

**MTN-018B**

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

**Breastfeeding 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 #: 11846**

**IND# 55,690**

**Protocol Chair:  
Flavia Matovu Kiweewa, MBChB, MSc. Epidemiology**

**Final Version 1.0**

**August 30, 2012**

# MTN-018B

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

### TABLE OF CONTENTS

<b>LIST OF ABBREVIATIONS AND ACRONYMS .....</b>	<b>5</b>
<b>PROTOCOL TEAM ROSTER.....</b>	<b>7</b>
<b>INVESTIGATOR SIGNATURE FORM .....</b>	<b>18</b>
<b>PROTOCOL SUMMARY .....</b>	<b>19</b>
<b>1 KEY ROLES .....</b>	<b>26</b>
1.1 PROTOCOL IDENTIFICATION.....	26
1.2 SPONSOR AND MONITOR IDENTIFICATION.....	26
1.3 MEDICAL OFFICER.....	26
1.4 NETWORK LABORATORY .....	27
1.5 DATA CENTER .....	27
1.6 STUDY OPERATIONS .....	27
<b>2 INTRODUCTION .....</b>	<b>27</b>
2.1 HIV PREVENTION AMONG BREASTFEEDING WOMEN .....	27
2.2 GUIDANCE FROM US FOOD AND DRUG ADMINISTRATION (FDA) ON CLINICAL LACTATION STUDIES.....	28
2.3 GUIDANCE FROM WORLD HEALTH ORGANIZATION ON INFANT FEEDING .....	29
2.4 RESULTS OF THE VOICE TRIAL.....	30
2.5 STUDY PRODUCT DESCRIPTION: TENOFOVIR DISOPROXIL FUMARATE .....	30
2.6 STUDY PRODUCT DESCRIPTION: EMTRICITABINE/TENOFOVIR DISOPROXIL FUMARATE .....	30
2.7 STUDY PRODUCT DESCRIPTION: 1% TENOFOVIR GEL .....	31
2.8 <i>IN VITRO</i> STUDIES.....	32
2.9 ANIMAL STUDIES .....	32
2.10 STUDIES OF ORAL TENOFOVIR AND EMTRICITABINE IN BREASTFEEDING WOMEN .....	33
2.11 RATIONALE .....	37
<b>3 OBJECTIVES .....</b>	<b>40</b>
3.1 PRIMARY OBJECTIVES .....	40
3.2 SECONDARY OBJECTIVES.....	40
<b>4 STUDY DESIGN.....</b>	<b>41</b>
4.1 IDENTIFICATION OF STUDY DESIGN .....	41
4.2 SUMMARY OF MAJOR ENDPOINTS.....	41
4.3 DESCRIPTION OF STUDY POPULATION .....	42
4.4 TIME TO COMPLETE ACCRUAL .....	42
4.5 STUDY GROUPS .....	42
4.6 EXPECTED DURATION OF PARTICIPATION .....	42
4.7 SITES .....	42
<b>5 STUDY POPULATION.....</b>	<b>43</b>

5.1	SELECTION OF THE STUDY POPULATION .....	43
5.2	INCLUSION CRITERIA – MOTHERS .....	43
5.3	EXCLUSION CRITERIA – MOTHERS.....	44
5.4	INCLUSION CRITERIA – INFANTS.....	45
5.5	EXCLUSION CRITERIA – INFANTS .....	45
5.6	CO-ENROLLMENT GUIDELINES .....	46
<b>6</b>	<b>STUDY PRODUCT .....</b>	<b>46</b>
6.1	REGIMEN .....	46
6.2	ADMINISTRATION.....	47
6.3	STUDY PRODUCT FORMULATION .....	47
6.4	STUDY PRODUCT SUPPLY AND ACCOUNTABILITY.....	48
6.5	STUDY PRODUCT DISPENSING.....	48
6.6	RETRIEVAL OF UNUSED STUDY PRODUCTS.....	48
6.7	STUDY PRODUCT ADHERENCE ASSESSMENT AND COUNSELING.....	49
6.8	CONCOMITANT MEDICATIONS.....	49
<b>7</b>	<b>STUDY PROCEDURES .....</b>	<b>50</b>
7.1	PRE-SCREENING .....	50
7.2	SCREENING .....	50
7.3	ENROLLMENT .....	53
7.4	FOLLOW-UP VISITS.....	54
7.5	FOLLOW-UP PROCEDURES FOR PARTICIPANTS WHO TEMPORARILY HOLD OR PERMANENTLY DISCONTINUE STUDY PRODUCT	60
7.6	PARTICIPANTS WHO BECOME PREGNANT .....	60
7.7	PARTICIPANTS WHO DISCONTINUE BREASTFEEDING .....	61
7.8	INTERIM VISITS.....	61
7.9	FINAL CONTACT.....	61
7.10	CLINICAL EVALUATIONS AND PROCEDURES.....	61
7.11	LABORATORY EVALUATIONS .....	62
7.12	SPECIMEN COLLECTION AND PROCESSING .....	63
7.13	SPECIMEN HANDLING .....	63
7.14	BIOHAZARD CONTAINMENT .....	63
<b>8</b>	<b>ASSESSMENT OF SAFETY .....</b>	<b>63</b>
8.1	SAFETY MONITORING AND REVIEW .....	63
8.2	ADVERSE EVENTS DEFINITIONS AND REPORTING REQUIREMENTS .....	64
8.3	EXPEDITED ADVERSE EVENT REPORTING REQUIREMENTS.....	65
8.4	REGULATORY REQUIREMENTS .....	66
8.5	SOCIAL HARMS REPORTING .....	67
<b>9</b>	<b>CLINICAL MANAGEMENT .....</b>	<b>67</b>
9.1	GRADING SYSTEM .....	67
9.2	DOSE MODIFICATION INSTRUCTIONS .....	67
9.3	GENERAL CRITERIA FOR TEMPORARY HOLD AND PERMANENT DISCONTINUATION OF STUDY PRODUCT .....	67
9.4	TEMPORARY PRODUCT HOLD/PERMANENT DISCONTINUATION IN RESPONSE TO OBSERVED ADVERSE EVENTS.....	68
9.5	MANAGEMENT OF SPECIFIC ADVERSE EVENTS .....	69
9.6	GENITAL SEXUALLY TRANSMITTED INFECTION/REPRODUCTIVE TRACT INFECTION.....	70
9.7	HIV INFECTION.....	70
9.8	HEPATITIS B INFECTION .....	71
9.9	PREGNANCY.....	71
9.10	CRITERIA FOR EARLY TERMINATION OF STUDY PARTICIPATION .....	71
<b>10</b>	<b>STATISTICAL CONSIDERATIONS.....</b>	<b>72</b>

10.1	OVERVIEW AND SUMMARY OF DESIGN.....	72
10.2	STUDY ENDPOINTS .....	72
10.3	SAMPLE SIZE AND POWER CALCULATIONS.....	73
10.4	PARTICIPANT ACCRUAL, FOLLOW-UP AND RETENTION.....	75
10.5	BLINDING .....	75
10.6	DATA AND SAFETY MONITORING AND ANALYSIS .....	75
<b>11</b>	<b>DATA HANDLING AND RECORDKEEPING .....</b>	<b>77</b>
11.1	DATA MANAGEMENT RESPONSIBILITIES .....	77
11.2	SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS .....	77
11.3	QUALITY CONTROL AND QUALITY ASSURANCE .....	77
<b>12</b>	<b>CLINICAL SITE MONITORING .....</b>	<b>77</b>
<b>13</b>	<b>HUMAN SUBJECTS PROTECTIONS .....</b>	<b>78</b>
13.1	INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES .....	78
13.2	PROTOCOL REGISTRATION .....	80
13.3	STUDY COORDINATION .....	80
13.4	RISK BENEFIT STATEMENT .....	81
13.5	INFORMED CONSENT PROCESS .....	84
13.6	PARTICIPANT CONFIDENTIALITY.....	85
13.7	SPECIAL POPULATIONS.....	86
13.8	COMPENSATION .....	86
13.9	COMMUNICABLE DISEASE REPORTING.....	86
13.10	ACCESS TO HIV-RELATED CARE.....	86
13.11	STUDY DISCONTINUATION .....	87
<b>14</b>	<b>PUBLICATION POLICY.....</b>	<b>87</b>
<b>15</b>	<b>APPENDICES .....</b>	<b>88</b>
	<b>APPENDIX I: SCHEDULE OF VISITS AND EVALUATIONS – MOTHERS.....</b>	<b>89</b>
	<b>APPENDIX II: SCHEDULE OF VISITS AND EVALUATIONS – INFANTS.....</b>	<b>90</b>
	<b>APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING – FOR MOTHERS – SCREENING/ENROLLMENT .....</b>	<b>91</b>
	<b>APPENDIX IV: ALGORITHM FOR HIV TESTING FOR MOTHERS – FOLLOW-UP .....</b>	<b>92</b>
	<b>APPENDIX V: ALGORITHM FOR HBV TESTING (MOTHERS) .....</b>	<b>93</b>
	<b>APPENDIX VI: SAMPLE INFORMED CONSENT FORM (SCREENING – MOTHERS AND INFANTS).....</b>	<b>94</b>
	<b>APPENDIX VII: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT – MOTHERS AND INFANTS).....</b>	<b>100</b>
	<b>APPENDIX VIII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS – MOTHERS) .</b>	<b>112</b>
	<b>REFERENCES.....</b>	<b>116</b>

## FIGURE

FIGURE 1: MTN-018 AND SUB-STUDIES .....	20
---	----

## TABLES

TABLE 1: HPTN 057 COHORT 1 .....	35
TABLE 2: MEDIAN (RANGE) TENOFOVIR CONCENTRATIONS IN INFANTS (COHORT 2) .....	35
TABLE 3: MINIMUM RATE DETECTABLE WITH 80% POWER FOR INFANT SAFETY OUTCOMES (ASSUMING N=115 MTN-016 CONTROL GROUP INFANTS) .....	74
TABLE 4: MINIMUM RATE DETECTABLE WITH 80% POWER FOR MOTHER’S SAFETY OUTCOMES (ASSUMING N=1000 VOICE CONTROL GROUP WOMEN) .....	75

## MTN-018B

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

#### LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
BV	bacterial vaginosis
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	confidence interval
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
FDA	Food and Drug Administration
FHCRC	Fred Hutchison Cancer Research Center
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practices
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HEC	hydroxyethylcellulose
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HSV-2	herpes simplex virus type 2
IND	investigational new drug
IoR	Investigator of Record
IRB	Institutional Review Board
LDMS	Laboratory Data Management System
µg	microgram
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 for Human Research Protections
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PK	pharmacokinetic(s)
PMPA	9-R-2-phosphonomethoxypropyl adenine
PMPApp	tenofovir diphosphate
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development
PrEP	pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
qd	quaque die (daily)
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	Statistical Data Management Center
SMC	Study Monitoring Committee
SOP	standard operating procedure
SSP	study specific procedures
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
ULN	upper limit of normal
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VS	vital signs
WHO	World Health Organization

**MTN-018B**

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

**PROTOCOL TEAM ROSTER**

**Protocol Chair**

**Flavia Matovu Kiweewa, MBChB, MSc. Epidemiology**

**Protocol Chair**

MU-JHU Research Collaboration

P.O. Box 23491, Kampala, Uganda

Phone: 256-414-541044/256-772-544759

Fax: 256-414-541044/256-414-532091

Email: [fmatovu@mujhu.org](mailto:fmatovu@mujhu.org)

## Site Investigators: South African MRC HIV CTU

**Nicola Coumi, MMed Sci**  
**Site Investigator**  
MRC – HPRU  
P.O. Box 70380  
Overport, KwaZulu-Natal 4067 South Africa  
Phone: 27-31-242-3644  
Fax: 27-31-242-3800  
Email: [nicola.coumi@mrc.ac.za](mailto:nicola.coumi@mrc.ac.za)

**Aren Pather, B. Pharm.**  
**Site Investigator**  
MRC – HPRU  
P.O. Box 70380  
Overport, KwaZulu-Natal 4067 South Africa  
Phone: 27-31-242-3644  
Fax: 27-31-242-3800  
Email: [apather@mrc.ac.za](mailto:apather@mrc.ac.za)

**Shayhana Ganesh, MBChB, Dip HIV Man**  
**Site Investigator**  
South African Medical Research Council  
P. O. Box 70380  
Overport, KwaZulu-Natal 4067 South Africa  
Phone: 27-31-242-3600  
Fax: 27-31-242-3800  
Email: [sganesh@mrc.ac.za](mailto:sganesh@mrc.ac.za)

**Yuki Sookrajh, MBChB**  
**Site Investigator**  
MRC – HPRU  
P.O. Box 70380  
Overport, KwaZulu-Natal 4067 South Africa  
Phone: 27-83-781-1027  
Fax: 27-31-902-7938  
Email: [yuki.sookrajh@mrc.ac.za](mailto:yuki.sookrajh@mrc.ac.za)

**Sharika Gappoo, MMed Sci**  
**Site Investigator**  
MRC – HPRU  
P.O. Box 70380  
Overport, KwaZulu-Natal 4067 South Africa  
Phone: 27-31-242-3645  
Fax: 27-31-242-3800  
Email: [Sharika.Gappoo@mrc.ac.za](mailto:Sharika.Gappoo@mrc.ac.za)

**Vijay Guddera, PhD**  
**Site Investigator**  
MRC – HPRU  
P.O. Box 70380  
Overport, KwaZulu-Natal 4067 South Africa  
Phone: 27-31-242-3644  
Fax: 27-31-242-3800  
Email : [vguddera@mrc.ac.za](mailto:vguddera@mrc.ac.za)

**Marwah Jenneker, MBChB**  
**Site Investigator**  
MRC – HPRU  
P.O. Box 70380  
Overport, KwaZulu-Natal 4067 South Africa  
Phone: 27-39-979-6327  
Fax: 27-39-979-4689  
Email: [mjenneker@mrc.ac.za](mailto:mjenneker@mrc.ac.za)

**Sarita Naidoo, B Sci**  
**Site Investigator**  
MRC – HPRU  
P.O. Box 70380  
Overport, KwaZulu-Natal 4067 South Africa  
Phone: 27-31-242-3667  
Fax: 27-31-242-3800  
Email: [Sarita.Naidoo@mrc.ac.za](mailto:Sarita.Naidoo@mrc.ac.za)



## Site Investigators: UZ-UCSF CTU

**Tsitsi Magure, MBChB, MMED, Obs and Gyn  
Site Investigator**  
UZ-UCSF Collaborative Research Programme  
15 Phillips Avenue, Belgravia  
Harare, Zimbabwe  
Phone: 263-1173-3948  
Fax: 263-4-704897  
Email: [tmagure@uz-ucsf.co.zw](mailto:tmagure@uz-ucsf.co.zw)

**Felix Muhlanga, MBChB, MMED, Obs and Gyn  
Site Investigator**  
UC-UCSF Collaborative Research Programme  
15 Phillips Avenue, Belgravia  
Harare, Zimbabwe  
Phone: 263 912 335 232  
Fax: 263 4 704 897  
Email: [fmhlanga@uz-ucsf.co.zw](mailto:fmhlanga@uz-ucsf.co.zw)

**Nyaradzo Mgodzi, MBChB  
Site Investigator/MTN-018 Protocol Chair**  
UC-UCSF Collaborative Research Programme  
15 Phillips Avenue, Belgravia  
Harare, Zimbabwe  
Phone: 263 912 264 616  
Fax: 263 4-704897  
Email: [nmmgodzi@uz-ucsf.co.zw](mailto:nmmgodzi@uz-ucsf.co.zw)

## Site Investigator: UKZN-CAPRISA HIV/AIDS CTU

**Gonasagrie Nair, MBChB  
Site Investigator**  
CAPRISA — eThekweni CRS  
3 Richards Road  
Durban 4001 South Africa  
Phone: 27-31-260-1917  
Fax: 27-31-307-7119  
Email: [nairg1@ukzn.ac.za](mailto:nairg1@ukzn.ac.za)

## Site Investigator: MU-JHU Research Collaboration

**Clemensia Nakabiito, MBChB, MMed, Obs/Gyn  
Site Investigator**  
MU-JHU Research Collaboration  
P.O. Box 23491  
Kampala, Uganda  
Phone: 256-414-541044/256-772-405332 (cell)  
Fax: 256-414-541044/256-414-532091  
Email: [cnakabiito@mujhu.org](mailto:cnakabiito@mujhu.org)

## Site Investigator: WITS HIV Research Group CTU

**Thesla Palanee, MMed Sci, PhD  
Site Investigator**  
WHI Research Centre CRS  
7 Esselen Street  
Hillbrow, Johannesburg 2038 South Africa  
Phone: 27-11-269-358-5471  
Fax: 27-11-27-86-554-1093  
Email: [tpalanee@rhru.co.za](mailto:tpalanee@rhru.co.za)

## Site Investigator: Soweto CTU

**Baningi Mkhize, MBChB  
Site Investigator**  
Perinatal HIV Research Unit – MTN Soweto CRS  
Chris Hani Baragwanath Hospital, Chris Hani Road  
Soweto, Johannesburg 1804 South Africa  
Phone: 27-11-989-9750  
Fax: 27-11-938-3973  
Email: [mkhizeb@phru.co.za](mailto:mkhizeb@phru.co.za)

**Microbicide Trials Network (MTN) Community Working Group (CWG)  
Representative**

**Londiwe Luthuli**  
**Community Liaison Officer**  
CAPRISA  
03 Richards Road Warwick Avenue  
Durban, Kwa-Zulu Natal 4000 South Africa  
Phone: 27-031-260-1944  
Fax: 27 031 3077119  
Email: [luthulil1@ukzn.ac.za](mailto:luthulil1@ukzn.ac.za)

## US National Institutes of Health (NIH)

### **Roberta Black, PhD**

#### **Microbicide Research Branch Chief**

National Institutes of Allergy and Infectious  
Diseases (NIAID)/Division of AIDS (DAIDS)  
6700 B Rockledge Dr., Room 5117  
Bethesda, MD 20817 USA  
Phone: 301-496-8199  
Fax: 301-402-3684  
Email: [rblack@niaid.nih.gov](mailto:rblack@niaid.nih.gov)

### **Heather Watts, MD**

#### **NICHD Medical Officer**

Eunice Kennedy Shriver National Institute of Child  
Health and Human Development (NICHD)  
6100 Executive Blvd., Room 4B11  
Bethesda, MD 20892-7510 USA  
Phone: 301-435-6874  
Fax: 301-496-8678  
Email: [hw59i@nih.gov](mailto:hw59i@nih.gov)

### **Scharla Estep, RPh, MS**

#### **DAIDS Protocol Pharmacist**

DAIDS, Pharmaceutical Affairs Branch  
6700 B Rockledge Dr., Room 4111  
Bethesda, MD 20817 USA  
Phone: 301-435-3746  
Fax: 301-402-1506  
Email: [sr72v@nih.gov](mailto:sr72v@nih.gov)

### **Jeanna Piper, MD**

#### **DAIDS Medical Officer**

NIAID/DAIDS  
6700 B Rockledge Dr., Room 5124  
Bethesda, MD 20892 USA  
Phone: 301-451-2778  
Fax: 301-402-3684  
Email: [piperj@niaid.nih.gov](mailto:piperj@niaid.nih.gov)

### **Michael J. Stirratt, Ph.D.**

#### **NIMH Representative**

National Institute of Mental Health  
6001 Executive Blvd, MSC-9619  
Bethesda, MD 20892 USA  
Phone: 301-443-6802  
Fax: 301-443-9719  
Email: [stirrattm@mail.nih.gov](mailto:stirrattm@mail.nih.gov)

## **Co-sponsors**

**Henry L. Gabelnick, PhD**  
**Co-sponsor Representative**

CONRAD

1911 North Fort Myer Dr., Suite 900

Arlington, VA 22209 USA

Phone: 703-524-4744

Fax: 703-524-4770

Email: [hgabelnick@conrad.org](mailto:hgabelnick@conrad.org)

**James Rooney, MD**

**Co-sponsor Representative**

Gilead Sciences

333 Lakeside Dr.

Foster City, CA 94404 USA

Phone: 650-522-5708

Fax: 650-522-5854

Email: [Jim\\_Rooney@gilead.com](mailto:Jim_Rooney@gilead.com)

## MTN Coordinating and Operations Center (CORE)

**Katherine Bunge, MD**  
**Protocol Safety Physician**  
Magee-Womens Hospital of UPMC  
300 Halket St.  
Pittsburgh, PA 15213 USA  
Phone: 412-917-9936  
Fax: 412-641-6170  
Email: [kbunge@mail.magee.edu](mailto:kbunge@mail.magee.edu)

**Sharon Hillier, PhD**  
**Principal Investigator**  
Microbicide Trials Network  
204 Craft Ave.  
Pittsburgh, PA 15213 USA  
Phone: 412-641-8933  
Fax: 412-641-6170  
Email: [shillier@mail.magee.edu](mailto:shillier@mail.magee.edu)

**Zvavahera Mike Chirenje, MD, FRCOG**  
**VOICE Protocol Co-chair**  
UZ-UCSF Collaborative Research Programme  
15 Phillips Ave., Belgravia  
Harare, Zimbabwe  
Phone: 263-4-704920  
Fax: 263-4-704897  
Email: [chirenje@uz-ucsf.co.zw](mailto:chirenje@uz-ucsf.co.zw)

**Betsy Herold, MD**  
**BSWG Representative**  
Albert Einstein College of Med., Yeshiva Univ.  
1300 Morris Park Ave., Forcheimer 702  
Bronx, NY 10461 USA  
Phone: 718-430-2974  
Fax: 718-430-8627  
Email: [bherold@aecom.yu.edu](mailto:bherold@aecom.yu.edu)

**Connie L. Celum, MD, MPH**  
**Co-principal Investigator**  
University of Washington  
325 Ninth Ave., Box 359927  
Seattle, WA 98104 USA  
Phone: 206-520-3825  
Fax: 206-520-3831  
Email: [ccelum@u.washington.edu](mailto:ccelum@u.washington.edu)

**Kenneth Ho, MD**  
**Protocol Safety Physician**  
University of Pittsburgh  
Keystone Bldg., Suite 533, 3520 Fifth Ave.  
Pittsburgh, PA 15213 USA  
Phone: 412 383 7178  
Fax: 412 383 2900  
Email: [hok2@upmc.edu](mailto:hok2@upmc.edu)

**Juliane Etima, B. Sc., M. A. Psy**  
**BRWG Representative**  
MU-JHU Research Collaboration  
P.O. Box 23491  
Kampala, Uganda  
Phone: 256-414-541-044  
Fax: 256-772-436-829  
Email: [jetima@mujhu.org](mailto:jetima@mujhu.org)

**Cindy Jacobson, PharmD**  
**Director, Pharmacy Affairs**  
Microbicide Trials Network  
204 Craft Ave.  
Pittsburgh, PA 15213 USA  
Phone: 412-641-8913  
Fax: 412-641-6170  
Email: [cjacobson@mail.magee.edu](mailto:cjacobson@mail.magee.edu)

**Beth Galaska Burzuk, MID**  
**Protocol Development Manager**  
Microbicide Trials Network  
204 Craft Ave.  
Pittsburgh, PA 15213 USA  
Phone: 412-641-5579  
Fax: 412-641-6170  
Email: [galaskaburzuk@upmc.edu](mailto:galaskaburzuk@upmc.edu)

**Jeanne Marrasso, MD, MPH**  
**VOICE Protocol Co-chair**  
Univ. of Washington, Div. of Allergy & I.D.  
Box 359932, 325 Ninth Ave.  
Seattle, WA 98104 USA  
Phone: 206-744-3679  
Fax: 206-221-4945  
Email: [jmm2@uw.edu](mailto:jmm2@uw.edu)

**Pamina Gorbach, MHS, DrPH**  
**BRWG Representative**  
UCLA S. of Med. Dep. of Epi. & Div. of Inf. Dis.  
10880 Wilshire Blvd., Suite 540  
Los Angeles, CA 90095-7353  
Phone: 310-794-2555  
Fax: 310-794-2808  
Email: [pgorbach@ucla.edu](mailto:pgorbach@ucla.edu)

**Barbara Mensch, PhD**  
**BRWG Representative**  
Population Council  
1 Dag Hammarskjold Plaza  
New York, NY 10017 USA  
Phone: 212-339-0640  
Fax: 212-755-6052  
Email: [bmensch@popcouncil.org](mailto:bmensch@popcouncil.org)

**Patrick Ndase, MBChB, MPH**  
**Regional Physician**  
Microbicide Trials Network  
Plot 131 Makindye Rd.  
Kampala, Uganda  
Phone: 256-753-080-489  
Fax: 256-41-532091  
Email: [pndase@u.washington.edu](mailto:pndase@u.washington.edu)

**Ian McGowan, MD, PhD, FRCP**  
**Co-principal Investigator**  
Microbicide Trials Network  
204 Craft Ave.  
Pittsburgh, PA 15213 USA  
Phone: 412-641-8999  
Fax: 412-641-6170  
Email: [imcgowan@pitt.edu](mailto:imcgowan@pitt.edu)

**Lisa Noguchi, CNM, MSN**  
**Scientific Director for Pregnancy Research**  
Microbicide Trials Network  
204 Craft Ave.  
Pittsburgh, PA 15213 USA  
Phone: 412-951-3133  
Fax: 412-641-6170  
Email: [lnoguchi@mail.magee.edu](mailto:lnoguchi@mail.magee.edu)

**Devika Singh MD, MPH**  
**Protocol Safety Physician**  
Box 359927, Department of Global Health, ICRC  
325 Ninth Ave.  
Seattle WA 98104 USA  
Phone: 206-744-8311  
Fax: 206-520-3831  
Email: [dsingh@u.washington.edu](mailto:dsingh@u.washington.edu)

**Christina M. Wyatt, MD**  
**Nephrotoxicity Consultant/Investigator**  
Box 1243, Mount Sinai School of Medicine  
One Gustave L. Levy Place  
New York, NY 10029 USA  
Phone: 212-241-6689  
Fax: 212-987-0389  
Email: [christina.wyatt@mssm.edu](mailto:christina.wyatt@mssm.edu)

## **MTN Network Laboratory (NL)**

### **Craig Hendrix, MD**

#### **MTN NL Pharmacology CORE Principal Investigator**

John Hopkins University  
600 North Wolfe St., Harvey 502  
Baltimore, MD 21287 USA  
Phone: 410-955-9707  
Fax: 410-955-9708  
Email: [cwhendrix@jhmi.edu](mailto:cwhendrix@jhmi.edu)

### **Edward Livant, BSMT (ASCP), MPH**

#### **MTN NL Research Manager**

Microbicide Trials Network  
204 Craft Ave.  
Pittsburgh, PA 15213 USA  
Phone: 412-641-3772  
Fax: 412-641-5290  
Email: [livantew@upmc.edu](mailto:livantew@upmc.edu)

### **John Mellors, MD**

#### **MTN Virology CORE Principal Investigator**

University of Pittsburgh Physicians  
3550 Terrace St.  
Scaife Hall, Suite 818  
Pittsburgh, PA 15261 USA  
Phone: 412-624-8512  
Fax: 412-383-7982  
Email: [mellors@dom.pitt.edu](mailto:mellors@dom.pitt.edu)

### **Urvi Parikh, PhD**

#### **MTN Virology CORE Associate Director**

University of Pittsburgh  
3550 Terrace St.  
S817B Scaife Hall  
Pittsburgh, PA 15261 USA  
Phone: 412-648-3103  
Fax: 412-648-8521  
Email: [ump3@pitt.edu](mailto:ump3@pitt.edu)

## **MTN CORE – FHI 360**

**Stephanie Horn**

**Protocol Research Specialist**

FHI 360

PO Box 13950

Research Triangle Park, NC 27709 USA

Phone: 919-544-7040 Ext. 11274

Fax: 919-544-0207

Email: [shorn@fhi360.org](mailto:shorn@fhi360.org)

**Karen Isaacs**

**Clinical Research Manager**

FHI 360

PO Box 13950

Research Triangle Park, NC 27709 USA

Phone: 919-544-7040 Ext. 11488

Fax: 919-544-0207

Email: [kisaacs@fhi360.org](mailto:kisaacs@fhi360.org)

**Cheryl Cokley**

**Community Program Associate**

FHI 360

PO Box 13950

Research Triangle Park, NC 27709 USA

Phone: 919-544-7040 Ext. 11359

Fax: 919-544-0207

Email: [ccokley@fhi360.org](mailto:ccokley@fhi360.org)

**Rhonda White, R. H. Ed.**

**Community Program Manager**

FHI 360

PO Box 13950

Research Triangle Park, NC 27709 USA

Phone: 919-544-7040 Ext. 11515

Fax: 919-544-0207

Email: [rwhite@fhi360.org](mailto:rwhite@fhi360.org)



## **MTN Statistical Data Management Center (SDMC)**

**Karen Patterson, MPH**  
**MTN SDMC Project Manager**  
FHCRC—SHARP  
1100 Fairview Ave. North, LE-400  
PO Box 19024  
Seattle, WA 98109-1024 USA  
Phone: 206-667-7052  
Fax: 206-667-4812  
Email: [karen@scharp.org](mailto:karen@scharp.org)

**Barbra Richardson, PhD**  
**MTN SDMC Co-principal Investigator**  
FHCRC—SHARP  
1100 Fairview Ave. North, M2-C200  
Seattle, WA 98109-1024 USA  
Phone: 206-731-2425 (T, W, TH)  
Phone: 206-667-7788 (M, F)  
Fax: 206-667-4378  
Email: [barbra@scharp.org](mailto:barbra@scharp.org)

**MTN-018B**

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

**INVESTIGATOR SIGNATURE FORM**

**Version 1.0**

**August 30, 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-018B

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

#### PROTOCOL SUMMARY

<b>Short Title:</b>	CHOICE-B Follow-up Study to MTN-003 (VOICE)
<b>IND Sponsor:</b>	Division of AIDS, NIAID, US NIH
<b>Protocol Chair:</b>	Flavia Matovu Kiweewa, MBChB, MSc. Epidemiology
<b>Sample Size:</b>	Up to approximately 400 mother-infant pairs, based on site investigator estimates for expected % of former VOICE participants breastfeeding during implementation of MTN-018
<b>Study Population:</b>	Healthy, HIV-uninfected breastfeeding women formerly enrolled in VOICE, and their infants
<b>Study Sites:</b>	CHOICE sites
<b>Study Duration:</b>	Total study duration will be for the duration of MTN-018, with possibility of extension
<b>Study Products:</b>	Unless emerging evidence at the time of implementation supports a different approach, MTN-018B study products are anticipated to be the same as MTN-018 study products.

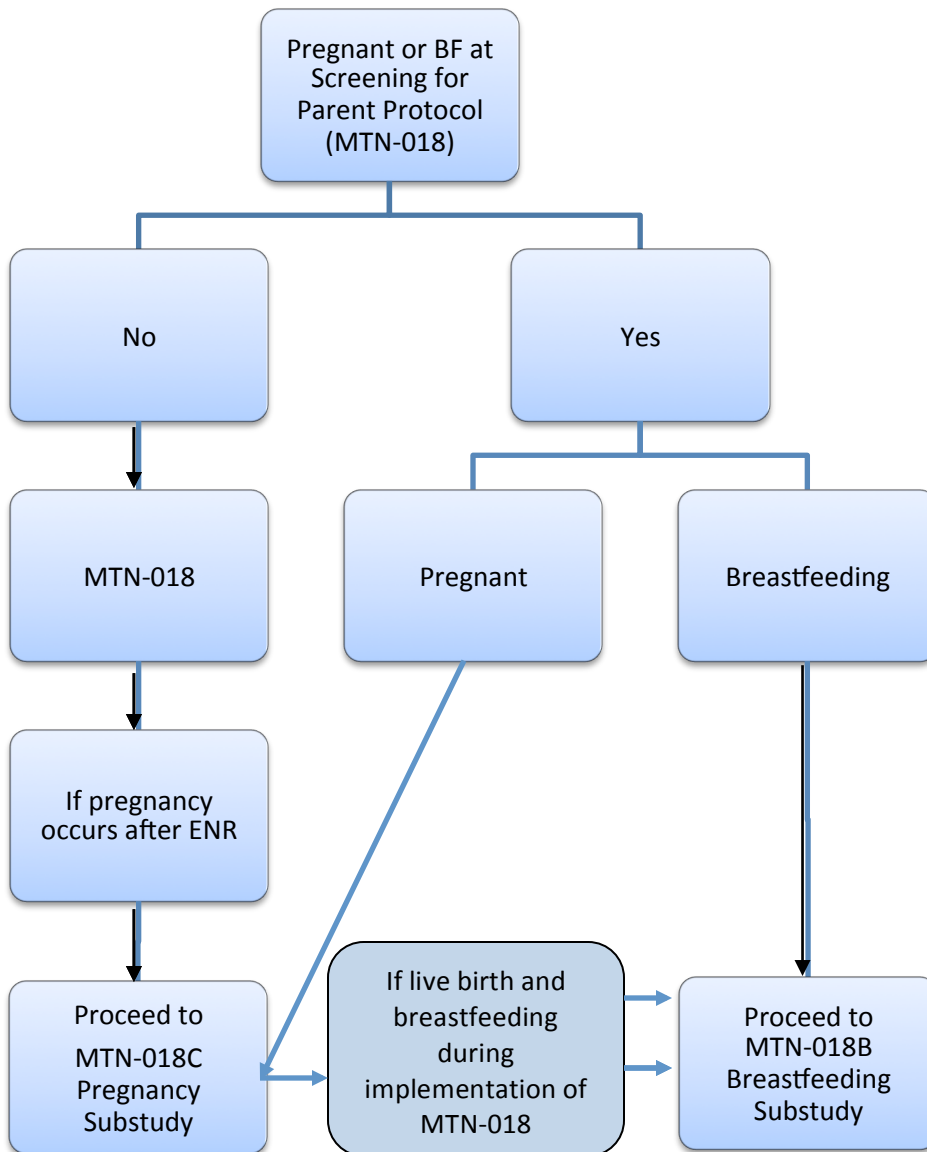
MTN-018B study products will include one or more of the following:

- 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-018B 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-018B is an open-label, multi-site trial. 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. Figure 2 illustrates the referral patterns among VOICE, MTN-018, MTN-018B, MTN-018C, and MTN-016.



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

Note: Simultaneous co-enrollment in MTN-018B and MTN-018C may be allowed with permission of the MTN-018 PSRT.

If only one product is selected to move forward in the parent protocol, MTN-018, MTN-018B participant mothers would receive that product.

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

At Month 1, participant mothers will confirm their desire to continue with the study product chosen at the Enrollment Visit, or request a change in study product. All changes in product selection following the Month 1 Visit must be approved by the IoR/designee. In general, one participant-initiated switch in study product will be permitted following Month 1; however, this does not preclude study product changes initiated by the IoR/designee for other reasons (e.g., toxicity or significant personal reasons, such as those impacting personal safety).

Participant mothers will not be randomized at Month 1 to one of two follow-up strategies, as in MTN-018, but will be followed monthly on study product for the duration of follow-up:

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

Mother-infant pairs have the option to join the PK Subset in MTN-018B, if the participant infant is less than three months old. Mother-infant pairs in the PK Subset have additional PK procedures listed in Section 7.4.2.

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

**Study Groups:** Final study groups will depend on selection of study product(s). Participant mothers' 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

## **Related Studies**

### MTN-018C

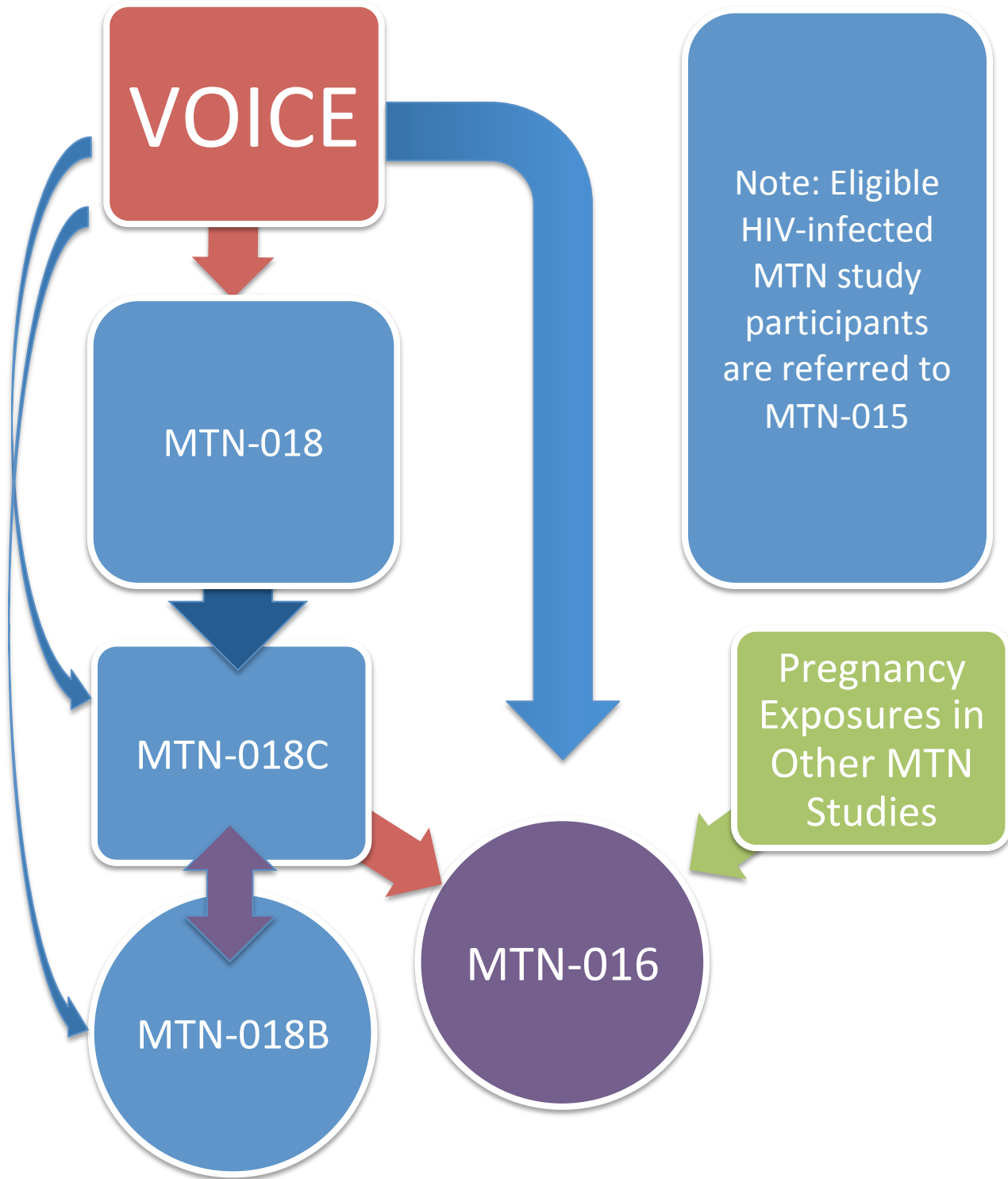
MTN-018C will enroll former VOICE participants who are pregnant into a protocol similar to CHOICE, except that participants will not be randomized to monthly vs. quarterly follow-up. Participants will choose their study product (if more than one product is selected for CHOICE). Mothers will be followed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

### MTN-003B

MTN-003B, the Bone Mineral Density Substudy, is an observational study in a subset of participants in the VOICE study to explore the effects of oral study products on bone mineral density. MTN-018B participant mothers who continue in follow-up from MTN-003B may have continued assessments of bone mineral density via DXA. MTN-018B provides an opportunity to contribute to the understanding of bone mineral density loss during lactation, which is potentially of greater significance in the context of tenofovir use, previously associated with decreased bone mineral density in the context of HIV treatment.

### MTN-016

MTN-016, the Prevention Agent Pregnancy Exposure Registry, is an observational cohort study assessing the impact of microbicides and PrEP on rates of pregnancy loss and malformations, as well as infant growth, health, and development. The study population consists of participants who became pregnant during MTN trials, or who had planned exposures in pregnancy safety studies, as well as babies from these pregnancies. This study also collects virologic and ARV drug resistance outcomes for HIV-infected infants and will compare those exposed to active vs. placebo drug in utero. Working with reproductive geneticists, MTN-016 screens abnormal exam findings for potential genetic and chromosomal disorders.



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

## STUDY OBJECTIVES

### Primary Objectives

1. **Safety (infants).** To compare health outcomes for breastfeeding infants of MTN-018B mothers to those of MTN-016 infants of mothers randomized to placebo product in VOICE
2. **Safety (mothers).** To compare health outcomes of MTN-018B participant mothers to those of VOICE participants taking the same active study product

### Primary Endpoints

1. **Safety (infants)**
  - Life-threatening event
  - Persistent or significant disability/incapacity
  - Hospitalization/prolongation of hospitalization
  - Death
2. **Safety (mothers)**
  - Grade 3 and higher clinical AEs
  - Grade 2 and higher laboratory AEs for the following categories
    - AST
    - ALT
    - Creatinine

### Secondary Objectives

1. **Growth.** To compare growth measurements of MTN-018B infants to those of MTN-016 infants whose mothers were randomized to placebo product in VOICE
2. **Pharmacokinetic Subset.** To characterize the pharmacokinetic profile of MTN-018B study product use in a subset of lactating women and infants
3. **Breastfeeding Outcomes.** To describe impact of study participation on infant feeding outcomes
4. **Adherence.** To evaluate adherence to daily regimens of MTN-018B study products

### Secondary Endpoints

1. **Growth**
  - Measurements of growth (weight, length/height, head circumference) for infants in the first year of life



## **2. Pharmacokinetic Subset**

- Maternal serum and milk drug levels
- Infant serum drug level by heel stick

## **3. Breastfeeding Outcomes**

- Duration of breastfeeding
- Timing and type of supplementation
- Reason(s) for weaning

## **4. Adherence**

- Adherence to study product by self-report, product counts, and serum 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 – Breastfeeding Sub-study

Short Title: CHOICE-B

Protocol Number: MTN-018B

Date: August 30, 2012

## 1.2 Sponsor and Monitor Identification

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

Sponsor: US NICHD  
6100 Executive Blvd.  
Bethesda, MD 20892 USA

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

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

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

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

## 1.3 Medical Officer

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

## **1.4 Network Laboratory**

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

## **1.5 Data Center**

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

## **1.6 Study Operations**

Study Operations: FHI 360  
PO Box 13950  
Research Triangle Park, NC 27709 USA

# **2 INTRODUCTION**

## **2.1 HIV Prevention among Breastfeeding Women**

Guidance from the World Health Organization supports the promotion of exclusive breastfeeding up to 6 months of age, with continued breastfeeding along with appropriate complementary foods up to two years of age.<sup>1</sup> It is not uncommon in many countries within the global south for breastfeeding to continue for several years. However, there is significant overlap between high-parity countries where extended breastfeeding is common and those most impacted by the HIV/AIDS epidemic. The average woman in a high-prevalence area of the epidemic spends many years of her life breastfeeding. Thus, breastfeeding women do not represent a separate, special population at risk for HIV, but in contrast a very significant proportion of the general population of women at any given time. In addition, the post-partum period may be a time of increased HIV acquisition risk for women, and primary HIV infection during breastfeeding puts infants at higher risk for HIV infection. In some parts of the world, cultural norms related to extramarital relationships and postpartum abstinence may contribute to the increased risk of HIV/AIDS faced by many women.

However, without adequate safety and pharmacokinetic data among breastfeeding infants, regulatory approval and public sector roll-out of effective PrEP and microbicides may exclude lactating women. In addition, excluding breastfeeding women from post-trial access to study products found to be safe and effective in VOICE could potentially contribute to one or more adverse outcomes, including early termination of

breastfeeding to become eligible for MTN-018 (putting some infants at increased risk of nutritional compromise and/or diarrheal disease), exclusion of a substantial proportion of women formerly enrolled in VOICE (up to 10%), and delay of important safety data for regulators.

## **2.2 Guidance from US Food and Drug Administration (FDA) on Clinical Lactation Studies**

The US FDA has drafted guidance for the conduct of clinical studies of lactation.<sup>2</sup> It is noted that it is highly likely that a woman will need and take medications while she is breastfeeding, potentially exposing her child to the effects of these medications. Surveys in various countries indicate that 90-99 percent of nursing mothers receive a medication during the first week postpartum, 17-25 percent of nursing mothers will take medication by 4 months postpartum and 5 percent of nursing mothers receive long-term drug therapy.<sup>3</sup>

The presence of a drug in breast milk does not necessarily indicate a health risk for the breastfed child. Detecting the presence or absence of the drug in milk is only the first step in determining risk. For most drugs, little scientific information is available about the extent of their passage into breast milk, their effects on milk production, their effects on the breast-fed infant, or whether a dose adjustment is needed to treat a lactating woman. Therefore, breastfeeding women and their health care providers must make decisions regarding treatment of maternal medical conditions in the absence of data. In some cases, this can result in a decision to stop breastfeeding so as to take needed drug therapy, thereby eliminating the benefits of breastfeeding for mothers and their infants. The American Academy of Pediatrics (AAP) has tried to fill the information void regarding infant safety by issuing consensus documents on the use of drugs in lactation or breast-feeding women<sup>4</sup>, but data upon which to make these assessments is sparse. Clinical lactation studies provide much needed additional data on which to base treatment decisions.

Since data on dosing lactating women are rarely available, most clinicians treat lactating women with the dose studied in and recommended for non-pregnant adults. This practice disregards the impact of the physiologic changes that occur during lactation and the effects of additional breast and milk compartments. A variety of potential differences in PK might be important in the postpartum and lactating periods, including differences caused by endogenous hormonal changes, altered body fat proportion, and changes in weight or muscle mass.

Circumstances for which the Agency recommends clinical studies in lactating women be done include:<sup>2</sup>

- A drug under review for approval is expected to be used by women of reproductive age
- After approval, use of a drug in lactating women becomes evident (e.g., via reports in the medical literature or lay press)

- A new indication is being sought for an approved drug and there is evidence of use or anticipated use of the drug by lactating women
- Marketed medications that are commonly used by women of reproductive age (e.g., antidepressants, antihypertensives, anti-infectives, diabetic and pain medications)

Lactating women and women of reproductive age are anticipated to be an important population for antiretroviral-based prevention of HIV, and therefore candidate PrEP and microbicide products should be subject to studies among lactating women.

The longitudinal design of MTN-018B is anticipated to capture some episodes of cessation of breastfeeding, although maternal dosing and maternal serum drug levels would continue following cessation. Because the same woman may be using active study product in both lactating and non-lactating states, it will be possible in this study for some to act as their own controls, a design aspect which will contribute to the understanding of the impact of lactation on study drug pharmacokinetics in healthy women.

### **2.3 Guidance from World Health Organization on Infant Feeding**

Over the past decades, evidence for the health advantages of breastfeeding and recommendations for practice have continued to increase. The World Health Organization (WHO) now states “with full confidence” that breastfeeding reduces child mortality and has health benefits that extend into adulthood.<sup>5</sup> On a population basis, exclusive breastfeeding for the first six months of life is the recommended way of feeding infants, followed by continued breastfeeding with appropriate complementary foods for up to two years or beyond.

To enable mothers to establish and sustain exclusive breastfeeding for six months, WHO and UNICEF recommend:

- Initiation of breastfeeding within the first hour of life;
- Exclusive breastfeeding - that is, the infant only receives breast milk without any additional food or drink, not even water;
- Breastfeeding on demand - that is, as often as the child wants, day and night;
- No use of bottles, teats or pacifiers.

Breast milk is the natural first food for babies, it provides all the energy and nutrients that the infant needs for the first months of life, and it continues to provide up to half or more of a child’s nutritional needs during the second half of the first year, and up to one-third during the second year of life.<sup>5</sup> Breast milk promotes sensory and cognitive development, and protects the infant against infectious and chronic diseases. Exclusive breastfeeding reduces infant mortality due to common childhood illnesses such as diarrhea or pneumonia, and helps for a quicker recovery during illness. Breastfeeding contributes to the health and well-being of mothers, helps to space children, reduces the

risk of ovarian cancer and breast cancer, increases family and national resources, is a secure way of feeding and is safe for the environment.<sup>5</sup>

Thus, MTN-018 is well-positioned to gather data on the potential impact of ARV-based prevention strategies on this critical area for infant health and survival. A subset of mothers and infants will contribute to the understanding of lactation pharmacokinetics within MTN-018B.

## **2.4 Results of the VOICE Trial**

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

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

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

### **2.5.1 Description**

Tenofovir disoproxil fumarate is approved by the US FDA under the trade name Viread<sup>®</sup> for treatment of HIV-1 infection in adults.<sup>6</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.<sup>6</sup>

### **2.5.2 Mechanism of Action**

Once absorbed, TDF is rapidly converted by diester hydrolysis to tenofovir.<sup>6</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 deoxyribonucleic acid (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>6</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-018B.<sup>7</sup>

### 2.6.1 Description

FTC is approved by the US FDA for treatment of HIV-1 infection in adults.<sup>8</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>9</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>9</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>8</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>8</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

Coformulation of FTC and TDF has been approved by the US FDA.<sup>9</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>9</sup>

## 2.7 Study Product Description: 1% Tenofovir Gel

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

### 2.7.1 Description

1% tenofovir 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>10</sup> Further information is available in the current version of the tenofovir gel investigator's brochure.<sup>10</sup>

## 2.7.2 Mechanism of Action

Tenofovir is an acyclic nucleotide analogue of adenosine monophosphate.<sup>10</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  $\gamma$ .

During preclinical evaluation, tenofovir demonstrated low oral bioavailability.<sup>10</sup> The form of tenofovir found in breast milk (tenofovir without phosphorylation) has low oral bioavailability and based on the clinical opinion of MTN investigators is not anticipated to be orally absorbed.

## 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-018B are included in the parent protocol, MTN-018.<sup>7</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, package insert and Investigator Brochure for the study products.<sup>6,9,10,11</sup>

To study tenofovir transfer into milk, two lactating macaques were given a subcutaneous dose of tenofovir (30 mg/kg of body weight). Peak concentrations and area under the curve values of tenofovir in milk were ~3 and ~20% of those detected in serum, respectively. This pilot pharmacokinetic study demonstrated that tenofovir, similar to most other drugs, is found in milk but at lower levels than in maternal blood. The available data suggest that such lower tenofovir levels in milk will most likely have no biological effects for the nursing infant.



## 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>8</sup> Detailed information on these studies is available in the VOICE protocol<sup>11</sup> and the package insert for the study product.<sup>8</sup>

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

Information regarding clinical studies of tenofovir and emtricitabine are included in the parent protocol, MTN-018.<sup>7</sup> Clinical studies with relevance to breastfeeding are included here.

### 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>12</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).<sup>12</sup>

Step 1 of TEmAA was administration of single dose TDF/FTC to the mother and Step 2 was administration of TDF/FTC to the mother and the newborn.<sup>12</sup> 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.<sup>12</sup>

### HPTN 057

The purpose of HPTN 057 is to evaluate the safety and pharmacokinetics of tenofovir disoproxil fumarate (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>13</sup> This study is a Phase I, open label, non-controlled trial. Eligible women and their infants were enrolled in one of four cohorts outlined below. Cohort 4 was added after reviewing the pharmacokinetic and safety data from Cohorts 1 and 3.

In Cohort 1, mothers receive a single 600 mg oral dose of TDF at onset of labor; infants are not dosed. In Cohort 2, mothers are not dosed; infants receive 4 mg/kg of the TDF oral suspension at birth (within 12 hours) and on Days 3 and 5 of life. In Cohort 3, mothers receive a single 900 mg oral dose of TDF at onset of labor and infants receive 6 mg/kg of the TDF oral suspension at birth (within 12 hours) and on Days 3 and 5 of life. Cohort 4 mothers receive a single 600 mg oral dose of TDF at onset of labor and infants receive 6 mg/kg of the TDF oral suspension daily for 7 days initiated at birth.

The primary objectives of HPTN 057 are the following:

1. To evaluate the safety and tolerance of intrapartum/neonatal TDF in HIV-infected women and their infants; and
2. 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.

In Cohort 1, mothers received TDF 600 mg at the onset of labor or 4 hours prior to cesarean delivery. Infants received TDF as soon as possible after birth, and on Days 3 and 5 of life. Maternal PK sampling for TDF plasma concentration occurred pre-dosing and at 1, 2, 4, 8, 12, 18-24, and 36-48 hours post-dosing. Cord blood was collected once, as well as infant blood for PK at 4, 12, 18-24, and 36-48 hours after birth. The mothers in this cohort delivered at median of 2.9 hours after dosing. Amniotic fluid samples were also collected from women who delivered via cesarean section at a median of 4.1 hours after dosing (n=5). Data from Cohort 1 are presented in Table 1 below.

**Table 1: HPTN 057 Cohort 1**

	<b>Median (range) of Maternal Tenofovir Levels</b>	
	<b>Pregnant Women, 600 mg (n=30)</b>	<b>Non-pregnant Adults, 600 mg</b>
<b>T<sub>max</sub> (hour)</b>	1.0 (1.0-8.0)	1.5
<b>C<sub>max</sub> (ng/mL)</b>	448 (110-928)	573
<b>AUC (ng*hour/mL)</b>	4221 (2767-24459)	4389
<b>T<sub>1/2</sub> (hours)</b>	19.5 (11.1-32.8)	11.9
<b>Tenofovir Concentrations in Breast Milk</b>		
<b>Day Collected</b>	<b>Number</b>	<b>Number with Detectable Tenofovir (concentration. [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 (TDF) 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 hours 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 2). The infant dosing schedule, however, did not maintain infant plasma tenofovir concentrations above 50 ng/mL, during the first week of life.

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

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

## 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>14</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 BF)?
4. What is the optimal intervention for the prevention of the infant morbidity and mortality associated with BF cessation?

The second question above is addressed via the Postpartum Component of PROMISE. This component is a strategy trial that will enroll and randomize consenting, eligible postpartum women who have a CD4 count > 350 cells/mm<sup>3</sup> and their uninfected infants within 1 week (7-12 days) following delivery to one of two study arms:

- *Arm A:* Maternal triple ARV prophylaxis through BF cessation or through 18 months postpartum, whichever comes first (with infant NVP prophylaxis through six weeks of age)
- *Arm B:* Infant NVP prophylaxis through BF cessation or through 18 months postpartum, whichever comes first (with no maternal prophylaxis)

At entry to Step 1, participants will be randomized to one of two arms:

- *Arm A (maternal prophylaxis):* Maternal triple ARV prophylaxis given from 7 (up to 12) days postpartum through BF cessation or through 18 months postpartum, whichever comes first unless stopped for toxicity, other medical reasons or confirmed infant HIV infection. The study-supplied maternal triple ARV regimen is LPV-RTV plus fixed dose combination FTC-TDF.
- *Arm B (infant prophylaxis):* Infant NVP prophylaxis given once daily given from 7 (up to 12) days of age (continued from the Antepartum Component study drug regimen) through BF cessation or through 18 months postpartum, whichever comes first unless stopped for infant HIV infection, toxicity, or other medical reasons.

Women will be followed until 96 weeks after the last woman on the Antepartum Component delivers (approximately 2-5 years, depending on the rate of accrual); infants will be followed through age 104 weeks.

The primary objectives of this component of PROMISE are the following:

1. To evaluate the comparative efficacy of giving daily maternal triple ARV prophylaxis versus daily infant NVP prophylaxis during BF to reduce cumulative HIV transmission from BF.
2. To assess the safety and tolerability of these ARV regimens for mother and infant.

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

## CAPRISA 004

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.<sup>15</sup> 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 herpes simplex virus type 2 (HSV-2) (CI: 22% - 70%). While data were not collected on breastfeeding infants, breastfeeding was not restricted within CAPRISA 004.

## MTN-008

MTN-008 is an expanded safety study of 1% tenofovir gel during pregnancy and breastfeeding, currently enrolling at two US sites.<sup>16</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.

## **2.11 Rationale**

### **2.11.1 Study Design**

The safety and effectiveness profile for VOICE study products is still under investigation. 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 of the 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 primary role of MTN-018B is to gather additional data on the safety profile of safe and effective VOICE products among breastfeeding mother-infant pairs. This sub-study targets former VOICE participants, rather than a non-VOICE cohort, in an attempt to gain important safety data in a population that should not otherwise be denied screening for a post-trial access protocol.

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.

As physiologic changes during lactation have the potential to alter maternal drug levels and thus potentially alter the efficacy of the drug, it is important that data be gathered on oral and topical PrEP use among nursing women and infants. MTN-018B will provide critical data on both drug levels in breast milk seen with long-term use, as well as an assessment of the potential impact that degree of drug exposure might have on nursing infants. The US FDA has identified these areas of study as key topics for investigation in clinical studies of medication use among lactating women.

This trial will use VOICE mothers and their infants who have enrolled in MTN-016 as comparison groups, rather than US norms or local demographic survey data, which would include very different populations of mothers and infants, and could potentially skew comparisons.

### **2.11.2 Breastfeeding and Infant Feeding Patterns**

While the parent protocol, MTN-018, will have the opportunity to answer behavioral research questions about preferences between types of products and product switching, these questions are not anticipated to be the primary focus of the behavioral objectives in MTN-018B. Rather, the potential impact of open label oral PrEP and microbicide use on infant feeding patterns is a key question for this cohort, as early weaning may have serious implications for infant health.

### **2.11.3 Adherence**

This protocol will have the opportunity to evaluate adherence to study products among breastfeeding mothers. MTN-008 will evaluate short-term adherence to a daily regimen of tenofovir gel, but this will be the first study to look at longer term adherence to known effective HIV chemoprevention strategies among breastfeeding women, whose adherence to products may be different from non-breastfeeding women, due to personal motivations related to protection from HIV, partner/family expectations and/or family responsibilities. Using a combination of interviewer-administered questionnaires, study product counts, and drug levels, MTN-018B will have the capacity to triangulate study data related to adherence. With these data, the study will have potential to explore

whether there is different adherence by study products among breastfeeding women, whether parity affects adherence to study product use, and whether HIV status of partner affects adherence to study product among breastfeeding women.

#### **2.11.4 Bone Mineral Density during Lactation**

During lactation, the mother experiences a transient but significant loss of bone mineral density, due to transfer of mineral from mother to infant.<sup>17</sup> The potential impact of oral tenofovir on the bone mineral density of breastfeeding mothers and their infants is not completely known but is under study in IMPAACT P1084s, Bone and Kidney Health Sub-study to PROMISE.<sup>18</sup> Emerging data from P1084s may be inserted here via a modification to the MTN-018B protocol.

MTN-018B provides an opportunity to contribute to the understanding of bone mineral density loss during lactation, which is potentially of greater significance in the context of tenofovir use, previously associated with decreased bone mineral density in the context of HIV treatment. MTN-018B participant mothers who continue in follow-up from MTN-003B may have continued assessments of bone mineral density via DXA. Optimally, via co-enrollment in MTN-003B<sup>19</sup> and pending continued funding, CHOICE-B participants may provide data within individuals for the following states:

- Baseline (pre-exposure to PrEP)
- During PrEP use (non-breastfeeding); and
- During MTN-018B study product use plus breastfeeding; and
- Post-breastfeeding (plus/minus MTN-018B study product)

#### **2.11.5 Safety Monitoring Strategy**

The decision to assess baseline renal, hepatic, and hematologic function and limit enrollment to healthy women stems from the protocol team's desire to minimize participant risk in this study of an agent intended for use in healthy women. The team acknowledges that the risk benefit ratio for participation in a trial is dramatically influenced by the indication for therapy.

The current WHO guideline for antiretroviral use in HIV-positive individuals suggests that laboratory monitoring should not be a barrier to initiating antiretroviral therapy.<sup>20</sup> 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-018B 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-018B 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**

1. **Safety (infants).** To compare health outcomes for breastfeeding infants of MTN-018B mothers to those of MTN-016 infants of mothers randomized to placebo product in VOICE
2. **Safety (mothers).** To compare health outcomes of MTN-018B participant mothers to those of VOICE participants taking the same active study product

#### **3.2 Secondary Objectives**

1. **Growth.** To compare growth measurements of MTN-018B infants to those of MTN-016 infants whose mothers were randomized to placebo product in VOICE
2. **Pharmacokinetic Subset.** To characterize the pharmacokinetic profile of MTN-018B study product use in a subset of lactating women and infants
3. **Breastfeeding Outcomes.** To describe impact of study participation on infant feeding outcomes
4. **Adherence.** To evaluate adherence to daily regimens of MTN-018B study products



## **4 STUDY DESIGN**

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

MTN-018B is an open-label, non-randomized, multi-site sub-study to MTN-018 for breastfeeding mother-infant pairs.

At the Enrollment Visit, and provided that more than one product is selected to move forward in MTN-018B, each participant selects the MTN-018B 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-018B, provided both are study products in MTN-018B. Participant mothers will be seen monthly and the infants will be seen quarterly.

At the Month 1 Visit, and provided that more than one product is selected to move forward in MTN-018B, each study participant mother identifies which product she would like to use (through Month 12). She will be asked about the reason(s) for her study product selection. The participant will then enter into approximately 11 additional months of scheduled follow-up on study product. However, participants who enroll later than six months after the onset of the study site's accrual period will have a contracted period of follow-up on product, which will end approximately 18 months after the onset of the study site's accrual period, unless the implementation of MTN-018B is extended at the request of DAIDS. Participants will then go off study product at follow-up Month 12 and return next at follow-up Month 14 for a Termination Visit, at which point participant mothers will undergo HIV testing to assess for possible masked HIV infection. The maximum duration of follow up will be 12 months of study product and 2 months off study product. The duration of follow up on study drug will be shortened for women enrolling late in the study such that the total duration of the study will be approximately 18 months.

Mother-infant pairs have the option to join the PK Subset in MTN-018B, if the participant infant is less than three months old. Mother-infant pairs in the PK Subset have additional PK procedures listed in Section 7.4.2.

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

For the primary objectives, safety endpoints for participant mothers will include grade 3 and higher clinical AEs, and grade 2 and higher laboratory AEs in the categories of AST, ALT, and creatinine.

For participant infants, safety endpoints will include the following:

- Life-threatening events
- Persistent or significant disability/incapacity
- Hospitalization/prolongation of hospitalization
- Death

For the secondary objectives, major endpoints will include the following:

- **Growth:** Measurements of growth (weight, length/height, head circumference) for infants in the first year of life;
- **Pharmacokinetic Subset:** Maternal serum and milk drug levels and Infant serum drug level by heel stick;
- **Breastfeeding Outcomes:** Duration of breastfeeding, timing and type of supplementation, and reason(s) for weaning; and,
- **Adherence:** Adherence to study product by self-report, product counts, and serum drug levels.

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

The study population will be healthy, HIV-uninfected, former VOICE participants who are breastfeeding and their breastfeeding infants.

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

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

#### **4.5 Study Groups**

Individual study groups depend upon selection of study product(s) for MTN-018B. 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 duration of participation for an individual participant enrolled in MTN-018B is approximately 14 months. However, follow-up may be truncated for those participants who enroll later than 6 months following the onset of the study site's accrual period.

#### **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, 5.3, 5.4 and 5.5 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-018B, 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) By self-report at Screening and Enrollment, currently breastfeeding at least one child
- 3) By self-report at Screening and Enrollment, intends to continue breastfeeding at least one child for at least the next 3 months
- 4) Able and willing to provide the following:
  - a) Written informed consent to be screened for and to take part in the study

- b) Written informed consent for all breastfeeding children to be screened for and take part in the study
  - c) Adequate locator information, as defined in site SOPs
- 5) HIV-uninfected based on testing performed by study staff at screening and 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 for the next 14 months
  - 7) For the PK Subset, mother provides written informed consent for mother and infant to participate in the PK Subset.

### **5.3 Exclusion Criteria – MOTHERS**

- 1) At Screening or Enrollment, one or more currently breastfeeding children ineligible for enrollment in MTN-018B.
- 2) Participant reported any of the following:
  - a) Known allergy to any of the study products (ever)
  - b) Post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to enrollment
  - c) 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)
- 3) Weight less than 35 kg at Screening
- 4) 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
- 5) At Screening, has any of the following laboratory abnormalities:
  - a) AST or ALT greater than 1.5 x site laboratory ULN
  - b) Serum creatinine greater than the site laboratory ULN for women
  - c) Positive for HBsAg
  - d) Urine dipstick positive for protein  $\geq 2+$
  - e) Urine dipstick positive for glucose  $\geq 2+$

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

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

- 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 Inclusion Criteria – INFANTS**

- 1) Mother eligible for and provides written informed consent for mother and infant to participate in MTN-018B
- 2) At enrollment, currently breastfeeding (defined as any suckling)
- 3) At enrollment, generally healthy, according to the judgment of the IoR/designee
- 4) At enrollment, according to the report of the mother, none of the following are applicable for the infant:
  - a. Participation in any research study involving drugs, vaccines, or medical devices 30 days or less prior to enrollment
  - b. Currently participating in other research studies involving drugs, vaccines, or medical devices
  - c. Expected to participate in other research studies involving drugs, vaccines, or medical devices for the next 14 months

*Note: previous or current participation in MTN-016 is not exclusionary.*

- 5) For the PK Subset, mother provides written informed consent for mother and infant to participate in the PK Subset
- 6) For the PK Subset, infant is less than 12 weeks old at Enrollment

#### **5.5 Exclusion Criteria – INFANTS**

- 1) 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

*Note: Examples of exclusionary infant conditions include severe intrauterine growth restriction, severe malformation, or illness in the infant.*

## 5.6 Co-enrollment Guidelines

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

- Participants may take part in ancillary studies approved by MTN-018B Protocol Chairs;
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-infected persons (e.g., MTN-015);
- Participants who become pregnant may take part in registries (e.g., MTN-016) and/or MTN-018C, the planned pregnancy sub-study to MTN-018 (PSRT consultation is required for simultaneous co-enrollment in MTN-018B and MTN-018C); and,
- Co-enrollment in MTN-003B, the Bone Mineral Density Substudy, is permissible.

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

## 6 STUDY PRODUCT

### 6.1 Regimen

At the Enrollment Visit, each participant will indicate their choice of one of the following regimens (pending selection of study product(s) for MTN-018B) 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 mother 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 participant mothers 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 participant mothers 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

1% tenofovir 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. 1% (w/w) tenofovir gel is a transparent, viscous gel. Each dose administered will be approximately 4 grams of gel containing approximately 40 mg of tenofovir. 1% tenofovir 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

1% tenofovir 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, participant mothers will return all unused study product, regardless of intent to continue or discontinue use of that study product. Participant mothers 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**

Participant mothers 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 or pharmacy visit, as applicable. 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 mother may be temporarily held or permanently discontinued. For temporary hold, study product should be retrieved within 5 working days. It is not necessary to retrieve products from participants for whom study product use is temporarily being held for less than 5 working 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. 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 each participant, all other unused supplies remaining in the participant mother's possession should be retrieved no later than the Month 12 Visit or the last study visit if earlier than 12 months. If the participant mother 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 mother 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 participant mothers and infants may use concomitant medications during study participation. For participant mothers and infants, all concomitant medications, over-the-counter preparations, vitamins and nutritional supplements, recreational drugs, and herbal preparations reported throughout the course of the study, beginning at Enrollment, will be recorded on case report forms (CRFs) designated for that purpose. Should a participant report use of a medication for which concomitant use poses

significant risk to the participant, according to the clinical judgment of the IoR/designee, the IoR/designee will institute a temporary product hold, for as long as the participant is taking the medication. Study product will be held for participants who report taking PEP for HIV exposure. Study product use may resume when such participants report completion of PEP and they are confirmed HIV-negative based on testing performed at the study site per the algorithm in the protocol for HIV testing during follow-up. All participant mothers will be counseled to avoid the use of spermicide and other non-study vaginal products (other than tampons during menstruation and female condoms). Participant mothers 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-018B 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 the local study site laboratories.

### **7.1 Pre-Screening**

Study staff may pre-screen potential study participant mothers 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 Institutional Review Board (IRB)/Ethics Committee (EC) requirements.

### **7.2 Screening**

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

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

- Co-enrollment assessment (site-specific)
- Informed consent for screening – mother and infant
- Demographic information – mother
- Demographic information – infant
- Behavioral assessment, including behavioral eligibility information
- Locator information
- Assign PTID for mother
- Assign PTID(s) for infant(s)
- Collect pediatric care provider contact information and records
- HIV pre- and post-test counseling, including risk reduction counseling
- Offer HIV counseling and testing for partner(s)
- Provision of condoms
- Reimbursement
- Schedule next visit (if applicable)

### **7.2.2 Clinical Procedures: Mother**

- Medical history (including exclusionary medical conditions and current medications)
- Infant feeding assessment (by maternal history)
- Physical exam, including vital signs
- Weight
- Pelvic 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
- 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
- Ascertainment of current contraceptive method (if any) and contraceptive counseling
- Provision of contraception, if indicated
- Offer / referral of partners for STI testing and treatment if applicable and indicated by site SOP
- Eligibility assessment

### **7.2.3 Clinical Procedures: Infant**

- Medical history (including exclusionary medical conditions and current medications)

- Physical exam and vital signs
- Growth measurements, including weight, length/height, head circumference
- Treatment or referral of conditions identified at Screening, according to local standard of care, as clinically indicated
- Eligibility assessment

#### **7.2.4 Laboratory Procedures: Mother**

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

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

On the day when Enrollment is anticipated, 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 (mother and infant)
- Update medical history and/or current medications, if applicable (mother and infant)
- Re-confirmation (by participant self-report) of medical eligibility information assessed at Screening (mother and infant)
- Re-confirmation (by participant self-report) of behavioral eligibility, specifically that the mother:
  - 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 of the mother and/or infant may be performed on the day of enrollment, if relevant for the confirmation of eligibility
- Urine collection and pregnancy test (mother)
- Blood collection and HIV serology, HIV pre- and post-test counseling (mother)
- Any other clinically indicated behavioral, clinical, or laboratory assessments

## 7.3 Enrollment

### 7.3.1 Administrative, Behavioral, and Regulatory Procedures

- Informed consent for Enrollment (mother and infant)
- Informed consent for specimen storage and possible future research testing (mothers) (not required for enrollment, may be deferred to later visit, up to 3 months following enrollment)

*Note: As infants in the PK Subset will have minimal blood taken (by heel stick when possible), it is not anticipated that leftover blood will be available for future research testing*

- Locator information
- Behavioral assessment (mothers)
- HIV/STI risk reduction counseling (mothers)
- Provision of condoms (mothers)
- Offer of HIV counseling and testing for partner(s) (mothers)
- Reimbursement (mother-infant pair)
- Schedule next visit (mother-infant pair)

### 7.3.2 Clinical Procedures

- Infant feeding assessment (mothers)
  - Type(s) and duration of infant feeding
- Concomitant medications
- Medical history
- Disclosure of available test results (to mothers, regarding mothers and infants), if indicated
- Treatment or referral of conditions, according to local standard of care (mothers and infants), as clinically indicated
- Assess/counsel re contraception (mothers)
- Provision of contraception, if indicated (mothers)
- Blood collection (mothers), may be collected together with any blood collected for final eligibility confirmation, with consent
- Initial participant study product selection (mothers)
- Provision of study product, instructions, and adherence counseling (mothers)

*Note: HBV-susceptible participant mothers will be given information and offered the HBV vaccine series starting at their MTN-018B enrollment visits, unless the mother was previously enrolled and received this information/vaccine series in the parent protocol, MTN-018. For enrolled participants who are susceptible but decline vaccination at enrollment, the vaccine series may be initiated at any time during follow-up. The hepatitis B vaccine is not considered a study product in MTN-018B.*

### 7.3.3 Laboratory Procedures

- Plasma archive (mothers)

*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.

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

For participants who do not complete scheduled visits within a visit window, the visit will be considered “missed” and relevant CRFs will be completed to document the missed visit. When participants miss visits at which creatinine, AST/ALT, and/or plasma archive are required, these procedures must be conducted at the participants’ next visit. See Section 7.5 for further procedural modifications that may be required during follow-up.

The last two scheduled visits for each participant are referred to as the Month 12 and the Termination Visit, 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 and Month 14/Termination Visit are specified in the MTN-018B SSP Manual ([www.mtnstopshiv.org](http://www.mtnstopshiv.org)).

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

- Review/Update locator information
  - At all visits
- 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

- 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 (mother)
  - Monthly up to and including Month 12
  - Month 14/Termination
  - Additionally whenever HIV testing is performed
- HIV/STI risk reduction counseling (mother)
  - At all visits
- Offer HIV counseling and testing to partners, if indicated
- Provision of condoms (mother)
  - At all scheduled visits
  - At interim visits if indicated
- Reimbursement
  - At scheduled visits
  - At interim visits as indicated per site SOP
- Schedule next visit (mother and infant)
  - At all 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 and menstrual history and concomitant medication review/update (mother and infant)
  - At all scheduled visits
  - Additionally at unscheduled visits in response to intercurrent symptoms/illnesses/ongoing AEs
- Infant feeding assessment (type and duration of feeding)
  - Monthly up to and including Month 12
  - Month 14/Termination

- Contraceptive counseling (mother), if indicated by site SOP
  - As needed at all visits
- Provision of contraception (mother), if indicated by site SOP
  - As needed at all visits prior to Month 14/Termination
- Study product selection/ confirmation (mother)
  - Month 1
  - At other visits prior to Month 12, if indicated and approved by IoR/designee
- Study product supplies, instructions, and adherence counseling (mothers)
  - At scheduled visits prior to Month 12
  - At interim visits if indicated
- Collect unused study product
  - Monthly, up until and including Month 12
  - At Month 14/Termination, if indicated
  - At interim visits, if indicated
- Pelvic exam (mother)
  - Month 12
  - When clinically indicated
- Pelvic swabs for STI and/or vaginitis testing (mother)
  - When indicated by local standard of care
- Bimanual exam (mother)
  - At all pelvic exams

*Note: If a participant is menstruating at a study visit during which a pelvic exam is clinically indicated, all other visit procedures will be conducted, and the participant may be scheduled for an interim visit (if not within visit window) to return to the clinic within approximately five days to complete her pelvic exam.*

- Physical exam
  - Mother
    - Month 12
    - Additionally when clinically indicated
  - Infant
    - Month 3
    - Month 6
    - Month 9
    - Month 12
    - Additionally when clinically indicated



- Weight
  - Mother
    - Month 6
    - Month 12
    - Additionally when clinically indicated
  - Infant
    - Month 3
    - Month 6
    - Month 9
    - Month 12
    - Additionally when clinically indicated
  
- Length/Height/Head circumference (infant)
  - Month 3
  - Month 6
  - Month 9
  - Month 12
  
- Urine collection (mother)
  - At all scheduled visits
  - Additionally when clinically indicated
  
- Breast milk collection (mothers in PK Subset)
  - Month 3
  - Month 6
  
- Blood collection (mother)
  - At all scheduled visits
  - When needed to perform confirmatory HIV testing per Appendix III
  - Additionally when clinically indicated
  
- Blood collection (infants in PK Subset)
  - Month 3
  - Month 6
  - At interim visits, if indicated
  
- Disclosure of available test results (mother)
  - At all scheduled visits
  - Additionally when clinically indicated
  
- Treatment of STI/Reproductive tract infection (RTI) (mother)
  - When clinically indicated
  
- Offer of STI testing, counseling, and treatment for partner(s), if indicated by site SOP

- When clinically indicated
- Collect AEs (mothers and infants)
  - At all scheduled visits
  - At interim visits, if indicated
- Treatment and/or referral for treatment of AEs, according to local standard of care (mother and infant)
  - When clinically indicated
- Hepatitis B vaccination (as indicated for consenting HBV susceptible participant mothers)
  - At visits corresponding with recommended time points for hepatitis B vaccine series

#### **7.4.3 Laboratory Procedures**

- Urine pregnancy test (mothers)
  - At all scheduled visits
  - Additionally at unscheduled visits when a participant reports a missed menstrual period
- Urine dipstick for protein and glucose (mothers) (for those most recently using oral study product)
  - Month 6
  - Month 12
  - At interim visits, if indicated
- STI testing (mothers)
  - When indicated by local standard of care
- Vaginitis testing (mothers)
  - When clinically indicated (symptomatic)
- HBsAg/HBsAb (mothers)
  - Check HBsAg at Month 12, for those who decline or have contraindications to vaccine series
  - When clinically indicated
- HIV serology (mothers)
  - Monthly up to and including Month 12
  - Month 14 Termination Visit
  - Additionally when clinically indicated

- Creatinine (mothers) (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 (mothers)
  - Month 6
  - Month 12
  - Additionally when indicated by Section 9 or clinical judgment of IoR/designee
  
- Blood study drug levels (mothers)
  - Month 3
  - Month 6
  - Month 12
  
- Milk study drug levels (mothers in the PK Subset)
  - Month 3
  - Month 6
  
- Blood study drug levels (infants in the PK Subset)
  - Month 3
  - Month 6
  - At interim visits, if indicated
  
- Plasma archive (mothers)
  - Month 6
  - Month 12
  - Month 14 Termination Visit
  - If instructed by MTN NL
  
- HIV-1 ribonucleic acid (RNA) polymerase chain reaction (PCR) (mothers)
  - If indicated
  
- CD4+ T-cell count (mothers)
  - If indicated
  
- Standardized and specialized HIV-1 resistance tests
  - If indicated

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

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

All participants who become HIV-infected on study will 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-018B 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-018B.

For those who continue MTN-018B 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 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 the study, if this is not otherwise accessible.

### **7.5.2 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.

## **7.6 Participants Who Become Pregnant**

Participant mothers who test positive for pregnancy following enrollment will be offered co-enrollment in MTN-016. Eligible participants will be offered co-enrollment into MTN-018C, at participating sites.

## **7.7 Participants who Discontinue Breastfeeding**

Participant mothers who report complete discontinuation of breastfeeding will continue to be prescribed study drug and be followed on a monthly basis for the duration of their originally scheduled participation in MTN-018B. Reasons for discontinuation of breastfeeding will be captured on case report forms. Participant mothers who discontinue breastfeeding one child (e.g., one twin or an older toddler), but continue breastfeeding another child will also continue to be prescribed study drug and be followed on a monthly basis for the duration of their originally scheduled participation.

Participant infants who have ceased breastfeeding will discontinue PK procedures (if they are in the PK Cohort) but remain in follow-up for the duration of their originally scheduled participation in MTN-018B. For women who discontinue breastfeeding before 12 months, then both the infant and the mother will continue to participate in MTN-018B. Total duration of study product for the mother is anticipated to be approximately 12 months.

## **7.8 Interim Visits**

Interim visits may be performed at any time for participant mothers or infants during the study, in response to participant concerns or other reasons, and/or to perform additional evaluations/procedures, as needed. Interim visits may include but are not limited to scheduling next visit, behavioral assessment, social harms assessment, provision of study product, urine dipstick for glucose and protein, and/or blood drug level. 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 for mothers and infants will include the following assessments:

- Vital signs
  - Oral temperature
  - Blood pressure (mothers only)
  - Pulse
  - Respirations

- Measurement of height/length (as applicable)
- Clinical assessments of
  - Head and eyes
  - Neck
  - Lymph nodes
  - Heart
  - Lungs
  - Abdomen
  - Extremities
  - Neurological
  - Skin
  - Breasts (mothers only)

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. Physical exams for infants will omit blood pressure, breast exam and pelvic exam from the list of assessments above.

### **7.11 Laboratory Evaluations**

The location of laboratory evaluations will depend on laboratory capacity.

- Urine pregnancy test
- Urine dipstick for protein and glucose
- Creatinine
- ALT and AST
- HBsAg/HBsAb
- HIV serology
- Plasma archive
- HIV-1 RNA PCR
- CD4+ T cell count
- Standardized and specialized HIV-1 resistance tests
- Blood tenofovir level
- Blood emtricitabine level, if applicable for MTN-018B
- Milk tenofovir level
- Milk emtricitabine level, if applicable for MTN-018B
- 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-018B 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.

# **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, 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 or their participant infants 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 (mothers and infants) regardless of severity and presumed relationship to study product. Study staff also will report on CRFs the following events reported by or observed in enrolled participants:

- All AEs of severity Grade 3 or higher for mothers
- All AEs of severity Grade 2 or higher for infants
- All laboratory values for mothers
- All serious AEs for mothers and infants, as defined by the International Conference on Harmonization Consolidated Guidance for Good Clinical Practice
- All AEs for mothers and infants 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 IIRs/designees will submit AE information in accordance with local regulatory agencies' or other local authorities' requirements. Site IIRs/designees also will submit AE information and any other relevant safety information to their IRBs/ECs in accordance with IRB/EC requirements.

## **8.5 Social Harms Reporting**

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 infant, or interfere with treatment deemed clinically necessary. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs. The PSRT is available for consultation as needed per site IoR.

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

### **9.1 Grading System**

AE severity grading is described in Section 8.2.

### **9.2 Dose Modification Instructions**

No dose modifications will be undertaken in this study.

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

A participant 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 mother or infant otherwise might be put at undue risk to 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.

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

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

##### **Grade 3**

If a participant mother or her participant infant develops a Grade 3 AE not specifically addressed below and judged by the IoR/designee to be not related to study product, the participant mother may continue product use. If a participant mother or her participant infant develops a Grade 3 AE not specifically addressed below and judged by the IoR/designee to be related to study product, the participant mother may have a temporary product hold initiated at the discretion of the IoR.

##### **Grade 4**

If a participant mother or her participant infant develops a Grade 4 AE not specifically addressed below (regardless of relationship to study product), the participant mother 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, 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.

## 9.6 Genital Sexually Transmitted Infection/Reproductive Tract Infection

The IoR/designee should manage STI/RTI per current WHO guidelines, available at <http://www.who.int/en/> 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.

## 9.7 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-018B. 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-018B.

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-018B.

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

help ensure the participant receives appropriate care. All follow-up actions, outcomes, counseling, and plans for next steps will be documented in participant study records. Results of study laboratory testing may be helpful in clinical management; these results will be provided to the participant and her medical provider in real-time.

## **9.8 Hepatitis B Infection**

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

## **9.9 Pregnancy**

Study participants will be offered, or referred to, contraceptive counseling and contraceptive methods during the course of the study. In addition, study staff will also provide participants with condoms and counseling on use of condoms ideally during every sex act during study participation. Participants will be instructed to come to the clinic for pregnancy testing in the event that delayed menses is noted. Pregnancy testing will be performed at all study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care. A participant 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).

Pregnant participants who co-enroll in the pregnancy sub-study may be provided study product in that context. To avoid dispensing study product simultaneously in more than one study, study sites will carefully track study drug dispensations by PTID.

MTN-018B participants who become pregnant during MTN-018B participation will be offered screening for MTN-016, the Prevention Agent Pregnancy Exposure Registry. All participants will be encouraged to breastfeed, according to current WHO recommendations.

## **9.10 Criteria for Early Termination of Study Participation**

Participants may voluntarily withdraw from the study for any reason at any time. The IoR also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. The IoR should notify the PSRT. Participants also may be withdrawn if study sponsors, government or

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

## **10 STATISTICAL CONSIDERATIONS**

### **10.1 Overview and Summary of Design**

MTN-018B is an open-label, non-randomized, multi-site sub-study to MTN-018 for breastfeeding mother-infant pairs. The main goal of the trial is to provide additional safety data in breastfeeding infants and their mothers for potentially supporting further pre-, peri-, and/or post- registration requirements and/or a change of label.

VOICE site investigators have estimated that approximately 400 women previously enrolled in the VOICE trial may be breastfeeding during the implementation of the parent protocol, MTN-018.

### **10.2 Study Endpoints**

#### **Primary Safety Endpoints: Infant**

Consistent with the primary study objective to compare health outcomes for breastfeeding infants of MTN-018B mothers to those of MTN-016 infants of mothers randomized to placebo product in VOICE, the following endpoints will be assessed:

- Life-threatening events
- Persistent or significant disability/incapacity
- Hospitalization/prolongation of hospitalization
- Death

#### **Primary Safety Endpoints: Mother**

Consistent with the primary study objective to compare health outcomes of MTN-018B participant mothers to those of VOICE participants taking the same active study product, the following endpoints will be assessed:

- Grade 3 and higher clinical AEs
- Grade 2 and higher laboratory AEs for the following categories:
  - AST
  - ALT
  - Creatinine



### **Secondary Endpoints: Growth**

Consistent with the secondary study objective to compare growth measurements of MTN-018B infants to those of MTN-016 infants of mothers randomized to placebo product in VOICE, the following endpoints will be assessed:

- Measurements of growth (weight, length/height, head circumference) for infants in the first year of life

### **Secondary Endpoints: Pharmacokinetic Subset**

Consistent with the secondary study objective to characterize the pharmacokinetic profile of MTN-018B study product use in a subset of lactating women and infants, the following endpoints will be assessed:

- Maternal serum and milk drug levels
- Infant serum drug level by heel stick

### **Secondary Endpoints: Breastfeeding Outcomes**

Consistent with the secondary study objective to describe the impact of study participation on infant feeding outcomes, the following endpoints will be assessed:

- Duration of breastfeeding
- Timing and type of supplementation
- Reason(s) for weaning

### **Secondary Endpoints: Adherence**

Consistent with the secondary study objective to evaluate adherence to daily regimens of MTN-018B 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 and Power Calculations**

Infant Safety Endpoints: Based on site investigator estimates for the expected percentage of former VOICE participants that will be breastfeeding during implementation of MTN-018, we expect approximately 400 mother-infant pairs to be eligible for participation in MTN-018B. MTN-018B is an observational study that will try to maximize the analysis of the available data. There are no plans to try to increase enrollment beyond that which will occur naturally in the course of the implementation of the parent protocol, MTN-018. The sample size will be recalculated following the completion of VOICE, if MTN-018 is anticipated to move forward.

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 safety data on approximately 115 infants in MTN-016 (the comparison group for MTN-018B infants). Because in MTN-018B 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 3 provides information regarding the minimum rate detectable with 80% power in safety outcomes for varying sample sizes of MTN-018B infants and varying estimates of safety outcome rates in the 115 MTN-016 placebo-exposed infants, assuming a 2-sided chi-square test with  $\alpha=0.05$ .

**Table 3: Minimum Rate Detectable With 80% Power for Infant Safety Outcomes (assuming n=115 MTN-016 control group infants)**

Estimate of proportion with outcome in MTN-016 placebo infants n=115	Minimum Rate Detectable with 80% Power with a sample size of MTN-018B infants of:		
	n=100	n=200	n=400
1%	9.4%	8.0%	7.2%
2%	11.5%	10.0%	9.1%
5%	16.8%	15.0%	14.0%
7%	19.9%	18.0%	16.9%
10%	24.3%	22.2%	21.0%

Thus, if a safety endpoint 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 10.0% (15.0% or higher rate in the MTN-018B infants) with information from n=200 MTN-018B infants.

**Maternal Safety Endpoints:** Based on site investigator estimates for the expected percentage of former VOICE participants that will be breastfeeding during implementation of MTN-018, we expect approximately n=400 mother-infant pairs to be eligible for participation in MTN-018B. Also based on estimates from VOICE we expect approximately 1000 participants in VOICE exposed to each of the three active products (the comparison group(s) for MTN-018B mothers). Because in MTN-018B 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 4 provides information regarding the minimum rate detectable with 80% power in safety outcomes for varying sample sizes of MTN-018B mothers and varying estimates of safety outcomes in the 1000 VOICE women exposed to a product assuming a 2-sided chi-square test with  $\alpha=0.05$ .

**Table 4: Minimum Rate Detectable With 80% Power for Mother’s Safety Outcomes (assuming n=1000 VOICE control group women)**

Estimate of proportion with outcome in VOICE women exposed to product	Minimum Rate Detectable with 80% Power with a sample size of MTN-018B mothers of the following:		
	n=100	n=200	n=400
1%	5.3%	4.1%	3.3%
2%	7.5%	5.9%	4.9%
5%	12.6%	10.5%	9.1%
7%	15.6%	13.3%	11.7%
10%	20.0%	17.2%	15.4%

Thus, if a safety endpoint is observed in 2% of VOICE participants on a particular active product, we would have 80% power to detect a minimum difference between the groups of 3.9% (5.9% or higher rate in the MTN-018B mothers) with information from n=200 MTN-018B mothers.

Infant Growth: Assuming growth z-scores in both the MTN-018B infants, and the MTN-016 infants have standard deviations of 1.0, assuming available growth data on n=115 MTN-016 infants, and using a two-sided t-test with  $\alpha=0.05$ , the study will have 80% power to detect a minimum difference in growth z-scores at a particular age of 0.383, 0.328, and 0.296 with sample sizes of n=100, n=200, and n=400 MTN-018B infants, respectively.

Pharmacokinetic subset: For the pharmacokinetic subset, a random subset of 10% of the mother-infant pairs will be selected to participate. Sample size exposed to each product will depend on the number of products included in the study and the proportion of women choosing each product.

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

Accrual is anticipated to be completed in approximately 12 months. The expected duration of participation for an individual participant enrolled in MTN-018B is approximately 14 months. However, to maximize the possibility that MTN-018B safety data will be available in a timely fashion, follow-up will be truncated for those participants who enroll later than 6 months following the onset of the study site’s accrual period. There is not a limit to the number of mother-infant pairs that will be allowed to participate in this study.

#### **10.5 Blinding**

This is an open-label and unblinded trial.

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

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.

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

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

### **10.6.2 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-018B product exposure group. Safety endpoints in mothers and infants will be described using proportions and 95% confidence intervals. Chi-square tests will be used to test for differences in the rates of primary safety endpoints in the infants in MTN-018B and infants in MTN-016. Multivariable logistic regression will be used to compare the odds of safety events in the two groups of infants controlling for any important differences in baseline characteristics in the two groups that also affect the safety outcomes. Similar analyses will be performed on the safety outcomes of the MTN-018B mothers comparing them to VOICE participants using the same product. Acknowledging that factors related to breastfeeding have been strongly linked to infant survival, infant deaths will be captured in the study database and analyzed during the analysis of the safety objective, and not as a breastfeeding outcome.

**Secondary Outcomes:** All analyses of growth outcomes will be stratified by MTN-018B product exposure group. The World Health Organization child growth standards will be used to calculate weight for height z-scores, height for age z-scores, and weight for age z-scores.<sup>21</sup> Mixed effects models will be used to compare z-score growth trajectories between the MTN-018B infants and MTN-016 infants, separately for each product included in MTN-018B. Multivariable models will be used to control for any important differences in baseline characteristics in the two groups that also may affect growth, such as site. Blood and breast milk samples will be analyzed for TFV concentration. These will be summarized using descriptive statistics. TFV concentrations will be compared between mothers and infants. Duration of breastfeeding will be described by product exposure group using Kaplan Meier curves of time to cessation of

breastfeeding. Timing of supplementation will be described by product exposure group using Kaplan Meier curves of time to initiation of supplementation. Type of supplementation, adherence to study product, and reason(s) for weaning 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**

Following the release of VOICE results, and pending the identification of effective products within VOICE, a modified version of this protocol will be distributed to study sites for submission to local IRBs/ECs. This modified version will incorporate all

relevant findings from VOICE, including consideration for the safety and effectiveness profiles of study drugs, as well as the rationale for and identification of study products in MTN-018/MTN-018B.

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.

Consistent with guidance in 45 Code of Federal Regulations 46, Part D, site IRBs/ECs are requested to assign the protocol one of the following designations:

- §46.404 Research not involving greater than minimal risk.
- §46.405 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects.
- §46.406 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- §46.407 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

It is anticipated that the study will be consistent with the designation of §46.405 for the following reasons:

- The study is not expected to move forward unless at least one product from VOICE is found to be safe and effective at reducing the risk of sexually transmitted HIV in women.
- Reducing the risk of HIV acquisition in a mother holds out the prospect of direct benefit to her baby, as maternal HIV/AIDS puts the breastfeeding infant at risk of HIV infection, as well as maternal illness and death, which is associated with significant health and social risk for the infant.

Subsequent to the initial review and approval, the responsible IRBs/ECs must review the study at least annually. Each IRB/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>22</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.

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. 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>23</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>15</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.

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

### 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
- Fat redistribution
- Lactic acidosis

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
- Fat redistribution
- Lactic acidosis

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.

Study drug may pass from the study products into breast milk. If study drug passes into breast milk, it is not expected that the amount would be enough to cause health problems for the baby. However, the effects of exposure on a nursing baby are unknown. If breast milk did absorb some study drug, possible side effects in the baby could include increased liver function tests, diarrhea, nausea, vomiting, and gas, but these effects would likely resolve quickly if they occurred.

#### **13.4.2 Benefits**

In a modification to this protocol, this section will describe the reduction in risk of HIV infection known for study products. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research. Participant infants may benefit if the risk of HIV acquisition in the mother is reduced.

Participants will receive HIV/STI risk reduction counseling, HIV testing, HBV testing, HBV vaccine series (if indicated and desired by participant), pregnancy testing, physical examination, pelvic examination, and routine laboratory testing related to liver and kidney function and increased access to care for their infants if conditions are found in quarterly examinations. 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 how 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**

TDF and FTC/TDF are designated as FDA use-in-pregnancy Category B. Additional general information can be found in the most recent Viread<sup>®</sup> and Truvada<sup>®</sup> package inserts.

Participants in MTN-018B will be counseled regarding the potential risks of drug exposure in pregnancy. Additionally, they will be offered contraception appropriate for breastfeeding mothers by the study site and referred to settings where contraception may be accessed in the community, if desired. Women who become pregnant during trial participation will be offered participation in MTN-018C and MTN-016.

### **13.7.2 Children**

The NIH has mandated that children be included in research trials when appropriate. This study will enroll breastfeeding children of participant mothers.

## **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 participant mothers 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 NIAID, the MTN, the US FDA, the OHRP, other government or regulatory authorities, site IRBs/ECs, CONRAD, and/or Gilead Sciences, Inc.

## **14 PUBLICATION POLICY**

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

## 15 APPENDICES



## APPENDIX I: SCHEDULE OF VISITS AND EVALUATIONS – MOTHERS

	SCR	ENR	MLY	M3	M6	M9	M12	M14/TER	INT
<b>ADMINISTRATIVE/BEHAVIORAL/REGULATORY</b>									
Co-enrollment assessment	X								
Informed consent (mother/infant)	X	X							
Demographic information	X								
Behavioral eligibility information	X								
Locator information	X	X	X	X	X	X	X	X	X
Assignment of PTID	X								
Pediatric provider contact/records	X								
HIV pre-/post-test	X		X	X	X	X	X	X	◆
HIV/STI risk reduction counseling	X	X	X	X	X	X	X	X	◆
Offer HIV counseling/testing partners	X	X	◆	◆	◆	◆	◆	◆	◆
Provision-condoms	X	X	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	X		◆
Social harms assessment				X	X	X	X		◆
Sharing assessment							X		
<b>CLINICAL</b>									
Infant feeding assessment, type, duration	X	X	X	X	X	X	X	X	◆
Study product selection		X	M1	◆	◆	◆			◆
Adherence counseling		X	X	X	X	X			◆
Concomitant medications	X	X	X	X	X	X	X	X	◆
Medical history	X	X	X	X	X	X	X	X	◆
Breast milk collection				PK	PK				
PE (including VS)	X		◆	◆	◆	◆	X	◆	◆
Pelvic examination	X		◆	◆	◆	◆	X	◆	◆
Pelvic swab for STI/vaginitis testing	◆		◆	◆	◆	◆	◆	◆	◆
Weight	X		◆	◆	X	◆	X	◆	◆
Urine collection	X		X	X	X	X	X	X	◆
Blood collection	X	X	X	X	X	X	X	X	◆
Collect AEs			X	X	X	X	X	X	◆
Test result disclosure	X	◆	X	X	X	X	X	X	◆
Treatment/referral (including STI/RTI)	◆	◆	◆	◆	◆	◆	◆	◆	◆
Partner STI test/treatment (if site SOP)	◆		◆	◆	◆	◆	◆	◆	◆
Assess/counsel re contraception	X	X	◆	◆	◆	◆	◆	◆	◆
Eligibility assessment	X								
Provision-study product		X	X	X	X	X			◆
Collect unused study product			X	X	X	X	X	◆	◆
Provision-contraception	◆	◆	◆	◆	◆	◆	◆		◆
Hepatitis B vaccination		◆	◆	◆	◆	◆	◆	◆	◆
<b>LABORATORY</b>									
Urine HCG	X		X	X	X	X	X	X	◆
Dipstick UA (protein, glucose)	X				X-oral		X-oral		◆
HIV serology	X		X	X	X	X	X	X	◆
HIV-1 RNA			◆	◆	◆	◆	◆	◆	◆
CD4+ T-cell count			◆	◆	◆	◆	◆	◆	◆
Standard/Specialized HIV-1 resistance			◆	◆	◆	◆	◆	◆	◆
Serum creatinine	X		◆	◆	X-oral	◆	X-oral	◆	◆
AST/ALT	X		◆	◆	X	◆	X	◆	◆
STI testing (per local standard of care)	◆		◆	◆	◆	◆	◆	◆	◆
Vaginitis testing (if symptomatic)	◆		◆	◆	◆	◆	◆	◆	◆
Plasma archive		X			X		X	X	◆
HBsAg/HBsAb*	X		◆	◆	◆	◆	HBsAg	◆	◆
Drug level-blood				X	X		X		◆
Drug level-milk				PK	PK				

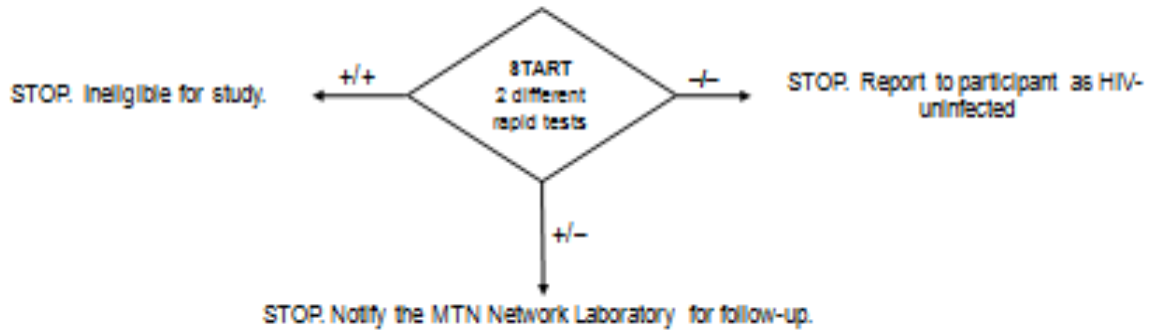
Note: SCR=Screening, ENR=Enrollment, MLY=Monthly up to and including M12, QLY=Quarterly, M6= Month 6, M12=Month 12, INT=Interim, X=required, ◆=if indicated. Section 7.2.5 describes final confirmation of eligibility as part of screening procedures performed on anticipated day of Enrollment. \*HBsAg/HBsAb testing may be omitted if completed HBV vaccination series or documented evidence of HBV immunity from VOICE. Informed consent for specimen storage and possible future research testing (mothers) is not required for enrollment, and may be deferred to later visit, up to 3 months following enrollment. PK=PK Subset. Oral=for those most recently using oral study product. Check HBsAg at Month 12 for those who decline or have contraindications to vaccine series.

## APPENDIX II: SCHEDULE OF VISITS AND EVALUATIONS – INFANTS

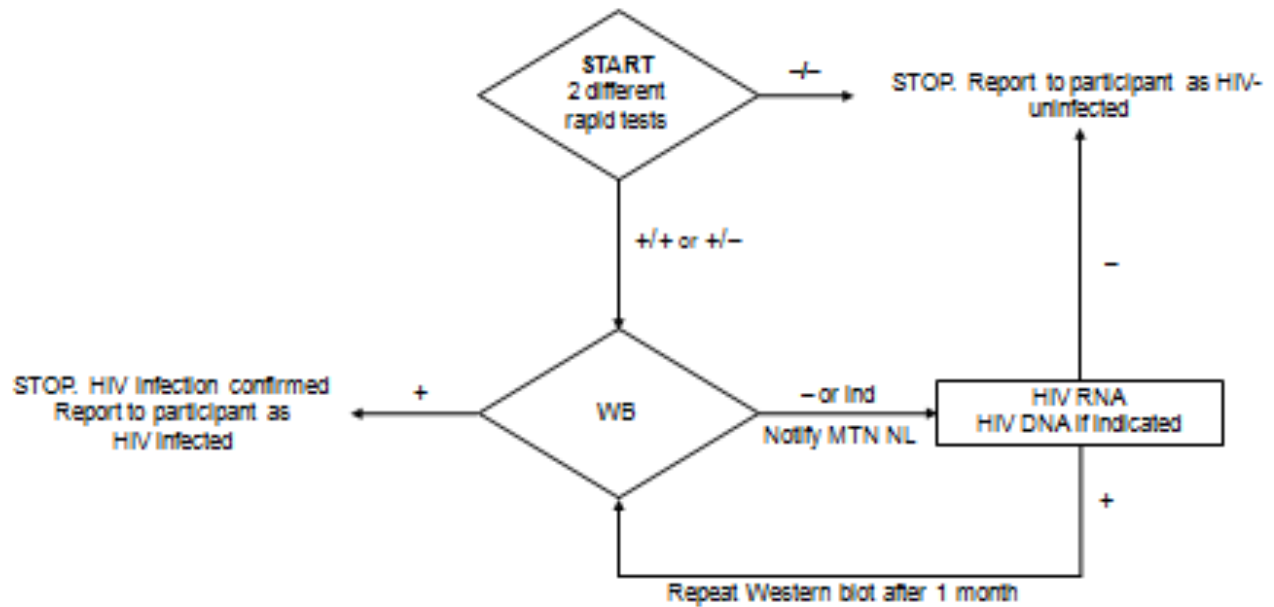
	SCR	ENR	MLY	M3	M6	M9	M12	INT
<b>ADMINISTRATIVE/BEHAVIORAL</b>								
Assignment of PTID(s)	X							
Demographic information	X							
<b>CLINICAL</b>								
Concomitant medications	X	X	X	X	X	X	X	◆
Collect/Update medical history	X	X	X	X	X	X	X	◆
Blood collection				PK	PK			◆
PE and VS	X			X	X	X	X	◆
Growth measurements	X			X	X	X	X	◆
Eligibility assessment	X							
Collect AEs			X	X	X	X	X	◆
Treatment/referral	◆	◆	◆	◆	◆	◆	◆	◆
<b>LABORATORY</b>								
Study drug level				PK	PK			◆

PK=PK Subset. Section 7.2.5 describes final confirmation of eligibility performed as part of screening procedures on anticipated day of Enrollment.

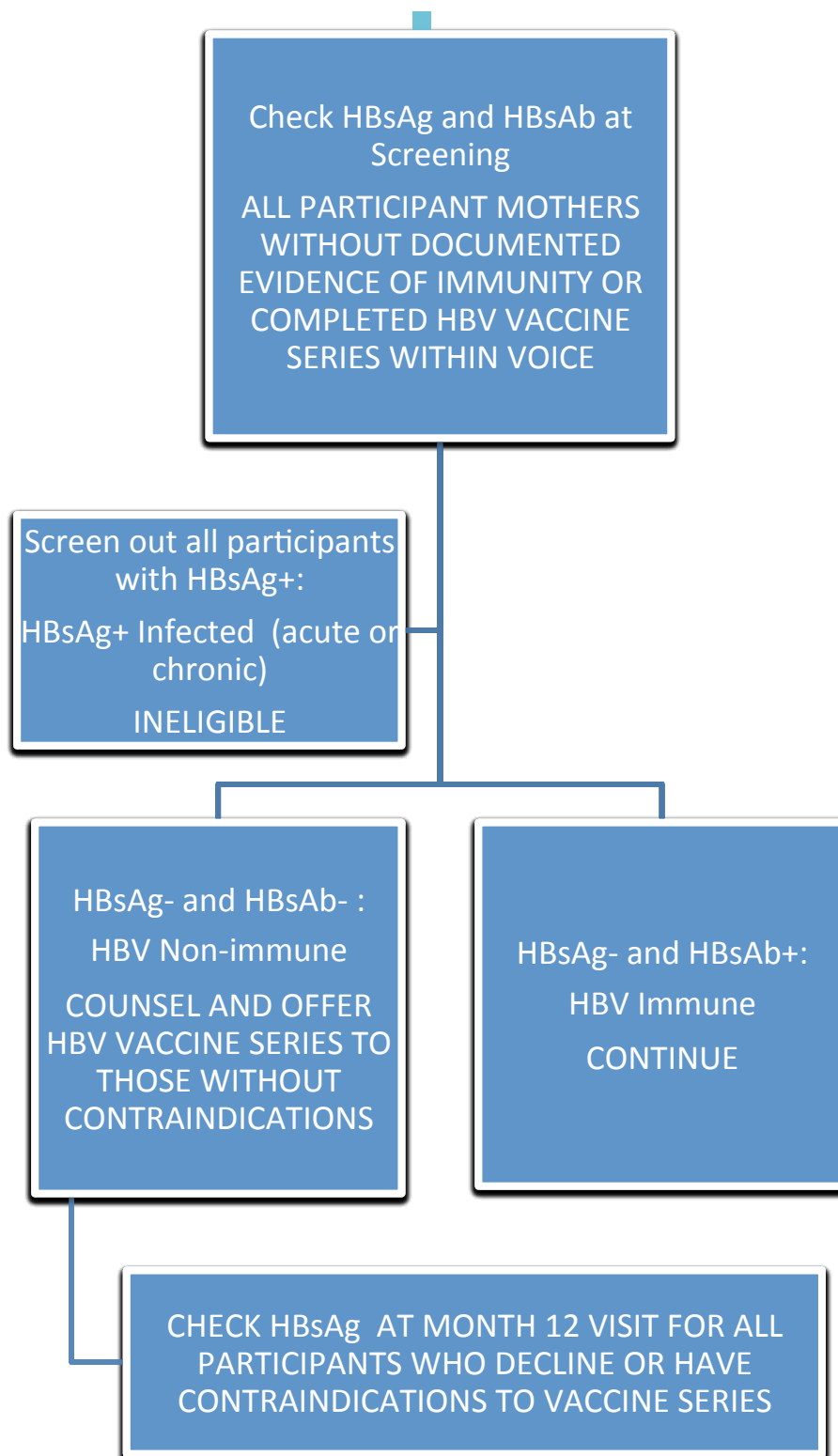
### APPENDIX III: ALGORITHM FOR HIV ANTIBODY TESTING – FOR MOTHERS – SCREENING/ENROLLMENT



## APPENDIX IV: ALGORITHM FOR HIV TESTING FOR MOTHERS – FOLLOW-UP



## APPENDIX V: ALGORITHM FOR HBV TESTING (MOTHERS)



**APPENDIX VI: SAMPLE INFORMED CONSENT FORM  
(SCREENING – MOTHERS AND INFANTS)**

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

**MTN-018B**

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

**[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 and your baby are eligible for a sub-study known as CHOICE-B. CHOICE-B is for breastfeeding women who were in the VOICE study before, who plan to continue breastfeeding for at least the next three months, and for breastfeeding babies of these women. CHOICE-B's main purpose is to collect more information about the safety of *[insert study products]* for breastfeeding women and their babies. CHOICE-B is also testing how much of the study drugs pass into breast milk and babies through breast milk. Truvada and Viread are approved (by the US Food and Drug Administration) drugs and tenofovir gel is an investigational study drug. Tenofovir gel, Truvada tablets and Viread tablets have not been approved for use in women who are breastfeeding or during pregnancy.

Screening includes questions, blood tests, a physical exam, and genital exam. Screening includes a physical exam and measurements for breastfeeding babies. The US NIH is funding the study. Up to about 400 women from VOICE and their babies will join CHOICE-B at different sites in Africa. Here we will explain the purpose of screening, risks and benefits to you and your baby, and what is expected of you and your baby. This form may have unfamiliar words. Please ask questions about anything you do not understand or want to learn more about. In this form, when we say "baby", we mean your breastfeeding baby or babies.

For you to join CHOICE-B, you and all your currently breastfeeding babies must be eligible for and take part in CHOICE-B. For example, if you are breastfeeding twins or a baby and a toddler, both children must be eligible for and participate in CHOICE-B. This is so we can monitor the health of all children you are breastfeeding.

**YOUR PARTICIPATION IS VOLUNTARY**

This form gives information about screening tests in CHOICE-B. Once you understand this form, and if you agree for you and your baby 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 and your baby 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 yourself and/or your baby at any time after signing this form, without losing your regular medical care. Even if you agree to do screening tests, you and your baby do not have to join CHOICE-B. If you decide not to have the screening tests, you can join another study later, if one is available and you qualify. However, you cannot join CHOICE if you or your baby are in another study of drugs, medical devices or vaginal products. Please tell us about any other studies you or your baby 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 and your baby are eligible for CHOICE-B. Some people may not be able to join CHOICE-B because of results of screening tests. You will receive test results even if you and your baby are not eligible to join CHOICE-B. The study doctors will also review your records from VOICE.

## **PROCEDURES**

For you to join CHOICE-B, all screening tests for you and your baby 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-B, you and your baby will have to do all screening tests again. Screening will begin after you discuss, understand and sign or make your mark on this form. We will answer all your questions before you sign or mark this form. Procedures at this visit will take about [*insert estimate*] hours to complete.

- We will ask where you live and other questions about you, your behavior, your health, how you feed your baby and your family planning method,
- We will ask questions about your baby, your baby's health, and your baby's healthcare provider. We will request copies of your baby's health records
- You will give urine for a pregnancy test and to test the health of your kidneys. If you are pregnant, you may be eligible for CHOICE-C, a sub-study for pregnant women.
- 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-B. If you have HIV, you are not eligible for CHOICE-B. 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.
- You will be offered HIV counseling and testing for your partner(s)
- If the tests show that you do not have HIV, the study staff will test your blood for:
  - The health of your liver and kidneys.
  - Hepatitis B, if a study doctor thinks this is necessary based on your blood tests from VOICE. This is a liver infection that can pass from mother to baby, through sex or through body fluids infected with hepatitis B. If tests show you have hepatitis B active in your liver, you are not eligible for CHOICE-B.

- You will have a physical exam including measurements of your weight
- Have an exam of your genital area and inside your vagina. Study staff may collect fluid from your vagina with a swab to test for infections, if necessary.
- You will get condoms.
- You will get treated for infections passed through sex, if needed.
- You will get family planning supplies, if you need them
- You will get referrals for other available services if you or your baby need them.
- *[if applicable: Your partner may get tested/treated for infections passed by sex]*
- Your baby will have a physical exam, and measurements of weight, height/length, and head.

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

### **Final Screening Procedures/Confirmation of Eligibility:**

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

- Explain test and exam results for you and your baby.
- Ask questions to update the information from your earlier visits.
- Test your urine for pregnancy. If you are not pregnant, study staff will talk with you about contraception and provide it if you need it.
- You will have testing for HIV, using the same procedures as above. If tests show you have HIV, you are not eligible for CHOICE-B. 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 screening test and exam results for you and your baby. If results show you and your baby are eligible for CHOICE-B, we will fully explain the study to you and answer any questions you have. If you decide for you and your baby to take part in CHOICE-B, you will be asked to sign another consent form. *[For applicable sites: You may sign the consent form for further participation in CHOICE before you finish the screening tests. This gives us permission to do final blood tests for screening and the first set of blood tests for women who enroll in CHOICE using one blood draw instead of two. We will talk with you more about this if you request it.]*

### **RISKS AND/OR DISCOMFORTS**

#### **MOTHERS**

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.

### **BABIES**

It is not expected that your baby will experience more than minimal risk or discomfort from the physical exam.

### **BENEFITS**

You and your baby may get no direct benefit from screening procedures. However, you will have a physical exam, genital exam, pregnancy test, and tests of your liver and kidneys. Your baby will have a physical exam. If results show you/your baby might have health problems, you/your baby 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. We will test your baby for HIV if you do not have another way to get this test for your baby. 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/your baby 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 or your baby may be withdrawn from screening tests without your consent if:

- You or your baby are found to be ineligible for CHOICE-B, or if CHOICE-B is stopped/canceled.
- The study staff feel that the screening tests would be harmful to you/your baby.
- You are not willing to find out your HIV test result, attend visits or complete screening.
- Other reasons, decided by the study staff.

### **COSTS TO YOU**

There is no cost to you for the screening tests for you or your baby. Treatments for you and/or your partner(s) for infections passed through sex (other than HIV and hepatitis B) are free of charge.

### **REIMBURSEMENT**

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

## **CONFIDENTIALITY**

Efforts will be made to keep your personal information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. We will use your personal information, if needed, to verify that you are not in other studies. Study publications will not use your/your baby's name or identify you or your baby 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 web site will include a summary of the results. You can search this website at any time.

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

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

*[Sites to include/amend the following if applicable:] [Local/state/national] regulations require us to report names of people who test positive for [HIV and other infections] passed during sex to [local health authority]. Outreach workers from [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to the confidentiality guidelines of [health authority].*

## **RESEARCH-RELATED INJURY**

*[Sites to specify institutional policy:]* It is unlikely that you or your baby will be injured as a result of having the screening tests and exams. If you or your baby are injured, *[institution]* will give you immediate treatment for your/your baby's injuries. You *[will/will not]* have to pay for this. You will be told where you/your baby 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 or your baby have a research-related injury, you should contact *[insert name]* at *[insert contact information]*. If you have questions about your/your baby's rights as a research participant, you should contact *[insert name or title of person on the IRB/EC or other organization appropriate for the site]* at *[insert physical address and telephone number]*. If you have questions about whom to contact at the research site, you should contact *[insert name of the investigator or community educator or Community Advisory Board 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 for you and your baby to have the screening tests and exams, 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
-------------------------	-------------------	------

If required by IRB:

Father's Name (print)	Father's Signature/Mark	Date
--------------------------	-------------------------	------

## **APPENDIX VII: SAMPLE INFORMED CONSENT DOCUMENT (ENROLLMENT – MOTHERS AND INFANTS)**

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

**MTN-018B**

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

**[DATE]**

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

You are being asked to volunteer for a sub-study known as CHOICE-B. CHOICE-B is for women who were in the VOICE study before and are now breastfeeding, and their babies. CHOICE-B's main purpose is to collect more information about the safety of [insert study products] for breastfeeding women and their babies. CHOICE-B is also testing how much of the study drugs pass into breast milk and babies through breast milk. The US NIH is funding the study. Up to about 400 women from VOICE and their babies will join CHOICE-B at different sites in Africa. Here we will explain the study's purpose, risks and benefits to you and your baby, and what is expected of you and your baby. This form may have unfamiliar words. Please ask questions about anything you do not understand or want to learn more about. In this form, when we say "baby", we mean your breastfeeding baby or babies.

For you to join CHOICE-B, you and all your currently breastfeeding babies must be eligible for and take part in CHOICE-B. For example, if you are breastfeeding twins or a baby and a toddler, both children must be eligible for and participate in CHOICE-B. This is so we can monitor the health of all children you are breastfeeding.

### **YOUR PARTICIPATION IS VOLUNTARY**

This form gives information about CHOICE-B. Once you understand this form, and if you agree for you and your baby 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. It is important that you know that you and your baby do not have to have to join CHOICE-B if you do not want to. You may decide not to join CHOICE-B, or to withdraw yourself and/or your baby at any time after signing this form, without losing your regular medical care. You cannot join CHOICE if you or your baby is in another study of drugs or medical devices or if you are in a study of vaginal products. Please tell us about any other studies you or your baby are in, or thinking of taking part in. This is very important for your safety.

### **PURPOSE OF THE STUDY**

**[VOICE results to be inserted here]**

The main purpose of CHOICE-B is to collect more information on the safety of [*insert study products*] for women who are breastfeeding and their breastfeeding babies. Truvada and Viread are approved (by the US Food and Drug Administration) drugs and tenofovir gel is an investigational study drug. Tenofovir gel, Truvada tablets and Viread tablets have not been approved for use in women who are breastfeeding or during pregnancy.

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.]

**CHOICE-B is testing [*insert number*] products.**

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

There is no placebo gel or placebo tablet in CHOICE-B. A placebo looks and feels the same as a real drug, but does not contain any active ingredient to prevent HIV.

We will ask you to choose a product to use during CHOICE-B. You can choose the gel or the tablet. You do not have to choose the same thing you used in VOICE.

**PK GROUP**

If you decide to join CHOICE-B, and you have at least one breastfeeding baby who is less than three months old, you and your baby have the option to join the PK Group. The PK Group will have the same procedures as other mothers and infants in CHOICE-B, plus extra tests to check the level of study drug in breast milk, and to see how much study drug passes to the baby.

**STUDY PROCEDURES**

If you decide to join CHOICE-B, your first visit will continue today, after you read, discuss, understand, and sign or make your mark on this form. Study staff will help you understand the form and answer your questions before you sign or mark this form. You will answer interview questions about your behavior. You will give [*insert*] teaspoons [or local equivalent] of blood that the study staff will keep here while you are in the study. If needed, they will test this blood later in the study to check on your health.

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

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

**At most visits, you will:**

- Tell staff if you and your baby had any health problems or problems related to study participation since your last visit
- Tell staff about medications, herbal treatments and supplements you and your baby are taking
- Tell staff any new information on where you and your baby live and how to keep in contact with you. If you miss a visit, we will try to contact you by [*site-specific methods*]. We also may visit your home. We will try to reach you through the contact people that you list. If we do this, we will not say why we want to reach you.
- Talk with staff about breastfeeding and how you are feeding your baby
- Talk with staff about sexual behavior and the use of your study product
- Bring your unused gel or tablets and bottles to be counted by study staff
- Talk with staff about HIV, HIV testing, and ways to avoid HIV and other infections passed through sex
- You will give [about X mL [*or local equivalent*]] of blood from your arm or finger] for HIV testing. We first do two tests that give results during your visit. Sometimes more tests are needed to know your HIV status. You will have testing (which may require you to return) until we know your status for sure. You will talk with staff about your results and how you feel about them. If tests show you have HIV, the US NIH requires that we send a sample of your blood to the US to check the results again. You must receive your HIV test results to stay in the study
- Give urine for a pregnancy test
- Get the results of tests done at the visit and at the previous visit
- Get treatment for most types of infections passed during sex if you need it
- Get referrals for other medical care and services if you need them
- Get condoms
- If needed, talk with staff about family planning and receive family planning supplies
- Get new supplies of gel or tablets
- Get instructions on how to use the product. If you use gel, for your safety, it is important that you only use the gel in your vagina, as instructed by study staff
- You will be asked to use the product once a day, at the same time

**It is very important that you do not ever share tablets or gel with anyone else who is either in or not in the study.**

**After 1 month, you will:**

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

**About every 3 months, you will:**

- Give blood to test for the level of study drug (test conducted in the US)

**About every 3 months, your baby will:**

- Have height/length, weight, and head measured
- Have a physical exam

**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
- Give blood that the study staff will keep here while you are in the study. If needed, they will test this blood to check on your health.
- Have your weight measured

**At your end of product visit (in about one year), you will:**

- Have a physical exam and pelvic exam
- Have procedures listed above, except that you will not receive any more gel or tablets. You will not use any more gel or tablets after this visit
- Talk with staff about whether others may have used your study product

**At your end of study visit, about two months after you finish product use (final scheduled study visit), you also will:**

- Answer questions about your sexual practices and the study gel or study tablets and your relationships with others

**IF YOU AND YOUR BABY ARE IN THE PK GROUP OF CHOICE-B**

If you and your baby are in the PK Group, you and your baby will have the procedures listed above. Every three months, you will also give breast milk to test for the level of study drug. After three months and after six months, your baby will also give a small amount of blood from the heel to check for the level of study drug. These tests will be conducted in the US.

**AT ANY TIME IN THE STUDY**

**If you or your baby have a medical problem, you will:**

- Tell the study staff and come in to get checked by a study doctor if necessary
- Have blood tests to check on the health of your liver/kidneys, if the study doctor thinks this is necessary

**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 or other vaginal infections, you will:**

- Have an exam of your genital area and inside your vagina
- Have tests for infections, if the study doctor thinks this is necessary
- Get treatment for most types of infections if you need it

**If you become pregnant:**

- You may be offered participation in MTN-018C and MTN-016, studies for pregnant women and their infants, if these studies are available at your study site
- Study staff will stay in contact with you to learn the results of your pregnancy

**If you become infected with hepatitis B, you will:**

- Stop using gel or tablets, but stay in the study as originally planned
- Give blood to test for liver problems, if you are in a group that uses tablets
- Be given referrals for medical care and other services you may need

**If you have a rash and fever:**

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

**If you withdraw or are discontinued from the study:**

- You must return your study product

**If you become infected with HIV:**

If you may have been infected with HIV, you will have at least three tests to confirm your results. Each time blood is drawn for these tests, you will also give blood (XX mL) to test for the amount of HIV in your blood, whether any HIV in your blood is resistant to medications used to treat HIV, and your CD4+ T-cell count. The CD4+ T-cell count is a test that measures the amount of damage HIV has done to your immune system. The immune system is the part of the body that fights off germs and infections. Results of resistance tests will be given to you. If HIV tests confirm that you have HIV, you will stop using gel or tablets. If you do not have your study products with you, a staff person may go to your home to collect them. We will also test your baby for HIV if you cannot get this test elsewhere. If you become HIV-infected while on study, you will discontinue study product and have follow-up visits at one month, 3 months, 6 months and 12 months after testing positive for HIV, either through MTN-015 (a study for those infected with HIV) or this study.

We will counsel you and refer you for medical care and other available services. We also will refer you to another study called MTN-015. You will be asked to have additional blood drawn after your HIV infection was detected. This blood will be used to check:



- Your CD4+ T-cell count
- The amount of HIV in your blood
- Whether the HIV in your blood is resistant to medications used to treat HIV

### **POSSIBLE FUTURE TESTS**

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

### **RISKS AND/OR DISCOMFORTS**

#### MOTHERS

Whenever your blood is drawn, you may:

- Feel discomfort or pain when your blood is drawn
- Feel dizzy or faint, but most women do not have this reaction
- Have more than expected bleeding, a bruise, swelling, small clot, or infection where the needle goes in your arm or finger

When you have genital exams, you may:

- Feel discomfort in your genital area and inside your vagina
- Have a small amount of vaginal bleeding which will stop shortly after the exam

When you answer computer questions:

There are few risks to you from answering the computer questions. Your answers will be stored on a larger computer here at [study site] that can only be accessed by authorized staff. Your answers will be transferred to the same place where your study forms are sent. As with all of your study information, every effort will be made to keep your personal information confidential. Your answers will be identified by your study number only (not your name). However, absolute confidentiality cannot be guaranteed.

#### **Gel Groups**

If you are in a group that uses gel, the gel could cause some bad effects. Some, but not all, women who used the gels in other studies have had:

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

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

#### **Tablet Groups**

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

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

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

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

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

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

**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. It is for this reason that you must stop using your study product if you get HIV. Study doctors are available to discuss this with you. If you do become infected with HIV during CHOICE, they can do blood tests to show which HIV medications might work best for you.

### **BABIES IN THE PK GROUP**

Whenever blood is drawn, your baby may:

- Feel discomfort, pain, or dizziness
- Have a bruise, swelling, clot, or possible infection where the needle goes in for the blood draw

[ANY POTENTIAL RISKS IDENTIFIED IN THE MTN-008 STUDY LACTATION COHORT WILL BE INSERTED HERE IN A MODIFICATION]

Your baby could have these effects or other effects that we do not yet know about. A small amount of study drug may pass from the study products into your breast milk. If study drug passed into your breast milk, it is not expected that the amount would be enough to cause health problems for the baby. However, the effects of exposure on a nursing baby are unknown. If your breast milk did absorb some study drug, possible side effects in the baby could include increased liver function tests, diarrhea, nausea, vomiting, and 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 become pregnant, the unborn baby could be exposed to study product.

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-B. 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 *[if applicable: and testing for other infections passed through sex]*. If you or your partner(s) have infections passed through sex, other than HIV and hepatitis B infection, you will be offered medicine to treat them, if needed. This study does not provide medication for treatment of HIV/AIDS. If you become infected with HIV, you will 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 learned during this study that might affect your willingness to stay in CHOICE-B, when other 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 if you or your baby could be harmed if you continued to take gel or tablets. Even if you stop using gel or tablets, you and your baby will stay in the study and have your monthly visits as planned (unless you are HIV-infected and join MTN-015).

## **IF YOU STOP BREASTFEEDING**

If you stop breastfeeding, you will continue with your study drug and stay in the study as planned. Your baby will have a final visit to check physical exam and growth, and then will stop study visits. Additional tests for the PK Group will also stop.

## **WHY YOU AND YOUR BABY 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.
- Study staff feel that staying in the study would be harmful to you or your baby.
- You are not willing to find out your HIV test results.
- You are not able to attend clinic visits or complete the study procedures.
- Other reasons, decided by the study staff.

If you withdraw early from the study, we will ask you and your baby to come in for a final visit with all the exams and tests listed above.

## **ALTERNATIVES TO PARTICIPATION**

[*Sites to include/amend the following if applicable:* There may be other studies here or in the community. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing, hepatitis B vaccine, and contraception. There may be other places your baby can go for check-ups. We will tell you about those places if you wish.]

## **COSTS TO YOU**

There is no cost to you for you and your baby to be in CHOICE-B. 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. PK Group: You will receive [\$xx] for you and your baby's time and effort for being in the PK Group.

## **CONFIDENTIALITY**

Efforts will be made to keep your and your baby's personal information confidential. However, it is not possible to guarantee confidentiality. Personal information may be

disclosed if required by law. Staff will use personal information, if needed, to verify that you and your baby 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 your baby's name, or identify you or your baby 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 web site will include a summary of the results. You can search this website at any time.

Your and your baby's records may be reviewed by MTN and study staff, as well as:

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

*[Sites to include/amend the following if applicable:] [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will contact them, according to confidentiality guidelines of [health authority].*

## **RESEARCH-RELATED INJURY**

*[Sites to specify institutional policy:] If you or your baby is injured, [institution] will give you/your baby immediate treatment for injuries. You [will/will not] have to pay for this. You will be told where you can get additional treatment for you/your baby. 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 sub-study, or if you or your baby have a research-related injury, you should contact [insert name] at [insert contact information]. If you have questions about your or your baby's rights as a research participant, you should contact [insert name or title of person on the IRB/EC or other organization appropriate for the site] at [insert physical address and telephone number]. If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or Community Advisory Board 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 for you and your baby to join the study, please sign your name or make your mark below.

List all participant infants:	This infant may join PK Group-Yes/No
1) _____	_____
2) _____	_____
3) _____	_____

I agree for me to join the PK Group:

\_\_\_\_\_ Yes

\_\_\_\_\_ No

_____ Participant Name (mother) (print)	_____ Participant Signature/Mark	_____ Date
---	-------------------------------------	---------------

_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff Signature	_____ Date
---	--------------------------------	---------------

_____ Witness Name (print)	_____ Witness Signature	_____ Date
-------------------------------	----------------------------	---------------

If required by IRB:

_____ Father's Name (print)	_____ Father's Signature/Mark	_____ Date
-----------------------------------	----------------------------------	---------------

## **APPENDIX VIII: SAMPLE INFORMED CONSENT (STORAGE AND FUTURE TESTING OF SPECIMENS – MOTHERS)**

**DIVISION OF AIDS, NIAID, NIH**

**MTN-018B**

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

**[insert date]**

**PRINCIPAL INVESTIGATOR:** [insert name]

**PHONE:** [insert number]

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

### **INTRODUCTION**

You have decided to take part in the CHOICE-B study, funded by the United States National Institutes of Health (NIH). While you are in CHOICE-B, there may be blood and breast milk taken from you that might be useful for future research. Breast milk is only collected from mothers who consent to join the PK Group. You are being asked to agree to storage of this blood and breast milk. This consent form tells you about the collection, storage, and use of your blood and breast milk. Please ask study staff any questions you may have. You will be asked to sign or make your mark on this form to indicate whether you agree to have your blood and breast milk 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 and breast milk collected and tested as part of CHOICE-B. During CHOICE-B, your blood and breast milk 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 and breast milk, after the CHOICE-B study is done, to use for future testing. If you agree to this, no additional blood and breast milk will be taken from you. Only leftover blood and breast milk will be kept and used for future testing.

### **HOW WILL YOU USE MY BLOOD AND BREAST MILK?**

Your blood and breast milk 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 and breast milk cells and substances in your blood and breast milk 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 and breast milk without first explaining the test to you and obtaining your permission. Some of these tests may be done outside of your country.

The researchers do not plan to contact you or your regular doctor with any results from tests done on your stored blood and breast milk. This is because research tests are often done using ways that are experimental, so the results do not usually help doctors manage your health. If a rare situation comes up in which the researchers decide that a test result is important for your health, the researchers will notify your study doctor and your study doctor will try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your contact information. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name and contact information.

Your blood and breast milk will not be sold or used directly to produce commercial products. Research studies wishing to use your blood and breast milk 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 AND BREAST MILK BE STORED?**

There is no time limit on how long your blood and breast milk will be stored. Your blood and breast milk 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 AND BREAST MILK BENEFIT ME?**

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

#### **WHAT ARE THE RISKS?**

There are few risks related to storing your blood and breast milk. When tests are done on the stored blood and breast milk, there is a small but possible risk to your privacy. It is possible that if others found out information about you that is learned from tests (such as information about your genes), it could cause you problems with your family (having a family member learn about a disease that may be passed on in families or learning who is the true parent of a child) or problems getting a job or insurance.

#### **WHAT ABOUT CONFIDENTIALITY?**

To keep your information private, your blood and breast milk 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 and breast milk to study, they will not be given your personal information. 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 web site will include a summary of the results. You can search this website at any time.

The results of future tests will not be included in your health records. Any publication about the results of future tests will not use your name or identify you personally. The researchers will do everything they can to protect your privacy. Every effort will be made to keep your personal information confidential. However, it is not always possible to guarantee confidentiality. Your personal information may be disclosed if required by law.

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

- the United States Food and Drug Administration (FDA)
- the United States Office for Human Research Protections
- the United States NIH or its study monitors
- [insert applicable local authorities, e.g., Ministry of Health, medicine control authority]
- [insert name of applicable Institutional Review Board (IRB)/Ethics Committee (EC)]
- the organizations that supply gel (CONRAD) and tablets (Gilead Sciences)

### **WHAT ARE MY RIGHTS?**

Allowing your blood and breast milk to be stored is completely voluntary. If you decide not to have any blood and breast milk stored other than what is needed to complete CHOICE-B, you can still remain in CHOICE-B, and your leftover blood and breast milk will be destroyed. If you decide now that your blood and breast milk can be stored for future research, you may change your mind at any time. However, you must contact your study doctor or nurse and let them know that you no longer want your samples used for future research. Your blood and breast milk 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 and breast milk, contact [insert the name of the investigator] at [insert physical address and telephone number].

If you have questions about your rights related to the storage and future testing of your blood and breast milk 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 Community Advisory Board 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-018B 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

---

- 1 Promoting proper feeding for infants and young children. 2011. (Accessed 06/09/2011, 2011, at <http://www.who.int/nutrition/topics/infantfeeding/en/index.html>.)
- 2 Administration FaD. Draft Guidance for Industry: Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling. Rockville, MD: US FDA, Office of Training and Communications, Division of Drug Information; 2005.
- 3 Bennett P, ed. Drugs and Human Lactation. Amsterdam: Elsevier; 1988.
- 4 American Academy of Pediatrics. The Transfer of Drugs and Other Chemicals Into Human Milk. Pediatrics 108: No. 3 September 1, 2001, pp. 776 -789.
- 5 Child and adolescent health and development: breastfeeding. 2011. (Accessed June 9, 2011, at [http://www.who.int/child\\_adolescent\\_health/topics/prevention\\_care/child/nutrition/breastfeeding/en/](http://www.who.int/child_adolescent_health/topics/prevention_care/child/nutrition/breastfeeding/en/).)
- 6 Gilead Sciences. Viread<sup>®</sup> (tenofovir disoproxil fumarate) tablets. Package Insert, August 2012.
- 7 MTN-018 Protocol. (Accessed June 7, 2012 at <http://www.mtnstopshiv.org/studies/2856>).
- 8 Gilead Sciences. Emtriva<sup>®</sup> (emtricitabine) tablets. Package Insert, November 2011.
- 9 Gilead Sciences. Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate) tablets. Package Insert, July 2012.
- 10 CONRAD. Investigator's Brochure: Tenofovir Gel (GS-1278). 12 November 2010.
- 11 MTN-003 Protocol. (Accessed June 7, 2012 at <http://www.mtnstopshiv.org/studies/70>).
- 12 Benaboud S, Pruvost A, Coffie P et al. Concentrations of Tenofovir and Emtricitabine in Breast Milk of HIV-1-Infected Women in Abidjan, Côte d'Ivoire, in the ANRS 12109 TEmAA Study, Step 2. Antimicrob. Agents Chemother 2011; 55 (3): 1315-1317.

- 
- 13 HPTN 057. (Accessed June 7, 2012 at [http://www.hptn.org/research\\_studies/hptn057.asp](http://www.hptn.org/research_studies/hptn057.asp)).
- 14 PROMISE Study. (Accessed June 7, 2012 at <http://clinicaltrials.gov/ct2/show/NCT01061151>).
- 15 Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* 2010;329:1168-74.
- 16 MTN-008 Protocol. (Accessed June 7, 2012 at <http://www.mtnstopshiv.org/studies/1637>).
- 17 Kovacs CS and Kronenberg HM. Maternal-Fetal Calcium and Bone Metabolism During Pregnancy, Puerperium, and Lactation. *Endocrine Reviews* 1997; 18 (6): 832-872.
- 18 IMPAACT P1084S. (Accessed June 7, 2012 at <http://clinicaltrials.gov/ct2/show/NCT01066858>).
- 19 MTN-003B Protocol. (Accessed June 7, 2012 at <http://www.mtnstopshiv.org/studies/1415>).
- 20 WHO. Antiretroviral therapy for HIV infection in adults and adolescents . 2010. (Accessed June 7, 2012 at <http://www.who.int/hiv/pub/arv/adult2010/en/index.html>).
- 21 The WHO Child Growth Standards. (Accessed June 7, 2012 at <http://www.who.int/childgrowth/en/>).
- 22 Mayer KH, Maslankowski LA, Gai F, et al. Safety and tolerability of tenofovir vaginal gel in abstinent and sexually active HIV-infected and uninfected women. *AIDS* 2006;20:543-51.
- 23 Schwartz, JL et al. Safety evaluation of 1% tenofovir gel in healthy men. *Int J STD AIDS*. 2009 Jun;20(6):384-6.