.<sup>22</sup> This study is a Phase I, open label, non-controlled trial. Eligible women and their infants will be enrolled in one of four cohorts outlined below. Irrespective of and outside of this Phase I study of TDF, all participating women and infants are offered the local standard of care antiretroviral regimen for prevention of mother to child HIV

transmission. Cohort 4 was added after reviewing the pharmacokinetic and safety data from Cohorts 1 and 3. The study aimed to enroll 110 fully evaluable mother/infant pairs.

Eligible women and their infants were enrolled in one of four cohorts. Cohort 1: Mothers received a single 600 mg oral dose of TDF at onset of labor; infants were not dosed. Cohort 2: Mothers were not dosed; infants received 4 mg/kg of the TDF oral suspension at birth (within 12 hours) and on Days 3 and 5 of life. Cohort 3: Mothers received a single 900 mg oral dose of TDF at onset of labor and infants received 6 mg/kg of the TDF oral suspension at birth (within 12 hours) and on Days 3 and 5 of life. Cohort 4 mothers received a single 600 mg oral dose of TDF at onset of labor and infants received 6 mg/kg of the TDF oral suspension daily for 7 days initiated at birth.

The primary objectives of HPTN 057 are the following:

- To evaluate the safety and tolerance of intrapartum/neonatal TDF in HIV-infected women and their infants; and
- To evaluate the pharmacokinetics of intrapartum/neonatal TDF in HIV-infected women and their infants and to determine maternal plasma exposure with single doses of 600 mg and, if necessary, 900 mg.

One of the secondary objectives is to measure TDF concentration in amniotic fluid and breast milk following maternal exposure to intrapartum TDF.

A total of 53 mother-infant pairs divided into two cohorts have been evaluated in this study in Malawi and Brazil. In Cohort 1, only the mother received TDF (600 mg). In Cohort 2, the infant received 4 mg/kg TDF as oral suspension. An investigation in a third cohort will have both the mother and infant receive TDF.

Data from Cohort 1 are presented in Tables 4 and 5 below.

**Table 4: Median (range) of Maternal Tenofovir Levels in HPTN 057 (Cohort 1)**

	<b>Pregnant women, 600 mg (n=30)</b>	<b>Nonpregnant adults, 600 mg</b>
<b>T<sub>max</sub> (hr)</b>	1.0 (1.0-8.0)	1.5
<b>C<sub>max</sub> (ng/mL)</b>	448 (110-928)	573
<b>AUC (ng*hr/mL)</b>	4221 (2767-24459)	4389
<b>T<sub>1/2</sub> (hrs)</b>	19.5 (11.1-32.8)	11.9

**Table 5: Tenofovir Concentrations in Breast Milk in HPTN 057 (Cohort 1)**

<b>Day Collected</b>	<b>#</b>	<b>Number with Detectable Tenofovir (conc [ng/mL])</b>
<b>1</b>	1	1 (17.8)
<b>2</b>	3	2 (106,6.3)
<b>4-6</b>	21	1 (15.7)
<b>41-44</b>	13	0
<b>79-89</b>	21	0

Mirochnick examined HPTN 057 PK of tenofovir disoproxil fumarate after single-dose administration to HIV-1 infected mothers; mothers and infants were followed for safety and tolerance. Of the 53 mother-infant pairs enrolled, breast milk was collected from 25 breastfeeding mothers who received a single 600 mg dose of TDF tablets at onset of labor or 4 hrs prior to cesarean section. Tenofovir was detectable in 4/25 (16%) breast milk samples collected during the infants' first week of life with concentration of 13 (6-18) ng/mL. It is unclear from the limited data set the extent of infant tenofovir exposure during breastfeeding with chronic maternal tenofovir dosing.

In Cohort 2, newborns received TDF 4 mg/kg as soon as possible after birth and on Days 3 and 5. PK sampling was done on Day 0 (cord blood, pre-dose and 2, 10 and 18-24 hours post-dose) and on Days 3 and 5 (at pre-dose, 2, 10, 18-24 and 36-48 hours post-dose). Results from Cohort 2 show that infant plasma tenofovir concentrations were greater at Day 0 than on Days 3 or 5 (Table 6). The infant dosing schedule, however, did not maintain infant plasma tenofovir concentrations above 50 ng/mL, during the first week of life.

**Table 6: Median (range) Tenofovir Concentrations in Infants (Cohort 2)**

Day of Dose	0 n=23	3 n=21	5 n=21	Adults 300 mg qd
T <sub>max</sub> (hr)	2.0 (1.6-10.0)	2.1 (1.9-43.9)	2.0 (1.8-18.0)	2.0
C <sub>max</sub> (ng/mL)	200 (66-428)	78 (27-363)	87 (22-252)	375
AUC (ng*hr/mL)	4013 (2003-8874)	2365 (728-8000)	1631 (884-4317)	3179
T <sub>1/2</sub> (hrs)	21.6 (16.0-124.5)	19.5 (6.8-44.0)	18.1 (5.2-61.3)	11.7
Cl/F (mL/kg/hr)	69 (134-1808)	1375 (566-3425)	1713 (451-3562)	584

#### Pediatric HIV/AIDS Cohort Study (PHACS)

The PHACS Surveillance Monitoring of Antiretroviral Toxicity (SMARTT) study enrolls HIV-exposed uninfected children in the US with annual follow-up to examine potential adverse effects of *in utero* ARV exposure.<sup>6</sup> In 2010, PHACS evaluated the association of TDF exposure during pregnancy with low birth weight (LBW, < 2.5kg) and infant growth at 1 year of age based on z-scores < -1.5 for length, weight, and head circumference (HC). Logistic regression models for LBW and growth outcomes were fit, adjusting for demographic and socioeconomic characteristics, maternal health status (CD4 < 250, viral load >1000 copies/mL) and substance use during pregnancy. 1855 children were enrolled in the SMARTT study as of February 2010 and had ARV information available. 380 (20%) were exposed *in utero* to TDF, increasing from 15% in 2003 to 38% in 2009. There was no increased risk of LBW for infants exposed vs. unexposed to TDF (21.2% vs. 19.5%, *P* = 0.46), and there remained no TDF effect after adjustment for HAART and other factors (adjusted odds ratio (AOR)=1.03, 95% CI: 0.81, 1.48, *P* = 0.56). However, among 470 1-year olds, those exposed *in utero* to TDF had marginally increased risk of low length and weight z-scores, while 1<sup>st</sup> trimester TDF exposure was associated with significantly increased risk of low HC z-score (AOR=2.48, 95% CI=1.17, 5.27, *P* = 0.02). While TDF use during pregnancy does not appear to increase the risk for low birth weight, it is possible that exposure may slow infant growth. It was concluded that further infant follow-up studies are warranted for monitoring the safety of TDF exposure during pregnancy.

## PROMISE

The Promoting Maternal-Infant Survival Everywhere (PROMISE) Protocol is a research protocol of the IMPAACT network designed to address in an integrated and comprehensive fashion four critical questions currently facing HIV-infected pregnant and postpartum women and their infants:<sup>23</sup>

1. What is the optimal intervention for the prevention of antepartum and intrapartum transmission of HIV?
2. What is the optimal intervention for the prevention of postpartum transmission in breastfeeding infants?
3. What is the optimal intervention for the preservation of maternal health after the risk period for prevention of mother-to-child-transmission ends (either at delivery or cessation of breastfeeding)?
4. What is the optimal intervention for the prevention of the infant morbidity and mortality associated with breastfeeding cessation?

The primary objectives of the antepartum component of PROMISE are:

- To evaluate the comparative efficacy of maternal antepartum triple ARV prophylaxis versus antepartum ZDV + sdNVP + Truvada tail to reduce antepartum and intrapartum HIV transmission, as measured by the transmission rate through 1 week (7-12 days) of age, when regimens are initiated >14 weeks gestation and prior to the onset of labor; and
- To assess and compare the safety and tolerability of these ARV regimens, including adverse pregnancy outcomes (e.g., stillbirths, prematurity, low birth weight and congenital anomalies)

It is anticipated that emerging data from the PROMISE study will be included here in a future modification.

### **2.10.3 Studies of 1% Tenofovir Gel in Pregnant Women**

Information regarding clinical studies of 1% tenofovir gel is included in the parent protocol, MTN-018.<sup>18</sup> Clinical studies with particular relevance to pregnancy are included here.

MTN-002 was a Phase 1, single-dose safety study of 1% TFV gel in term pregnancy.<sup>24</sup> Sixteen healthy, HIV-negative women with uncomplicated pregnancy at term undergoing planned cesarean delivery received a single dose of 1% tenofovir gel prior to delivery. Maternal serum drug concentrations were collected over 24 hours, specimens of amniotic fluid, cord blood, placental and endometrial tissue were collected during surgery, and maternal/neonatal AEs were tabulated. All 16 women had detectable serum TFV concentrations and 15 (93.8%) of 16 infants had detectable concentrations in cord blood. The median maternal  $C_{max}$  and fetal cord blood TFV concentrations were 4.3 and 1.9 ng/ml, respectively. Median tissue TFV concentrations

were similar to maternal serum TFV concentrations and median TFV diphosphate concentrations were below the limit of quantification. No AEs were related to TFV gel exposure. Single application of TFV gel in term pregnancy produces very low serum and tissue concentrations that are consistent with concentrations in non-pregnant women. Fetal exposure after vaginal dosing is also low. These findings supported further investigation of TFV gel in pregnancy.

MTN-008 is an expanded safety study of 1% tenofovir gel during pregnancy and breastfeeding, currently enrolling at two US sites.<sup>25</sup> In the Pregnancy Cohort, women at term gestation use tenofovir gel or placebo gel vaginally on a daily basis for one week, with safety monitoring and pharmacokinetic assessments performed throughout dosing and follow-up. Provided that no safety concerns are identified in this first group, a second group of women at near term gestation will enroll for the same schedule of gel dosing and follow-up. In the Lactation Cohort, mothers and their infants (about 1 to 6 months old) will enroll for one week of open-label maternal dosing of 1% tenofovir gel. Safety assessments will occur for both mothers and babies, with tenofovir levels checked in maternal blood, infant blood (via heel stick), and mothers' breast milk.

MTN-019 is a planned Phase 2 extended safety study of 1% tenofovir gel in pregnancy, anticipated to be implemented at US and African sites.<sup>26</sup> MTN-019 will enroll four sequential cohorts, each with approximately 90 healthy pregnant women; all cohorts will be randomized to tenofovir vs. placebo gel (2:1) for a 4-week exposure. Cohorts will be filled sequentially and move progressively to earlier gestations of pregnancy. This protocol will collect valuable information on the potential impact of tenofovir gel on the vaginal microenvironment of pregnant women, as well as general health and perinatal outcomes.

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 ( $P = 0.183$ ).<sup>13</sup> 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. Study gel was held starting at the time of pregnancy diagnosis. 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.

The MTN-016 Prevention Agent Pregnancy Exposure Registry aims to assess the potential impact of candidate HIV prevention agents in pregnancy, including the potential impact on rates of pregnancy loss and major malformations.<sup>27</sup> MTN-016 is also examining infant growth and health outcomes, including developmental milestones in the first year of life. 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 and the NIAID/DAIDS Prevention Trials Data and Safety Monitoring Board. Outcomes from MTN-016 will be unblinded when VOICE is unblinded (projected late 2012). MTN-016 is also amassing data from MTN-002, MTN-008, and MTN-019 (planned). Women with pregnancy exposures in MTN-018 and its sub-studies

would also be offered participation (along with any infants resulting from these pregnancies) in MTN-016.

## **2.11 Rationale**

### **2.11.1 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, if not more, VOICE study products will be found to be safe and effective as prophylaxis for HIV. 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 the parent protocol, MTN-018, is the collection of additional safety data and the examination of multiple approaches to safety monitoring. The role of MTN-018C is to gather additional data on the safety profile of safe and effective VOICE products among pregnant women.

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. The parent protocol, 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.

Physiologic changes during pregnancy have the potential to alter the safety and tolerability profiles of PrEP and microbicides, for this reason and the reasons discussed previously, it is important that data be gathered on oral and topical PrEP use among pregnant women. MTN-018C will provide key data for the field and for regulators on pregnancy outcomes following extended use of antiretroviral based prevention strategies.

The MTN-018C and MTN-016 protocols will work together to collect a full spectrum of data regarding the impact of exposure during pregnancy to tenofovir-based HIV prevention strategies. The potential concern regarding infant growth at 1 year following *in utero* tenofovir exposure can be further examined within MTN-016, as growth measurements in the first year of life are built into this pregnancy registry, already implemented at VOICE sites.



### **2.11.2 Adherence Component**

Recent findings from the iPrEx and CAPRISA 004 trials highlight the critical connection between drug adherence and level of protection from HIV infection.<sup>13,28</sup> It is currently unknown what impact pregnancy may have on a woman's incentive or ability to adhere to a daily regimen of TFV gel, TDF or TDF/FTC. The first trial of repeat dosing of tenofovir gel in pregnancy is currently underway (MTN-008), but the prescribed length of dosing is very brief (7 days). Another trial currently in development (MTN-019) will provide data on adherence to tenofovir gel over a slightly longer period of use (28 days). As all trials of prescribed use of oral TDF and FTC/TDF during known pregnancy have been in the context of treatment for HIV/AIDS and/or PMTCT, it is difficult to extrapolate rates of adherence from those trials to the context of HIV prevention. Arguably, adherence could be higher in the pregnant than in the non-pregnant state, due to incentive to avoid HIV infection while on the brink of the greater responsibility of motherhood and/or concern for possible perinatal transmission, or lower, due to physical discomfort with inserting applicators and/or fear of adverse drug effects on the developing fetus. Women might be more or less tolerant of study products with side effects similar to those already occurring as normal discomforts of pregnancy (e.g., nausea, increased vaginal discharge, etc.). Greater attention to the mother's health and investment in the pregnancy outcome by the woman's partner and family may also impact her ability and desire to adhere. Partner support may be greater for pregnant women, especially those in serodiscordant relationships. Thus, adherence to an HIV prevention strategy may be different during pregnancy and is a worthwhile area for study.

Among MTN-018C participants, it may be possible to compare rates of adherence to those rates observed in MTN-018, or to the non-pregnant state during VOICE; however, any higher rates of adherence in MTN-018C compared to those in VOICE should be interpreted with caution, due to the fact that MTN-018C will only move forward if there are VOICE study products known to be effective. MTN-018C will use participant self-report, study drug counts, and drug levels to describe the adherence profile associated with a prescribed daily regimen of study product.

### **2.11.3 Safety Monitoring Strategy**

With the intent of more intensive monitoring during pregnancy, MTN-018C participants will not be randomized to a monthly vs. quarterly monitoring strategy. Rather, all MTN-018C participants will be followed monthly. Monthly monitoring will permit close observation of pregnancy growth and health, and will facilitate rapid study product hold, in the event of a significant pregnancy complication and/or adverse drug reaction.

Within MTN-018, the parent protocol, 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-018C 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-018C 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.

### **3 OBJECTIVES**

#### **3.1 Primary Objectives**

- To compare pregnancy outcomes from MTN-018C participants to those of VOICE participants who became pregnant during VOICE
- To compare health outcomes for infants born to MTN-018C participants to those of MTN-016 infants of VOICE mothers in the first 30 days of life

#### **3.2 Secondary Objectives**

- To compare pregnancy morbidities among MTN-018C participants with those of MTN-016 participant (VOICE) mothers

- To describe the extended safety profile of study products among MTN-018C participants
- To evaluate adherence to daily regimens of MTN-018C study products

## **4 STUDY DESIGN**

### **4.1 Identification of Study Design**

MTN-018C is an open-label, multi-site sub-study to MTN-018 for pregnant women.

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

At the Month 1 Visit, and provided that more than one product is selected to move forward in MTN-018C, each study participant identifies which product she would like to use for the remainder of follow-up. She will be asked about the reason(s) for her study product selection. The participant will then enter into monthly follow-up on study product until her pregnancy outcome has occurred. Participants who are not breastfeeding then continue monthly follow-up on study drug until Month 12 (based on date of Enrollment for MTN-018 or MTN-018C, depending on initial enrollment) and return in 8 weeks for a Termination Visit, at which point participants will undergo HIV testing to assess for possible masked HIV infection. Participants who are breastfeeding will be offered screening for MTN-018B.

### **4.2 Summary of Major Endpoints**

Primary objectives will be addressed via the following endpoints:

- **Pregnancy outcomes**
  - Any of the following reported by participant mothers or obtained from medical records
    - Full-term live birth
    - Premature live birth
    - Stillbirth/intrauterine fetal demise
    - Spontaneous abortion
    - Ectopic pregnancy
    - Other pregnancy outcomes

- **Infant Outcomes**

- Any of the following reported by participant mothers or obtained from medical records for the first 30 days of infant's life
  - Life-threatening event
  - Persistent or significant disability/incapacity
  - Hospitalization/prolongation of hospitalization
  - Death

Secondary objectives will be addressed via the following endpoints:

- **Pregnancy morbidities**

- Intrapartum hemorrhage
- Postpartum hemorrhage
- Chorioamnionitis
- Hypertensive disorders of pregnancy
- Gestational diabetes
- Placenta previa
- Placenta accreta
- Placental abruption
- Preterm premature rupture of membranes
- Premature rupture of membranes at term ( $\geq 37$  weeks gestational age)
- Sepsis during pregnancy or first 42 days following pregnancy outcome

- **Extended Safety Profile**

- Grade 2 or higher adverse events (AEs) (laboratory)
  - AST/ALT
  - Creatinine
- Grade 2 or higher AEs (clinical)

- **Adherence**

- Self-report
- Product counts
- Drug levels

#### **4.3 Description of Study Population**

The study population will be healthy, HIV-uninfected, former VOICE participants who are pregnant.

#### **4.4 Time to Complete Accrual**

The time to complete accrual in MTN-018C is anticipated to be approximately 12 months.

## **4.5 Study Groups**

Individual study groups depend upon selection of study product(s) for MTN-018C. Groups may include one or more of the following:

- 1% tenofovir vaginal gel
- TDF 300 mg tablet
- FTC/TDF 200 mg/300 mg tablet

## **4.6 Expected Duration of Participation**

The expected maximum duration of participation for an individual participant enrolled in MTN-018C is approximately 14 months; at a minimum, all enrolled participants will have follow-up until pregnancy outcome can be ascertained, or until it is determined by the MTN-018 PSRT that the pregnancy outcome cannot be ascertained.

## **4.7 Sites**

Study sites will be MTN-018 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 according to guidance for recruitment of the VOICE Cohort in the parent protocol, MTN-018.

### **5.1.2 Retention**

Once a participant is enrolled in MTN-018C, 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 mother 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 – MOTHERS**

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

- 1) Previously enrolled in VOICE
- 2) 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
- 3) Currently pregnant, confirmed by positive pregnancy test performed by study staff at screening and on the day of enrollment
- 4) Per participant report, sexually active, defined as having vaginal intercourse at least once in the three months prior to screening
- 5) HIV-uninfected based on testing performed by study staff at screening and on the day of enrollment (per applicable algorithms in protocol appendices)
- 6) At screening and enrollment, agrees not to participate in other research studies involving drugs, vaccines, medical devices, or vaginal products while enrolled in MTN-018C

## **5.3 Exclusion Criteria – MOTHERS**

- 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) 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
- 3) Has any of the following, as determined by the IoR designee:
  - a) Hypertensive disorder of pregnancy
  - b) Undiagnosed genital bleeding
  - c) Cervical cerclage
  - d) Placenta previa
  - e) Intrauterine growth restriction
  - f) Pre-gestational or gestational diabetes
  - g) Treatment for preterm labor
  - h) Reasonable evidence that the pregnancy will not continue for a period of at least one month following Enrollment, as determined by the clinical judgment of the IoR/designee
- 4) Weight less than 35 kg at Screening
- 5) 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.*

- 6) Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives

#### **5.4 Co-enrollment Guidelines**

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

- Participants may take part in ancillary studies approved by MTN-018C 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 may take part in registries (e.g., MTN-016). Additional pregnancy testing to confirm eligibility for MTN-016 may be performed within MTN-018C, as needed.
- With permission of the Protocol Safety Review Team (PSRT), participants may co-enroll in MTN-018B and MTN-018C (study product will not be dispensed simultaneously to the same participant in more than one trial).

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

## **6 STUDY PRODUCT**

### **6.1 Regimen**

At the Enrollment Visit, each participant will indicate their choice of one of the following regimens (pending selection of study product(s) for MTN-018C) 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, participant mothers will identify their chosen study product for the duration of the trial. Thereafter, one participant-initiated change to a different 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 participant mothers 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<sup>®</sup>) 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<sup>®</sup>) 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% (w/w) 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<sup>®</sup>) tablets and FTC/TDF (Truvada<sup>®</sup>) 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 return to the study clinic and the pharmacy each month. Study products will be dispensed only to enrolled participants, upon receipt of a written prescription signed by an authorized prescriber. Products will be dispensed in quantities sufficient until the next scheduled study visit. Dispensing will take place on the day of enrollment and at each scheduled follow-up visit, except at the 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 products must be retrieved (optimally within 24 hours) and returned to the study site pharmacy when study product use is permanently discontinued for HIV seroconversion. For temporary hold 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. 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.

Medications with significant nephrotoxic potential should be avoided when possible. Should a participant report use of any of these medications, the IoR/designee will institute a temporary product hold, for as long as the participant is taking the contraindicated medication.

Study product 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 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 Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites are provided in the MTN-018C Study Specific Procedures (SSP) Manual available at [www.mtnstopshiv.org](http://www.mtnstopshiv.org). Unless otherwise specified, the laboratory procedures listed in this section are performed at 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 guidance in the SSP Manual, as well as 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. For participants transferring from MTN-018 to MTN-018C, the following tests may be omitted: AST/ALT, serum creatinine, HBsAg, and HBsAb. However, if AST/ALT and creatinine were not performed in the past six months, they must be repeated during screening. Procedures/tests done within an MTN-018 visit may substitute for the same procedures indicated for screening in MTN-018C, if they occur within one calendar day of the MTN-018C Screening Visit.

### **7.2.1 Administrative, Behavioral, and Regulatory Procedures**

- Co-enrollment assessment (site-specific)
- Informed consent for screening
- Demographic information
- Behavioral assessment and behavioral eligibility information
- Locator information
- Assign PTID
- Collect obstetric care provider and contact information, and planned location for delivery (make arrangements to collect information if not yet available)
- HIV pre- and post-test counseling, including HIV/STI risk reduction counseling
- Offer/refer HIV/STI counseling and testing for partner(s)
- Provision of condoms
- Reimbursement
- Schedule next visit (if applicable)

### **7.2.2 Clinical Procedures**

- Medical history
- Concomitant medications
- Menstrual history
- Physical exam (including vital signs)
- Weight
- Obstetric symptom review, including genital bleeding, contractions/pelvic pain, possible loss of amniotic fluid, normal fetal movement (if expected for gestational age)
- Review available antenatal records
- Conduct or refer for obstetric ultrasound, unless an ultrasound report is available and complete (comments on estimated gestational age and normalcy of pregnancy, according to the judgment of the IoR/designee)
- Obstetric abdominal exam
  - Symphysis-fundal height, if appropriate for gestational age
  - Fetal heart tones (by Doppler, fetoscope or ultrasound) if appropriate for estimated gestational age and deemed clinically appropriate by IoR/designee
- Pelvic/bimanual exam to include the following:
  - Visual inspection
  - Pelvic swab collection, if indicated by signs or symptoms of vaginitis or sexually transmitted infection (STI)
  - Bimanual exam with estimated gestational age by exam
- Documentation of estimated gestational age
- Urine collection
- Blood collection
- Disclosure of available test results

- Treatment or referral of conditions identified at Screening, according to local standard of care, as clinically indicated
- Eligibility assessment

### **7.2.3 Laboratory Procedures**

- Urine pregnancy test
- Urine dipstick for protein and glucose
- HIV serology
- Serum creatinine (may be omitted if transferring from MTN-018)
- AST/ALT (may be omitted if transferring from MTN-018)
- HBsAg/HBsAb (may be omitted for participants who completed HBV vaccination series, or who have documented evidence of HBV immunity from VOICE) (may be omitted if transferring from MTN-018)
- STI testing, if indicated by local standard of care
- Vaginitis testing, if symptomatic

### **7.2.4 Final Screening Procedures and Confirmation of Eligibility**

On anticipated day of Enrollment, 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
- Documentation of estimated gestational age (see guidance in Section 7.15)
- Obstetric symptom review (according to Section 7.2.2)
- Update medical history and current medications, review antenatal records
- 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
- Clinical examinations 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 Procedures**

- 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
- Update obstetric care provider and contact information, and planned location for delivery (make arrangements to collect information if not yet available)
- Behavioral assessment
- HIV/STI risk reduction counseling
- Provision of condoms
- Offer/refer HIV/STI counseling/testing for partner(s)
- Reimbursement
- Schedule next visit

### **7.3.2 Clinical Procedures**

- Disclosure of available test results
- Treatment or referral of conditions, according to local standard of care, as clinically indicated
- Blood collection, may be collected together with any blood collected for final eligibility confirmation, with consent
- Initial participant study product selection
- Provision of study product, instructions, and adherence counseling

### **7.3.3 Laboratory Procedures**

- Plasma archive

*Note, plasma archive is collected on all participant mothers on the day of Enrollment, and may be collected during 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. For MTN-018C participants previously enrolled in MTN-018, follow-up on product continues through pregnancy outcome and monthly thereafter until the visit window for the participant's originally scheduled (within MTN-018) Month 12 Visit, if this window has not yet been reached. For participants not previously enrolled in MTN-018, follow-up on product continues through pregnancy outcome and monthly thereafter until 12 months after enrollment into MTN-018C. However, MTN-018C participants who enroll in MTN-018B will terminate participation in MTN-018C. In the event that a pregnancy ends prematurely (e.g., in miscarriage), participants may continue to receive study product and follow-up within MTN-018C until their previously anticipated end of follow-up.

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 7.6 – 7.7.2 for further procedural modifications that may be required during follow-up. Due to unpredictable timing, the Pregnancy Outcome Visit is not considered a routine scheduled follow-up visit, but is considered separately in the next section (Section 7.5).

The last two scheduled visits for each participant are referred to as the Month 12 Visit and the Termination Visit, respectively. The Month 12 Visit will serve as all participants’ last routine follow-up visit. The Month 14/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 Visit and Month 14/Termination Visit are specified in the MTN-018C SSP Manual ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)).

#### **7.4.1 Administrative, Behavioral, and Regulatory Procedures**

- Review/Update locator information
  - At all visits
- Update obstetric care provider and contact information, and planned location for delivery (make arrangements to collect information if not yet available)
  - At scheduled visits
  - At interim visits, if indicated
- Behavioral assessment
  - Month 1
  - Month 6
  - Month 12
  - Month 14/Termination
  - At interim visits, if indicated
- Adherence assessment
  - Month 1
  - Month 3
  - Month 6
  - Month 9
  - Month 12
  - At interim visits, if indicated
- Study product-sharing assessment
  - Month 12



- Social harms assessment
  - Month 3
  - Month 6
  - Month 9
  - Month 12
  - At interim visits, if indicated
- HIV pre- and post-test counseling
  - Monthly up to and including Month 12
  - Month 14/Termination
  - At interim visits, if indicated
- HIV/STI risk reduction counseling
  - At scheduled visits
  - At interim visits, if indicated
- Offer HIV/STI testing, counseling and treatment for partner(s), if indicated by site SOP
  - When clinically indicated
- Provision of condoms
  - At scheduled visits
  - At interim visits if indicated
- Reimbursement
  - At scheduled visits
  - At interim visits per site SOP
- Schedule next visit
  - At scheduled visits except the Month 14/Termination Visit (at the Month 14/Termination Visit, next (off-study) visit is scheduled only if needed, i.e., to provide test results and counseling, follow-up on AEs, etc.)
  - At interim visits if indicated

#### **7.4.2 Clinical Procedures**

- Interval (i.e., since last visit) medical/antenatal history and concomitant medication review/update
  - At all scheduled visits
  - Additionally at unscheduled visits in response to intercurrent symptoms/illnesses/ongoing AEs
- Obstetric symptom review (according to Section 7.2.2)
  - At all scheduled visits prior to pregnancy outcome

- Obstetric abdominal exam, with symphysis-fundal height, if appropriate for gestational age, and fetal heart tones (by Doppler, fetoscope or ultrasound) if appropriate for gestational age and deemed clinically appropriate by IoR/designee
  - At scheduled visits
  - At other visits when clinically indicated
- Pelvic exam with bimanual exam
  - Month 12
  - When clinically indicated
- Pelvic swabs for STI and/or vaginitis testing
  - When indicated by local standard of care
- Documentation of estimated gestational age
  - At all visits prior to pregnancy outcome
- Physical exam (including vital signs)
  - Month 12
  - Additionally when clinically indicated
- Weight
  - Month 6
  - Month 12
  - Additionally when clinically indicated
- Urine collection
  - Month 6
  - Month 12
  - Additionally when clinically indicated
- Blood collection
  - At all scheduled visits
  - When needed to perform confirmatory HIV testing per Appendix II
  - Additionally when clinically indicated
- Disclosure of available test results
  - At all scheduled visits
  - Additionally when clinically indicated
- Treatment/Referral
  - When clinically indicated
- Collect AEs
  - At all scheduled visits
  - At interim visits, if indicated

- Treatment and/or referral for treatment of AEs, according to local standard of care
  - When clinically indicated
- Contraceptive counseling
  - At all scheduled visits for participants who are maintained in follow-up following a pregnancy outcome
- Study product selection/ confirmation
  - Month 1
  - At other visits prior to Month 12, if indicated and approved by IoR/designee
- Study product supplies and instructions
  - At scheduled visits prior to Month 12
  - At interim visits, if indicated
- Adherence counseling
  - Month 1
  - Quarterly, except omitted at Month 12
- Collect unused study product
  - Monthly up until and including Month 12
  - At Month 14/Termination Visit, if indicated
  - At interim visits, if indicated
- Hepatitis B vaccination (as indicated by local guidelines for pregnant women for consenting HBV susceptible participants)
  - At visits corresponding with recommended time points for hepatitis B vaccine series

#### **7.4.3 Laboratory Procedures**

- Urine pregnancy test
  - At all scheduled visits for participants who are maintained in follow-up following a pregnancy outcome
- Urine dipstick for protein and glucose (for those most recently using oral product)
  - Month 6
  - Month 12
  - At interim visits, if indicated
- STI testing
  - When indicated by local standard of care

- Vaginitis testing
  - When clinically indicated (symptomatic)
- HBsAg/HBsAb
  - Check HBsAg at Month 12 (unless documented history of immunity or documented history of completed HBV vaccine series).
  - When clinically indicated
- HIV serology
  - Monthly up to and including Month 12
  - Month 14/Termination Visit
  - Additionally 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
- Blood study drug levels
  - Month 6
  - Month 12
  - At interim visits, if indicated
- Plasma archive
  - Month 6
  - Month 12
  - Month 14/Termination Visit
  - At other visits, if indicated (if instructed by MTN NL)
- HIV-1 RNA polymerase chain reaction (PCR)
  - If indicated
- CD4+ T-cell count
  - If indicated

## **7.5 Pregnancy Outcome Visit**

Participants will be instructed to contact the site when pregnancy outcome occurs. All pregnancy outcomes will be captured on case report forms. Study site staff (by phone

or in person) will collect information regarding pregnancy outcome and adverse events for the mother (and infant, if applicable) at this visit. With documented written permission of the participant, available clinical records for mother (and infant, if applicable) will be reviewed for possible adverse events. This visit is conducted within 42 days after the date of the pregnancy outcome. If necessary, to assess for SAEs during the neonatal period (first 30 days of life), site staff may re-contact participants.

The following information will be collected, at a minimum:

- Locator information
- Concomitant medications
- Review of obstetric care records
- Medical history
- Adverse events

Other procedures may be included, if indicated, at this visit, e.g., physical exam, treatment/referral, etc.

## 7.6 Follow-up after Pregnancy Outcome

**Table 7: Follow-up after Pregnancy Outcome**

<b>Pregnancy Outcome</b>	<b>Next Step</b>	<b>Notes/Rationale</b>
Live birth outcome, regardless of previous enrollment in MTN-018 – Breastfeeding	Screen for MTN-018B.	If participant does not want self and/or infant to join or either is ineligible for MTN-018B, all CHOICE and CHOICE sub-study participation terminates. This allows safety monitoring of breastfeeding infant(s) exposed to study products. Follow-up for this participant and her infant would include those procedures designated in MTN-016, if she has enrolled herself or infant in MTN-016.
Live birth outcome, previously enrolled in MTN-018 – Not breastfeeding	Continue monthly follow-up on study drug within MTN-018C only if participant has not reached (and until) 12 months past the time of enrollment into MTN-018.	Total combined time on study product within MTN-018 and MTN-018C sub-studies will vary depending upon the timing of the MTN-018 study visit at which pregnancy was diagnosed.
Non-live birth outcome (e.g., miscarriage), previously enrolled in MTN-018	Continue monthly follow-up on study drug within MTN-018C only if participant has not reached (and until) 12 months past the time of enrollment into MTN-018.	However, follow-up always continues through the time of pregnancy outcome, and extends past that point if additional time remains in the originally scheduled 12-month follow-up period for her participation in MTN-018.
Non-live birth outcome (e.g., miscarriage), NOT previously enrolled in MTN-018	Continue monthly follow-up on study drug within MTN-018C until participant has reached 12 months past the time of enrollment into MTN-018C.	This approach avoids the logistical and other burdens that would be associated with returning the participant to the parent study.

## **7.7 Follow-up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product**

### **7.7.1 Participants Who Become Infected with HIV**

All participants who become HIV-infected on study will stop study product and be referred for HIV care and treatment. Participants who become infected with HIV will be encouraged to enroll in MTN-015. If enrollment into MTN-015 is declined or delayed then women will be followed in MTN-018C at one month, 3 months, 6 months and 12 months after seroconversion. Participants will be offered enrollment in MTN-015 ([www.mtnstopshiv.org](http://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-018C; however, all pregnancy outcomes and congenital anomalies will be captured for MTN-018C participants, regardless of participation in MTN-015.

For those who continue MTN-018C follow-up and do not enroll in MTN-015, study visits will occur at 1, 3, 6, and 12 months after seroconversion. At each visit, blood will be collected for plasma archive, CD4+ T cell count and HIV RNA. Other study procedures including provision of study product, study product instructions, product adherence counseling, product adherence assessment, study product sharing assessment will be discontinued. HIV/STI risk reduction counseling will be modified to address primary and secondary prevention for infected women.

Participant mothers who become HIV-infected on study will have HIV and resistance testing for their infants provided by this study and/or MTN-016, if this is not otherwise accessible. Women who seroconvert during pregnancy will be referred for immediate initiation of antiretroviral prophylaxis according to local standard of care.

### **7.7.2 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 advised by the MTN-018 PSRT, before terminating study participation. Reason(s) for discontinuation will be captured for the study database.

## **7.8 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.

## 7.9 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.

## 7.10 Clinical Evaluations and Procedures

Physical Exams will include the following assessments:

- Vital signs
  - Temperature
  - Blood pressure
  - Pulse
  - Respirations
- Measurement of height
- Clinical assessments of
  - Head and eyes
  - Neck
  - Lymph nodes
  - Heart
  - Lungs
  - Abdomen
  - Extremities
  - Neurological
  - Skin

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 for mothers will be conducted per guidelines in the parent protocol, MTN-018.

## **7.11 Laboratory Evaluations**

The location of laboratory evaluations will depend on laboratory capacity.

- Urine pregnancy test
- 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-018C
- Vaginitis testing
- STI testing

## **7.12 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](http://www.mtnstopshiv.org)), DAIDS laboratory requirements, MTN-018C Study Specific Procedures Manual ([www.mtnstopshiv.org](http://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.

## **7.13 Specimen Handling**

Specimens will be handled in accordance with requirements in the parent protocol, MTN-018.

## **7.14 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 Dangerous Goods Regulations. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

### **7.15 Calculation of Gestational Age**

Inconsistency or concern about the accuracy of the estimated gestational age requires further assessment with ultrasonography. Useful measurements include the crown–rump length of the fetus during the first trimester and the biparietal diameter or head circumference and femur length during the second trimester. Because of the normal variations in size of infants in the third trimester, dating the pregnancy at that time is less reliable ( $\pm 21$  days). The variation by ultrasonography generally is  $\pm 7$  days up to 20 weeks of gestation,  $\pm 14$  days between 20 and 30 weeks of gestation, and  $\pm 21$  days beyond 30 weeks of gestation. If the estimated gestational age by the participant's last menstrual period differs from the ultrasound estimate by more than these accepted variations, the ultrasound estimate of gestational age should be used instead of the patient's menstrual cycle estimate.

## **8 ASSESSMENT OF SAFETY**

### **8.1 Safety Monitoring and Review**

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, NICHD Medical Officer, Protocol Safety Physician, CONRAD Medical Officer (if 1% tenofovir 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. It is anticipated that a single MTN-018 PSRT will be used for MTN-018 and all related sub-studies.

### **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 participant mothers 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 mother, whenever possible, records from all non-study medical providers related to untoward medical occurrences for both mothers and infants 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, or obtained from medical records:

- All AEs of severity Grade 2 or higher for mothers
- All laboratory values for mothers
- All serious AEs for mothers, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
- All serious AEs for infants in the first 30 days of life
- All AEs for mothers that result in product hold or permanent discontinuation of study product use in the mother by the IoR or designee

Adverse event severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated 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. Adverse events not included in the Female Genital Grading Table will be graded by the DAIDS AE Grading Table Version 1.0, December 2004 (Clarification dated 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.

A serious adverse event will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), as an AE occurring at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or

require intervention to prevent one of the outcomes listed in the definition above.

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. Degrees of relatedness will be categorized according to current DAIDS-approved guidelines. Per the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), the relationship categories that will be used for this study are:

- *Related*: There is a reasonable possibility that the AE may be related to the study agent(s)
- *Not Related*: There is not a reasonable possibility that the AE is related to the study agent(s)

### **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](mailto: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](mailto:DAIDSRSCSafetyOffice@tech-res.com)).

For all EAEs submitted, sites must file an RSC update with the final or stable outcome unless the initial EAE submitted had a final or stable outcome noted already.

#### **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:

- Tenofovir disoproxil fumarate 300 mg tablet
- Emtricitabine/tenofovir disoproxil fumarate 200 mg/300 mg tablet

- 1% tenofovir gel and the gel applicator

### **8.3.3 Grading Severity of Events**

The most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009), Addenda 1 (Female Genital Table for Use in Microbicide Studies) will be used and is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. Adverse events not included in these tables will be graded by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (clarification dated August 2009). In cases where an AE is covered in both tables, the DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification dated August 2009), Addendum 1 (Female Genital Table for Use in Microbicide Studies) will be the grading scale utilized.

### **8.3.4 Expedited AE Reporting Period**

The expedited AE reporting period for this study is as defined in Version 2.0 of the DAIDS EAE manual. After the protocol-defined AE reporting period, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions 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 in the mother at any time if s/he feels that continued product use would be harmful to the mother or her pregnancy, 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.

### **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 mother 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 mother is determined to be HIV-uninfected per the algorithm in Appendix III, she may resume product use.
- Report of use of PEP by participant mother for HIV exposure. The participant mother may resume product use when she reports completion of PEP and is confirmed HIV negative based on testing performed at the study site per the algorithm in Appendix III.
- Clinical suspicion of acute HIV infection in participant mother.
- Participant mother 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 mother 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 III; 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. This section applies to complications of pregnancy, as well as other AEs.

##### **Grade 1 or 2**

In general, a participant mother 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**

Participant mothers 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. Participant mothers 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 Adverse Events**

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, pre-eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count), fatty liver of pregnancy, or viral hepatitis as the cause of elevation in AST and/or ALT of any grade. The IoR/designee must carefully assess the participant mother 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 mother should then be followed at an interval determined by the site IoR/designee until levels are Grade  $\leq 1$ , 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 in the participant mother  $\geq$  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.

### **9.5.3 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/> or relevant locally regulated guidelines. 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.

### **9.5.4 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-018C 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, and counseled regarding available strategies for prevention of perinatal transmission of HBV.

## **9.6 HIV Infection**

A participant mother who has a positive rapid test for HIV must have study product held. If the participant mother is subsequently determined to be HIV-uninfected according to the algorithm in Appendix III, study product may be resumed. If HIV infection is confirmed, study product will be permanently discontinued by the IoR/designee. Participants identified as infected with HIV will be managed or referred for management according to the local standard of care. If not otherwise accessible, HIV testing and drug resistance testing for infants of HIV-infected mothers will be provided within MTN-018C and/or MTN-016. All participants will be provided with relevant referrals for prevention of mother-to-child transmission of HIV. Participants will receive results of resistance testing performed in MTN-018C.

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-018C.

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



Results of study laboratory testing may be helpful in clinical management; these results will be provided to the participant and her medical provider in real-time.

### **9.7 Antenatal Care**

Study participants will be referred to antenatal care, as needed, by site staff. The IoR/designee will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care. A participant who is pregnant at the Termination Visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). All participants will be encouraged to breastfeed, according to current WHO recommendations.

### **9.8 Signs/Symptoms of Labor**

Temporarily product hold should be instituted once labor or rupture of membranes is suspected by the participant or the IoR/designee. If labor and/or rupture of membranes are ruled out, study product should be resumed.

### **9.9 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**

MTN 018C is an open-label, non-randomized, multi-site sub-study to MTN-018 for pregnant women and their infants. The main goal of the study is to provide additional safety data for potentially supporting further pre-, peri-, and/or post- registration requirements and/or a change of label.

VOICE site investigators have estimated that approximately 300 women previously enrolled in the VOICE trial may be pregnant during the implementation of the parent protocol, MTN-018. However, MTN-018C will not have an upper limit on the number of pregnant who may be enrolled.

## **10.2 Study Endpoints**

### **Primary Endpoints: Pregnancy Outcomes**

Consistent with the primary study objective to compare pregnancy outcomes from MTN-018C participants to those of VOICE participants who became pregnant during VOICE, the following endpoints will be assessed:

- Any of the following reported by participant mothers or obtained from medical records:
  - Full-term live birth
  - Premature live birth
  - Stillbirth/intrauterine fetal demise
  - Spontaneous abortion
  - Ectopic pregnancy
  - Other pregnancy outcomes

### **Primary Endpoints: Infant Outcomes**

Consistent with the primary study objective to compare health outcomes for infants born to MTN-018C participants to those of MTN-016 infants of VOICE mothers in the first 30 days of life, the following endpoints will be assessed:

- Any of the following reported by the participant mothers or obtained from medical records for the first 30 days of infant's life:
  - Life-threatening event
  - Persistent or significant disability/incapacity
  - Hospitalization/prolongation of hospitalization
  - Death

### **Secondary Endpoints: Pregnancy Morbidities**

Consistent with the secondary study objective to compare pregnancy morbidities among MTN-018C participants to those of MTN-016 participant (VOICE) mothers the following endpoints will be assessed:

- Intrapartum hemorrhage
- Postpartum hemorrhage
- Chorioamnionitis
- Hypertensive disorders of pregnancy
- Gestational diabetes
- Placenta previa
- Placenta accreta

- Placental abruption
- Preterm premature rupture of membranes
- Premature rupture of membranes at term ( $\geq 37$  weeks gestational age)
- Sepsis during pregnancy or first 42 days following pregnancy outcome

### **Secondary Endpoints: Extended Safety Profile**

Consistent with the secondary study objective to describe the extended safety profile of study products among MTN-018C participants, the following endpoints will be assessed:

- Grade 2 or higher adverse events (AEs) (laboratory)
  - AST/ALT
  - Creatinine
- Grade 2 or higher AEs (clinical)

### **Secondary Endpoints: Adherence**

Consistent with the secondary study objective to evaluate adherence to daily regimens of MTN-018C study products the following endpoints will be assessed:

- Adherence to study product by self-report, product counts, and serum drug levels

## **10.3 Sample Size**

Pregnancy Outcome and Morbidity Endpoints: Based on site investigator estimates for the expected percentage of former VOICE participants that will be pregnant during implementation of MTN-018, we expect approximately 300 pregnant women to be eligible for participation in MTN-018C, although no formal upper limit on enrollment is anticipated. Also based on estimates from VOICE and MTN-016, we expect approximately 500 pregnancies during the course of VOICE. Assuming that 40% of these pregnancies are among women in the placebo arms of the trial (2 of the 5 arms of VOICE) we expect pregnancy data on approximately 200 women to be available for comparison with pregnancy data in MTN-018C.

Because in MTN-018C there could be anywhere from one to three products for women to choose from, and we do not know what proportion will choose a particular product, it is difficult to predict the number of pregnant women exposed to each of the one to three products. Table 7 provides information regarding the minimum rate detectable with 80% power in pregnancy outcomes or morbidities for varying sample sizes of MTN-018C pregnant women and varying estimates of pregnancy outcome and morbidity rates in the 200 VOICE pregnant women randomized to placebo assuming a 2-sided chi-square test with  $\alpha=0.05$ . The sample size will be recalculated following the completion of VOICE, if MTN-018 is anticipated to move forward.

**Table 7: Minimum Rate Detectable With 80% Power for Pregnancy Outcomes and Morbidities (assuming n=200 VOICE control group pregnancies)**

Estimate of proportion with outcome in VOICE placebo participants	Minimum Rate Detectable with 80% Power with a sample size of MTN-018C women of:		
	n=100	n=200	n=300
n=200			
1%	7.5%	6.2%	5.4%
5%	14.9%	13.0%	11.9%
10%	22.3%	20.0%	18.6%
20%	35.1%	32.3%	30.6%
50%	66.9%	63.8%	62.0%

Thus, if a pregnancy outcome or morbidity is observed in 10% of pregnancies in the VOICE placebo control group, we would have 80% power to detect a minimum difference between the groups of 10% (20.0% or higher rate in the MTN-018C pregnancies) with information from n=200 MTN-018C women. Note that if in VOICE there are no significant differences in pregnancy outcomes between the active product arms and the placebo arms, pregnancy outcome data from women in the active product arms of VOICE could also be used for these analyses which would substantially increase statistical power. Similarly, if there are no differences in pregnancy morbidities in the different arms of VOICE, pregnancy morbidity data from women in the active product arms could be used for comparison with MTN-018C.

Infant Outcomes: Based on site investigator estimates for the expected percentage of former VOICE participants that will be pregnant during implementation of MTN-018, we expect approximately 300 pregnant women to be eligible for participation in MTN-018C resulting in approximately 200 live births. Also based on estimates from VOICE and MTN-016, we expect approximately 500 pregnancies during the course of VOICE, resulting in approximately 350 live births. Assuming that 40% of these births are to women in the placebo arms of the trial (2 of the 5 arms of VOICE), and assuming 80% of these women enroll in MTN-016 we expect infant outcome data on approximately 115 infants in MTN-016 (the comparison group for MTN-018C infants).

Because in MTN-018C there could be anywhere from one to three products for women to choose from, and we do not know what proportion will choose a particular product, it is difficult to predict the number of mother-infant pairs exposed to each of the one to three products. Table 8 provides information regarding the minimum rate detectable with 80% power in infant outcomes for varying sample sizes of MTN-018C infants and varying estimates of infant outcome rates in the 115 MTN-016 placebo exposed infants assuming a 2-sided chi-square test with  $\alpha=0.05$ .

**Table 8: Minimum Rate Detectable With 80% Power for Infant Outcomes (assuming n=115 MTN-016 control group infants)**

Estimate of proportion with outcome in MTN-016 placebo infants	Minimum Rate Detectable with 80% Power with a sample size of MTN-018C infants of:	
	n=100	n=200
n=115		
1%	4.8%	4.3%
2%	7.4%	6.6%
5%	13.3%	12.1%
7%	16.8%	15.4%
10%	21.5%	19.8%

Thus, if an infant outcome is observed in 5% of infants in the MTN-016 control group, we would have 80% power to detect a minimum difference between the groups of 8.3% (13.3% or higher rate in the MTN-018C infants) with information from n=100 MTN-018C infants. Note that if in VOICE/MTN-016 there are no significant differences in infant outcomes between the active product arms and the placebo arms, infant outcome data from infants of mothers in the active product arms of VOICE could also be used for these analyses which would substantially increase statistical power.

#### **10.4 Participant Accrual, Follow-up and Retention**

Accrual is anticipated to be completed in approximately 12 months. The expected maximum duration of participation for an individual participant enrolled in MTN-018C is approximately 14 months.

#### **10.5 Blinding**

This is an open-label and unblinded study.

#### **10.6 Data and Safety Monitoring and Analysis**

##### **10.6.1 Study Monitoring Committee (SMC)**

No Data and Safety Monitoring Board (DSMB) oversight is planned for this study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and study or lab issues. These reviews will take place approximately every 4 to 6 months, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. The SMC may consider recommending termination of this study if recruitment and retention are lower than targeted, or if study data quality is poor.

##### **10.6.2 Data and Safety Monitoring Board (DSMB)**

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

### 10.6.3 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). In general, when use of formal testing to assess differences between groups 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. To assess baseline differences between groups, participants will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics.

**Primary Outcomes:** All analyses of primary outcomes will be stratified by MTN-018C product exposure group. Pregnancy outcomes will be described using proportions and 95% confidence intervals. Chi-square tests will be used to test for differences in the rates of pregnancy outcomes in MTN-018C and pregnancy outcomes in placebo arm participants of VOICE/MTN-016, separately for each individual outcome and overall. Data from the active product arms of VOICE may also be used if there are no differences between VOICE randomization groups in pregnancy outcomes. Multivariable logistic regression models will be used to compare the odds of pregnancy outcomes in the two groups controlling for any important differences in baseline characteristics in the two groups that also affect the pregnancy outcomes. This will be done for each outcome and also overall. Similar analyses will be performed on the infant outcomes of the MTN-018C infants comparing them to VOICE/MTN-016 infants in the placebo arm. Again, data from the active product arms of VOICE may also be used if there are no differences between VOICE randomization groups in infant outcomes.

**Secondary Outcomes:** All analyses will be stratified by MTN-018C product exposure group. Pregnancy morbidities will be described using proportions and 95% confidence intervals. Chi-square tests will be used to test for differences in the rate of pregnancy morbidities in MTN-018C and pregnancy morbidities in placebo arm participants of VOICE/MTN-016, separately for each individual morbidity and overall. Data from the active product arms of VOICE may also be used if there are no differences between VOICE randomization groups in pregnancy morbidities. Multivariable logistic regression models will be used to compare the odds of pregnancy morbidities in the two groups controlling for any important differences in baseline characteristics in the two groups that also affect the pregnancy morbidity. This will be done for each morbidity and also overall.

Extended safety outcomes and adherence to study product will be described using frequency tables for each product exposure group.

## **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, the Office for Human Research Protections (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 and related sub-studies, 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-018C 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-018C.



Each participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms, and study-related documents (such as participant 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. Please review the current DAIDS Protocol Registration Manual for up-to-date information regarding protocol registration for sub-studies.

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 and related sub-studies 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 level of effectiveness of the study products and as a result increase their HIV risk behaviors while in the study.

Data on participant risk behaviors and the occurrence of other potential social harms will be collected from all participants on a quarterly basis.

The following side effects have been associated with the use of 1% tenofovir gel:

#### 1% Tenofovir Gel

Administration of tenofovir 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.<sup>29</sup> Although 92% of participants reported at least 1 AE, 87% of those reported AEs were mild, and 70% of the AEs were limited to the genitourinary tract. Four severe AEs were reported, with only one, lower abdominal pain, thought to be product-related. The risks associated with tenofovir gel are believed to be less than those identified for systemic use. Some of the possible side effects of the study gel are dryness, itching, burning, or pain in the genital area.

#### MTN-008

Information on possible side effects for mothers and infants identified in the MTN-008 study Pregnancy Cohort will be included here in a modification to the protocol.

In the HPTN 050 Phase 1 study of tenofovir gel, serum PK analysis in a subset of participants demonstrated that there is no clinically significant systemic toxicity.<sup>29</sup> Fourteen of 25 women with PK results had low, but detectable, serum tenofovir levels. Given that Phase 1 data demonstrate measurable plasma concentrations of tenofovir in some participants, participants with hepatitis B infection might be at risk for development of tenofovir resistant hepatitis B. However, participants with known hepatitis B infection will not be eligible for enrollment. It is not known what effect tenofovir gel could have on the HIV virus or HIV disease progression in HIV-infected participants or their partners. There is a theoretical risk that tenofovir absorbed systemically from oral TDF or vaginal tenofovir gel could result in mutations of the HIV virus in participants who become infected with HIV during the study, or their partner, if the partner is infected with HIV. Limited resistance data from HPTN 050 show no new

resistance mutations in plasma or cervicovaginal lavage specimens after 14 days of tenofovir gel use. No participant had high level tenofovir mutations (e.g., K65R).

In a male tolerance study of 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.<sup>30</sup> 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.<sup>13</sup> No renal disorders were observed in the study. Mild, self-limiting diarrhea was more common among women who used tenofovir gel (16.9 percent) compared to women who used the placebo gel (11.0 percent). No tenofovir resistance was observed among the women who became infected with HIV in the tenofovir 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. Breastfeeding was not restricted in CAPRISA 004.

#### Tablets

The following side effects have been associated with the use of oral 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.

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

- 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.

One study found among 1-year olds exposed *in utero* to TDF a marginally increased risk of low length and weight z-scores, with 1<sup>st</sup> trimester exposure associated with significantly increased risk of low head circumference z-score.

#### **13.4.2 Benefits**

In a modification to this protocol, this section will describe the reduction in risk of HIV infection known for the MTN-018C 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, HBV 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 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 import to this study:

- The importance of safer sex behaviors for reducing risk of HIV acquisition.
- 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.
- What medical information will be collected and for how long it will be used.

The informed consent process will include an assessment of each potential participant mother'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:

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

## 13.7 Special Populations

### 13.7.1 Pregnant Women

Based on an assessment of currently understood potential risks and benefits associated with the study products and procedures, this protocol may be conducted, as specified in the US Code of Federal Regulations, Subchapter A – Protection of Human Subjects, Subpart B, 46.204 – Research involving pregnant women or fetuses.

According to Subpart B, pregnant women or fetuses may be involved in research if all of the following conditions are met:

- Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.*** These studies have occurred and Section 2 of this protocol refers to this information.
- The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.*** Due to projected low fetal exposure to tenofovir via maternal tenofovir gel use, associated risks are expected to be minimal. Evidence from the Antiretroviral Pregnancy Registry does not indicate significant risk to the fetus associated with *in utero* exposure to maternal use of oral tenofovir in any trimester. In addition, recent evidence pointing to the protective effect of tenofovir gel against HIV and HSV-2 in women holds out the prospect of direct benefit to both the woman and the fetus, as primary maternal infection with HIV or HSV poses significant risk to the fetus. As all participants are pregnant, they are known to be sexually active in the recent past, and therefore belong to the group of persons who could benefit from PrEP or microbicide use. If CHOICE proceeds, it will be because VOICE has yielded at least one safe and effective intervention. Further information on the evidence surrounding the potential protective benefits of tenofovir gel is also included in Section 2.

- c. ***Any risk is the least possible for achieving the objectives of the research.*** The protocol has minimized risk by including intensive monthly monitoring for the rapid identification and management of adverse events.
- d. ***If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part.*** The protocol includes an informed consent process consistent with all applicable requirements in the CFR.
- e. ***If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.*** This section is not applicable.
- f. ***Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.*** This information has been included in the Sample Informed Consent documents, will be included in site-specific informed consent documents, and will be covered thoroughly during the informed consent process.
- g. ***For children as defined in 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part.*** This section is not applicable to MTN-018C, as children under 18 years old will not be enrolled.
- h. ***No inducements, monetary or otherwise, will be offered to terminate a pregnancy.*** Inducements to terminate a pregnancy will not be offered by study site staff.
- i. ***Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.*** Individuals engaged in MTN-018C will have no part in decisions as to the timing, method, or procedures used to terminate a pregnancy by participants.
- j. ***Individuals engaged in the research will have no part in determining the viability of a neonate.*** Individuals engaged in MTN-018C will have no part in determining the viability of a neonate.



### **13.7.2 Children**

The NIH has mandated that children be included in research trials when appropriate. This study will not enroll children 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. Testing for HIV will be offered for infants of HIV-infected mothers, if this is not otherwise accessible for the participant.

#### **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 multiple parties at the US NIH, 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.

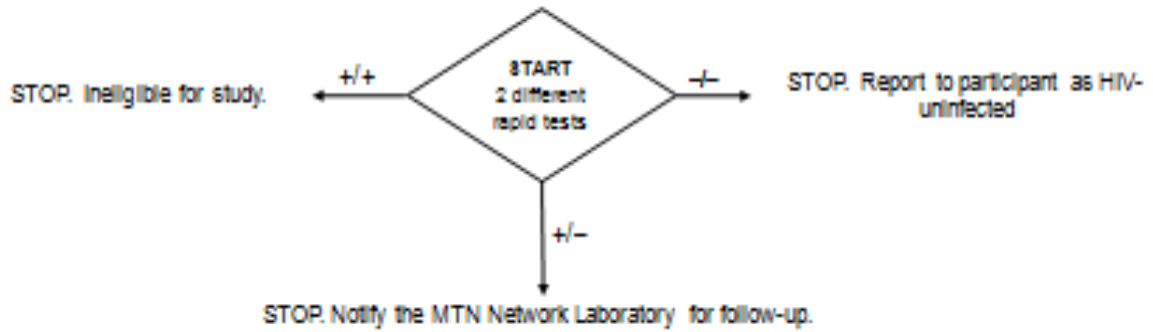
## 15 APPENDICES

## APPENDIX I: SCHEDULE OF VISITS AND EVALUATIONS

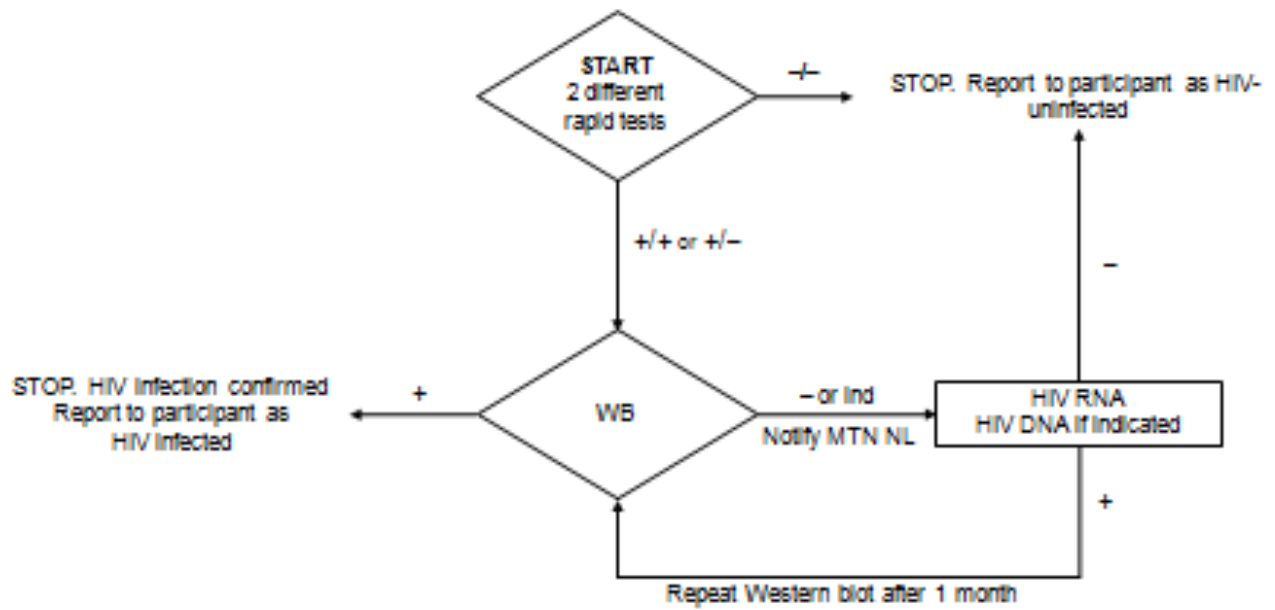
	SCR	ENR	MLY	QLY	M6	PO	M12	M14/TER	INT
<b>ADMINISTRATIVE/BEHAVIORAL/REGULATORY</b>									
Co-enrollment assessment	X								
Informed consent(s)	X	X							
Assignment of PTID	X								
Locator information	X	X	X	X	X	X	X	X	X
Demographic information	X								
Obstetric provider contact/records/delivery location	X	X	X	X	X	X	X	X	◆
Behavioral eligibility information	X								
HIV pre-/post-test counseling	X		X	X	X		X	X	◆
Reimbursement	X	X	X	X	X	X	X	X	◆
Schedule next visit	◆	X	X	X	X	X	X	◆	◆
Behavioral assessment	X	X	M1		X		X	X	◆
Adherence assessment			M1	X	X		X		◆
Social harms assessment				X	X		X		◆
HIV/STI risk reduction counseling	X	X	X	X	X		X	X	◆
Offer/refer HIV/STI counsel/test partners	X	X	◆	◆	◆		◆	◆	◆
Provision - condoms	X	X	X	X	X	◆	X	X	◆
Sharing assessment							X		
<b>CLINICAL</b>									
Concomitant medications	X	X	X	X	X	X	X	X	◆
Medical history / review antenatal records	X	X	X	X	X	X	X	X	◆
Menstrual history	X								
Obstetric symptom review	X		X	X	X				
Blood collection	X	X	X	X	X	◆	X	X	◆
Urine collection	X		◆	◆	X	◆	X	◆	◆
PE (including VS)	X		◆	◆	◆	◆	X	◆	◆
Weight	X		◆	◆	X	◆	X	◆	◆
Conduct/refer U/S if not available/complete	X								
Obstetric abdominal exam	X		X	X	X	◆	X	X	◆
Pelvic examination (with visual/bimanual)	X		◆	◆	◆	◆	X	◆	◆
Pelvic swab for STI/vaginitis testing	◆		◆	◆	◆	◆	◆	◆	◆
Collect AEs			X	X	X	X	X	X	◆
Treatment/referral	◆	◆	◆	◆	◆	◆	◆	◆	◆
Test result disclosure	X	X	X	X	X	◆	X	X	◆
Document estimated gestational age	X		X	X	X				◆
Eligibility assessment	X								
Study product selection		X	M1	◆	◆				◆
Adherence counseling		X	M1	X	X				◆
Provision - study product and instructions		X	X	X	X				◆
Collect unused study product			X	X	X	◆	X	◆	◆
<b>LABORATORY</b>									
Plasma archive		X	◆	◆	X	◆	X	X	◆
HIV serology	X		X	X	X		X	X	◆
HBsAg*	▣		◆	◆	◆		X+	◆	◆
HBsAb*	▣		◆	◆	◆		◆	◆	◆
Serum creatinine	▣		◆	◆	X-oral		X-oral		◆
AST/ALT	▣		◆	◆	X		X	◆	◆
Drug level (blood)					X		X		◆
Urine HCG	X		◆	◆	◆	◆	◆	◆	◆
Urine dipstick (protein, glucose)	X				X-oral		X-oral		◆
STI testing (if local standard of care)	◆		◆	◆	◆	◆	◆	◆	◆
Vaginitis testing	◆		◆	◆	◆	◆	◆	◆	◆

- NOTE: X=scheduled, ◆=as indicated, M1=Month 1, QLY=Quarterly, M6=Month 6, PO=Pregnancy Outcome, INT=Interim, += susceptible participants not vaccinated against HBV, "Oral" = participants most recently using oral product, ▣=may omit if MTN-018 transfer
- \*HBsAg/HBsAb may be omitted if HBV-immune (per VOICE documentation) or completed HBV vaccine series. If administered, HBV vaccine occurs at visits consistent with recommended time points for vaccine series.
- Consent for specimen storage can be obtained ≤3 months after ENR. Procedures/tests for MTN-018 visit may substitute for same procedures for screening in MTN-018C, if they occur within 1 calendar day of MTN-018C Screening Visit. Additional procedures (e.g., HIV, urine HCG) are performed on day of enrollment as part of final screening procedures and confirmation of eligibility (Section 7.2.4). Monthly visit procedures also occur at quarterly visits, Month 6 and Month 12. Contraception/counseling is offered to women following pregnancy outcome who remain in follow-up. Urine HCG done at all scheduled visits for those who are maintained in follow-up after a pregnancy outcome. HIV RNA and CD4+ may be checked if indicated during f/u, as part of the HIV testing algorithm in Appendices II and III.

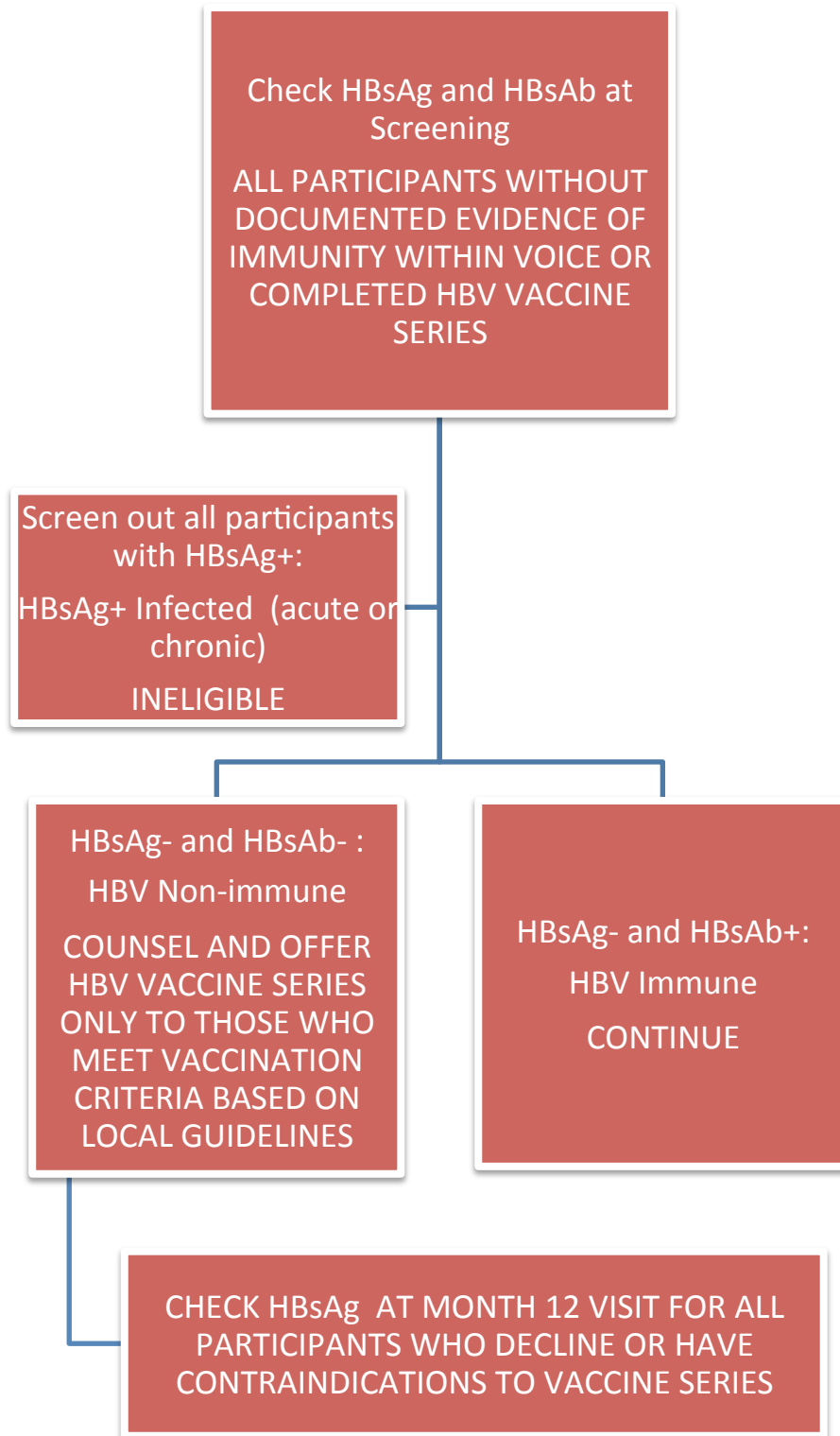
## APPENDIX II: ALGORITHM FOR HIV ANTIBODY TESTING FOR SCREENING/ENROLLMENT



## APPENDIX III: ALGORITHM FOR HIV TESTING FOR FOLLOW-UP



## APPENDIX IV: ALGORITHM FOR HBV TESTING



## APPENDIX V: SAMPLE INFORMED CONSENT FORM (SCREENING)

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

MTN-018C

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

[Insert date]

**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 study known as CHOICE-C. CHOICE-C is for pregnant women who were in VOICE. CHOICE-C's purpose is to collect more information about the safety of [*insert study products*] during pregnancy. Screening includes questions, blood tests, and physical and genital exams. The US NIH is funding the study. About 300 women from VOICE will join CHOICE at sites in Africa. 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 in CHOICE-C. Once you understand the 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-C. 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-C 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-C. Some people may not be able to join CHOICE-C because of results of screening tests. You will receive test results even if you are not eligible to join CHOICE-C. Study doctors will also review your records from VOICE, and from CHOICE, if you were enrolled in CHOICE before you fell pregnant.



## PROCEDURES

For you to join CHOICE-C, 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-C, you will have to do all screening tests again. Screening will begin after you discuss, understand and sign or mark 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, your behavior, your health and pregnancy, your antenatal care provider, and where you plan to deliver.
- You will give urine for a pregnancy test and to test the health of your kidneys.
- 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-C. If you have HIV, you are not eligible for CHOICE-C. 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 you were not already enrolled in CHOICE, 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-C.
- You will have a physical exam, weight check, measurement of your abdomen, and check of the baby's heartbeat (depending on age of your pregnancy)
- 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 have or be referred for an ultrasound of your pregnancy
- You will get condoms and treatment 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-C. 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, and test your urine for pregnancy. If you are not pregnant, you are not eligible for CHOICE-C. You will have HIV testing with the same procedures as above. If tests show you have HIV, you are not eligible for CHOICE-C. 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 results. If results show you are eligible for CHOICE-C, we will fully explain the study to you and answer any questions. If you decide to take part in CHOICE-C, you will be asked to sign another consent form. *[For applicable sites: You may sign the consent form for further participation in CHOICE-C 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-C using one blood draw instead of two. We will talk with you more about this if you request it.]*

### **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 be ineligible for CHOICE-C, or if CHOICE-C is stopped.
- 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 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. The study is not able to pay for your routine antenatal care or delivery.

## **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. A description of this clinical trial will be available on [ClinicalTrials.gov](http://ClinicalTrials.gov), as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your records may be reviewed by Microbicide Trials Network (MTN), its representatives and study staff, as well as:

- the United States Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), and the United States National Institutes of Health (NIH) or its study monitors
- [insert applicable local authorities, e.g., IRB, medicine control authority] (an IRB /EC protects the rights and well being of people in research)
- 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:] 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 screening tests, please sign your name or make your mark below.

Participant Name (print)	Participant Signature/Mark	Date
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Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
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Witness Name (print)	Witness Signature	Date
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## **APPENDIX VI: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT)**

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

**MTN-018C**

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

**[DATE]**

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

### **INFORMED CONSENT**

You are being asked to take part in a study known as CHOICE-C. CHOICE-C is for pregnant women who were in VOICE. The purpose of CHOICE-C is to collect more information on the safety of [*insert study products*]. The US NIH is funding the study. We expect that about 300 women from VOICE will join CHOICE-C at different sites in Africa. We will explain the study's purpose, 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 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 THE STUDY**

[VOICE results to be inserted here]. 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.] The study is expected to finish in [*insert*]. Each woman will be in CHOICE-C for up to about a year, depending on whether they started in CHOICE first or not, and how far along their pregnancy is. The study will compare the outcomes of pregnancies in CHOICE-C with those of participants who fell pregnant during the VOICE study, as well as the health of infants in their first month. CHOICE-C is testing the safety of [*insert number*] products from VOICE in pregnancy.

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

Viread and Truvada tablets have been approved by the US Food and Drug Administration (FDA). Tenofovir gel is an investigational (experimental) study drug. We will ask you to choose a product to use during CHOICE-C. You can choose gel or tablet. There is no placebo gel or placebo tablet in CHOICE-C. You do not have to choose the same thing you used in VOICE. 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 asked about the reasons for your study product selection
- 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 to only use 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 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 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 mark this form. Study staff will help you understand the form and answer your questions before you sign or mark this form.

You will answer questions about your sexual practices. You will give [*insert*] teaspoons [*or local equivalent*] of blood for the study staff to keep here while you are in the study. If needed, they will test this blood later in the study to check on your health. We will also need to look at your antenatal care and delivery charts while you are in CHOICE-C. If you join CHOICE-C, you will come to study visits every month until your pregnancy is over. The procedures done at the monthly 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 your medications, herbal treatments and supplements
- 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 contact people you list. If we talk to them, we will not say why we want to reach you.
- Bring your unused gel or tablets and bottles to be counted by study staff
- Have a check of your pregnancy, including the baby's heartbeat; this check does not replace your usual antenatal care
- 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
- 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 and new supplies of gel or tablets

After 1 month, you will also:

- Tell study staff if you would like to continue using the study product you chose
- Be allowed to change to a different CHOICE-C study product if you want
- Answer questions about sexual practices and use of gel or tablets

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 test of the amount of study drug in your blood

After your delivery, you will also:

- Stop taking your study product
- Come in to the clinic for a check-up once before your baby is six weeks old
- Talk to study staff about your delivery and the health of your baby
  - If you are breastfeeding, we will tell you about a study that is testing the safety of the study products for breastfeeding women and their babies
  - If you are not breastfeeding, you will keep taking study product until it has been 1 year since you started in CHOICE (or CHOICE-C, if you were never in CHOICE)

At your end of product (Month 12) visit, you will:

- Have a physical exam, pelvic exam and check of your weight
- 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

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 use tablets
- Be given referrals for medical care and other services you may need

If you have a problem with your pregnancy:

- You will come in to get checked by a study doctor

If your pregnancy ends earlier than expected, you may continue to receive your study product and attend the visits previously expected for you.

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. If 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. If you become infected with HIV on study, and do not enroll in MTN-015, you will have study visits at 1, 3, 6, and 12 months after your positive HIV test.

You will be asked to have another blood draw (XXmL). This blood will be used to check:

- Your CD4+ T-cell count. This is a test that measures the amount of damage HIV has done to the immune system. The immune system is the part of the body that fights off infections.
- The amount of HIV in your blood.
- Whether the HIV in your blood is resistant to medications used to treat HIV. Results of resistance tests will be given to you.

If you miss your daily study product dose, you should take the missed dose as soon as possible, unless the next dose is due within 6 hours.

### **POSSIBLE FUTURE TESTS**

Some of the blood that you give during CHOICE-C 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-C.



## **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

## **Study Gel**

It is possible the gel could cause some bad effects. You could have these effects or other effects that we do not know about. Some, but not all, women who used the gel in other studies have had:

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

## **Study Tablets**

General Disclaimer: The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site.

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:

- Abdominal pain, upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness, dizziness
- Depression
- Headache
- 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.

**Immune Reconstitution Syndrome:** In some people with advanced HIV infection, symptoms from other infections or certain diseases may occur soon after starting combination anti-HIV treatment but can also occur later. Some of these symptoms may be life threatening. If you start having new symptoms, or notice that existing symptoms are getting worse after starting your antiretroviral therapy, tell your healthcare provider right away.

**Use of Combination Antiretroviral Drugs:** The use of potent antiretroviral drug combinations may be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs and arms
- Breast enlargement

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. This is why you must stop using your study product if you get HIV. Study doctors can discuss this with you. If you do become infected with HIV during CHOICE-C, they can do blood tests to show which HIV medications might work best for you.

Viread, Truvada and tenofovir gel have not been approved for use in pregnant women. Information on the effects of the study products on a developing fetus is limited. Other

studies have not shown bad effects of the study products on pregnancy, fetuses, or babies of women who use the gels or tablets when pregnant. One study showed a slightly higher chance of smaller head measurements at one year old, among babies whose mothers used tenofovir for HIV treatment when they were pregnant.

A small amount of tenofovir may pass from the study drugs into your breast milk. We do not know if tenofovir passes into breast milk after women receive the vaginal form of tenofovir. Even though this may be possible, there is only a small chance that any tenofovir may pass from the gel into the breast milk. If your breast milk did absorb some tenofovir, possible effects in the baby could include increased liver function tests, diarrhea, nausea, vomiting, and flatulence (gas), but we would expect those side effects to be brief and resolve quickly if they occurred. You should let your baby's pediatrician and the study staff know if you believe your baby is experiencing any problems.

#### 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-C. 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.

#### **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. 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-C, 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, 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). 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.

### **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.

### **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 also may be other places where you can go for HIV counseling and testing, hepatitis B vaccine, and contraception. We will tell you about those places if you wish.]*

### **COSTS TO YOU**

There is no cost to you to be in CHOICE-C. 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. A description of this clinical trial will be available on [ClinicalTrials.gov](http://ClinicalTrials.gov), as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your records may be reviewed by Microbicide Trials Network (MTN), its representatives and study staff, as well as:

- the US Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), and the US National Institutes of Health (NIH) or its study monitors
- [insert applicable local authorities, e.g., IRB, medicine control authority] (an IRB /EC protects the rights and well being of people in research)
- 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 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 study, 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 VII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS)**

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

**MTN-018C**

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

**[insert date]**

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

**Short Title for the Study: CHOICE-C**

#### **INTRODUCTION**

You have decided to take part in the CHOICE-C study, funded by the United States National Institutes of Health (NIH). While you are in CHOICE-C, 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-C. During CHOICE-C, 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-C 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 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. A description of this clinical trial will be available on [ClinicalTrials.gov](http://ClinicalTrials.gov), as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Your records may be reviewed by Microbicide Trials Network (MTN), its representatives and study staff, as well as:

- the United States Food and Drug Administration (FDA), Office for Human Research Protections (OHRP), the United States NIH or its study monitors
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert names of applicable IRBs/ECs] (an IRB /EC protects the rights and well being of people in research)
- 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-018C 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

## REFERENCES

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