

**MTN-042**

**Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy**

**Microbicide Trials Network**

**Funding Agencies:**

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

**Grant Numbers:**

**UM1AI068633, UM1AI068615, UM1AI106707**

**DAIDS Protocol ID: 38544**

**IND Sponsor:**

**DAIDS**

**IND #: 139,598**

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**Version 2.0**

**May 20, 2021**

MTN-042

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TABLE OF CONTENTS

TABLE OF CONTENTS .....	2
LIST OF ABBREVIATIONS AND ACRONYMS .....	6
PROTOCOL TEAM ROSTER .....	10
INVESTIGATOR SIGNATURE FORM .....	19
PROTOCOL SUMMARY .....	20
1 KEY ROLES .....	24
1.1 Protocol Identification .....	24
1.2 Sponsor and Monitor Identification .....	24
1.3 Medical Officer .....	25
1.4 Clinical Laboratories .....	25
1.5 Data Centers .....	26
1.6 Study Operations .....	26
2 INTRODUCTION .....	27
2.1 Pregnancy and HIV in Sub-Saharan Africa .....	27
2.2 Description of DPV VR and Truvada Tablet .....	28
2.3 Nonclinical Studies – DPV .....	30
2.4 Nonclinical Studies – Truvada .....	32
2.5 Clinical Studies – DPV .....	33
2.6 Clinical Studies – Truvada .....	37
2.7 Cross-resistance to ART .....	40
2.8 Acceptability and Adherence .....	41
2.9 Rationale for Study Design .....	43
3 OBJECTIVES .....	46
3.1 Primary Objectives .....	46
3.2 Secondary Objectives .....	46
3.3 Exploratory Objectives .....	47
4 STUDY DESIGN .....	47
4.1 Identification of Study Design .....	47
4.2 Summary of Major Endpoints .....	47
4.3 Description of Study Population .....	48
4.4 Time to Complete Accrual .....	48
4.5 Expected Duration of Participation .....	49
4.6 Sites .....	49
5 STUDY POPULATION .....	49
5.1 Selection of the Study Population .....	49
5.2 Inclusion Criteria .....	50
5.3 Exclusion Criteria .....	51
5.4 Infant Enrollment .....	52
5.5 Co-enrollment Guidelines .....	53

6	STUDY PRODUCT .....	53
6.1	Regimen.....	53
6.2	Administration .....	54
6.3	Study Product Formulation.....	54
6.4	Supply and Accountability .....	55
6.5	Retrieval of Study Product.....	56
6.6	Concomitant Medications and Practices .....	56
6.7	Prohibited Medications .....	56
6.8	Condoms.....	57
7	STUDY PROCEDURES .....	57
7.1	Pre-Screening .....	58
7.2	Visit 1: Screening Visit .....	59
7.3	Visit 2: Enrollment Visit (Day 0).....	60
7.4	Follow-up Visits/Contacts Prior to Pregnancy Outcome.....	61
7.5	Follow-up Visits After Pregnancy Outcome.....	66
7.6	Semi-annual PPO Visits/Early SEV for Infants.....	70
7.7	Follow-up Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product.....	71
7.8	Final Contact.....	74
7.9	Behavioral Evaluations.....	74
7.10	Counseling .....	75
7.11	Clinical Evaluations and Procedures.....	75
7.12	Laboratory Evaluations .....	77
7.13	Calculation of Gestational Age .....	78
7.14	Specimen Management .....	79
7.15	DAIDS Laboratory Oversight.....	79
7.16	Biohazard Containment.....	79
8	ASSESSMENT OF SAFETY .....	80
8.1	Safety Monitoring .....	80
8.2	Clinical Data Safety Review .....	80
8.3	Adverse Events Definitions and Reporting Requirements.....	80
8.4	Expedited Adverse Event Reporting Requirements .....	84
8.5	Social Harms Reporting .....	85
8.6	Regulatory Requirements .....	85
9	CLINICAL MANAGEMENT .....	86
9.1	Grading System .....	86
9.2	Dose Modification Instructions .....	86
9.3	General Criteria for Temporary/Permanent Discontinuation of Study Product ..	86
9.4	Temporary Product Hold/Permanent Discontinuation in Response to Observed Adverse Events.....	87
9.5	Other Clinical Findings .....	87
9.6	HIV Infection.....	90
9.7	Criteria for Early Termination of Study Participation.....	90
10	ANALYTICAL CONSIDERATIONS.....	91
10.1	Overview and Summary of Design.....	91
10.2	Study Endpoints.....	91

10.3	Primary Study Hypotheses.....	92
10.4	Sample Size and Power Calculations .....	93
10.5	Participant Accrual, Follow-up and Retention.....	94
10.6	Randomization .....	95
10.7	Data and Safety Monitoring Procedures .....	95
10.8	Analyses.....	96
11	DATA HANDLING AND RECORDKEEPING .....	97
11.1	Data Management Responsibilities.....	97
11.2	Source Documents and Access to Source Data/Documents .....	98
11.3	Quality Control and Quality Assurance .....	98
12	CLINICAL SITE MONITORING .....	98
13	HUMAN SUBJECTS PROTECTIONS .....	99
13.1	Institutional Review Boards/Ethics Committees .....	99
13.2	Protocol Registration.....	99
13.3	Study Coordination.....	100
13.4	Risk Benefit Statement.....	100
13.5	Informed Consent Process.....	103
13.6	Participant Confidentiality.....	104
13.7	Special Populations.....	104
13.8	Compensation .....	108
13.9	Communicable Disease Reporting.....	108
13.10	Access to HIV-related Care.....	108
13.11	Study Discontinuation .....	108
14	PUBLICATION POLICY.....	109
15	APPENDICES.....	109
	APPENDIX I: Table of Visits and Study Procedures – Mothers .....	110
	APPENDIX II: Table of Visits and Study Procedures – Infants.....	113
	APPENDIX III: Algorithm For HIV Testing – SCREENING/ENROLLMENT .....	114
	APPENDIX IV: Algorithm For HIV Testing – FOLLOW-UP .....	115
	APPENDIX V: Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORT 1.....	116
	APPENDIX VI: Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORT 2.....	130
	APPENDIX VII: Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORT 3.....	144
	APPENDIX VIII: Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography) – INFANT.....	158
	REFERENCES.....	169

### List of Figures and Tables

Figure 1:	Study Visit Schedule – Cohort 1 .....	21
Figure 2:	Study Visit Schedule – Cohort 2 .....	22
Figure 3:	Study Visit Schedule – Cohort 3 .....	22
Figure 4:	Expected Maximum Duration of Product Use by Study Cohort .....	54
Figure 5:	Study Visit Schedule – Cohort 1 .....	57
Figure 6:	Study Visit Schedule – Cohort 2 .....	58

Figure 7: Study Visit Schedule – Cohort 3 .....	58
Table 1: Retrieval of Study Product .....	56
Table 2: Visit 1 – Screening Visit .....	59
Table 3: Visit 2 – Enrollment Visit .....	60
Table 4: Phone Contacts Prior to Pregnancy Outcome .....	62
Table 5: Bi-weekly Visits After 36 <sup>th</sup> Week of Gestation .....	62
Table 6: 2-week Visit (Cohorts 2-3) .....	64
Table 7: 4-week Visit(s) (Cohorts 2-3) .....	65
Table 8: PPO Visit – Mothers.....	66
Table 9: PPO Visit – Infants.....	67
Table 10: 1-week PPO Phone Contact – Mothers .....	68
Table 11: 1-week PPO Phone Contact – Infants .....	68
Table 12: 6-week PPO/SEV/Early SEV – Mothers .....	68
Table 13: 6-week PPO Visit – Infants .....	70
Table 14: Semi-annual PPO Visits/Early SEV .....	70
Table 15. Protocol-required Infant Blood Draw Volumes by Study Arm and by Clinic Visit .....	78
Table 16. Guidelines for Redating based on Ultrasonography .....	79
Table 17. Probability (%) of observing an event given different “true” event rates by cohort size .....	93
Table 18. Confidence intervals for endpoint rate (proportion of participants with endpoint) given number of endpoints (rows) in with number of participants (columns).....	94

## MTN-042

### Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

#### LIST OF ABBREVIATIONS AND ACRONYMS

ADAPT	Alternative Dosing to Augment PrEP Pill Taking
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine transaminase
ANC	antenatal clinic
ART	antiretroviral therapy
ARV	antiretroviral
ASCP	American Society of Clinical Pathology
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
AST	aspartate aminotransferase
AUC	area under the curve
AVAC	Global Advocacy for HIV Prevention
BMC	bone mineral content
BPM	beats per minute
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BUN	blood urea nitrogen
BV	bacterial vaginosis
CAB	Community Advisory Board
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CBC	complete blood count
CDC	U.S. Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
$C_{max}$	maximum concentrations
$C_{min}$	minimum concentrations
CMRB	Clinical Microbicide Research Branch
CONRAD	Contraception Research and Development
CRF	case report form
CRMS	Clinical Research Management System
CROI	Conference on Retroviruses and Opportunistic Infections
CRL	crown-rump length
CRS	clinical research site
CT	Chlamydia trachomatis
CTA	clinical trial agreement
CTU	clinical trials unit
CVF	cervicovaginal fluid
CWG	Community Working Group
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	di-aminopyrimidine
DBS	dried blood spot
DLV	delavirdine
DNA	deoxyribonucleic acid

DOD	directly observed dosing
DPV	dapivirine
DREAM	Dapivirine Ring Extended Access and Monitoring
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EBL	estimated blood loss
EC	Ethics Committee
EC <sub>50</sub>	50% effective concentration
EDD	estimated delivery date
EFV	efavirenz
EMA	European Medicines Agency
FDA	Food & Drug Administration (U.S.)
FHCRC	Fred Hutchinson Cancer Research Center
FHR	fetal heart rate
FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
FTP	File Transfer Protocol
g	grams
GA	gestational age
GC	<i>Neisseria gonorrhoeae</i>
GCP	Good Clinical Practice
GEE	generalized estimating equations
GMP	good manufacturing practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	health care provider
HEENT	Head, Eye, Ear, Nose and Throat
HHS	Department of Health and Human Services (U.S.)
HIV-1	human immunodeficiency virus-1
HOPE	HIV Open-label Prevention Extension
HPTN	HIV Prevention Trials Network
HSV	herpes simplex virus
IAS	International AIDS Society
IATA	International Association of Air Transport
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICRC	International Clinical Research Center
IDI	in-depth interview
IMPAACT	International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group
IND	Investigational New Drug
IoR	Investigator of Record
IPM	International Partnership for Microbicides
iPrEX	Iniciativa Profilaxis Pre-Exposición
IPV	intimate partner violence
IQR	interquartile range
IRB	Institutional Review Board
IRP	Interim Review Panel
KOH	potassium hydroxide
3TC	lamivudine
LC	Laboratory Center

LDMS	Laboratory Data Management System
LMP	last menstrual period
LOC	Leadership and Operations Center
µg	microgram
µM	micromolar ( $10^{-3}$ mol/m <sup>3</sup> )
mg	milligram
mL	milliliter
MO	Medical Officer
MSC	Mail Stop Code
MSM	men who have sex with men
MTCT	mother-to-child transmission
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
MU-JHU	Makerere University – John Hopkins University Research Collaboration
NAAT	nucleic acid amplification test
ng	nanogram
NGO	non-governmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NICHHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIMH	National Institute of Mental Health
nM	nanomolar ( $10^{-6}$ mol/m <sup>3</sup> )
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NRTI	nucleoside reverse transcriptase inhibitor
NVP	nevirapine
OHRP	Office for Human Research Protections
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
pg	picogram
PI	Principal Investigator
PID	pelvic inflammatory disease
PK	pharmacokinetic
PMTCT	prevention of mother-to-child transmission
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc.
PPO	post-pregnancy outcome
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PROM	premature rupture of membranes
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PTID	participant identification
PUEV	Product Use End/Early Termination Visit
RE	regulatory entity
RHI	Reproductive Health and HIV Institute
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event

SAHPRA	South African Health Products Regulatory Authority
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SCORE	Site Clinical Operations and Research Essentials
SDMC	Statistical Data Management Center
SEV	study exit visit
SMC	Study Monitoring Committee
SOP	standard operating procedure
SSA	sub-Saharan Africa
SSP	study specific procedure(s)
STI	sexually transmitted infection
SUSAR	suspected, unexpected serious adverse reaction
TDF	tenofovir disoproxil fumarate
TEAE	treatment emergent adverse event
TFV	tenofovir
TFV-DP	tenofovir diphosphate
TMC-120	dapivirine
TV	trichomonas vaginalis
UA	urinalysis
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UPMC	University of Pittsburgh Medical Center
URAI	unprotected receptive anal intercourse
USA	United States of America
UTI	urinary tract infection
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VR	vaginal ring
WHO	World Health Organization
ZDV	zidovudine

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**MTN-042**

**Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy**

**INVESTIGATOR SIGNATURE FORM**

Version 2.0; May 20, 2021

A Study of the Microbicide Trials Network

**Funded by:**

Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases  
US Eunice Kennedy Shriver National Institute of Child Health and Human Development  
US National Institute of Mental Health  
US National Institutes of Health (NIH)

**IND Sponsor:**

DAIDS (DAIDS Protocol ID: 38544)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference for Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain all study documentation for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. DAIDS will inform the investigator/institution as to when these documents no longer need to be retained.

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

\_\_\_\_\_  
Name of Investigator of Record (print)

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

## MTN-042

### Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

#### PROTOCOL SUMMARY

<b>Short Title:</b>	DELIVER: A Phase 3b Safety Study of the Dapivirine Ring and PrEP in Pregnant Women
<b>IND Sponsor:</b>	DAIDS
<b>Funders:</b>	Division of AIDS, NIAID, NIMH, NICHD, US NIH
<b>Protocol Chair:</b>	Katherine Bunge, MD, MPH Bonus Makanani, MBBS, FCOG(SA)
<b>Protocol Co-Chair:</b>	Lee Fairlie, MBChB, FCPaedS
<b>Sample Size:</b>	Approximately 550 women and their infants
<b>Study Population:</b>	Healthy, HIV-uninfected pregnant females, 18-40 (inclusive) years old, with an uncomplicated singleton pregnancy who are willing to be randomized to study product, and their infants
<b>Study Sites:</b>	MTN-042 site(s) selected by the MTN Executive Committee
<b>Study Hypotheses:</b>	<ul style="list-style-type: none"><li>• Daily use of Truvada oral tablet or dapivirine (DPV) vaginal matrix ring (25 mg) inserted once every 4 weeks will be generally safe and well-tolerated by the participants and their fetuses/infants.</li><li>• Participants who use Truvada oral tablet daily or insert the DPV vaginal matrix ring (25 mg) once every 4 weeks will experience similar distributions of pregnancy outcomes to the general population.</li></ul>
<b>Study Design:</b>	Phase 3b, two-arm, open label, multi-site, randomized (2:1 in Cohorts 1-2 and 4:1 in Cohort 3) trial (DPV vaginal ring [VR], Truvada oral tablet), with onset of dosing period to occur within the following gestational age (GA) ranges:  Cohort 1: 36 0/7 weeks – 37 6/7 weeks 150 women Cohort 2: 30 0/7 weeks – 35 6/7 weeks 150 women Cohort 3: 12 0/7 weeks – 29 6/7 weeks 250 women
<b>Study Duration:</b>	The total duration of study participation for each participant will vary depending on gestational age at time of enrollment and length of pregnancy prior to pregnancy outcome, and will range from approximately 12 weeks or less for Cohort 1 to approximately 36 weeks or less for Cohort 3. Participants who become infected with

HIV will continue in study follow-up with a modified study visit/procedure schedule for a minimum of twelve months. Also, infants born to MTN-042 participants will be followed for approximately 52 weeks (i.e., one year).

**Study Products:**

- Silicone elastomer matrix VR containing 25 mg of DPV
- Oral tablets (Truvada) containing 200 mg emtricitabine/300 mg tenofovir disoproxil fumarate (FTC/TDF)

**Study Regimen:**

Within Cohorts 1 and 2, participants will be randomized to the above study products in a 2:1 ratio (100 VR: 50 tablet). Cohort 3 participants will be randomized to the above study products in a 4:1 ratio (200 VR: 50 tablet). Participants randomized to the DPV VR will use one VR continuously for approximately one month, replacing the VR each month. Participants using Truvada tablet will take one tablet orally per day. Participants will use their assigned study product until their pregnancy outcome but no later than 41 6/7 weeks of gestation.

**Figure 1: Study Visit Schedule – Cohort 1**

<b>Cohort 1</b>	Screening
Enrollment Window	Enrollment
36 0/7 weeks of gestation– 37 6/7 weeks of gestation	Every odd-numbered week after Enrollment (e.g., follow-up weeks 1, 3, 5) until pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Every even-numbered week after Enrollment (e.g., follow-up weeks 2, 4, 6) until pregnancy outcome
<b>Infants enroll</b> →	Post-pregnancy outcome (delivery hospital/facility or clinic)
	1-week post-pregnancy outcome (phone, home or clinic as needed per local standard of care)
<b>Mothers exit</b> →	Approximately 6 weeks post-pregnancy outcome
	Approximately 6 months post-delivery
	Approximately 12 months post-delivery

**Figure 2: Study Visit Schedule – Cohort 2**

<b>Cohort 2</b>	Screening
Enrollment Window	Enrollment
	30 0/7 weeks of gestation – 35 6/7 weeks of gestation
	1-week (phone, home or clinic as needed per local standard of care)
	2-week
	3-week (phone, home or clinic as needed per local standard of care)
	4-week
	Every odd-numbered week after 36th week of gestation (e.g., follow-up weeks 5, 7, 9) until pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Every even-numbered week including and after 36th week of gestation (e.g., follow-up weeks 6, 8, 10) until pregnancy outcome
<b>Infants enroll</b> →	Post-pregnancy outcome visit (delivery hospital/facility or clinic)
	1-week post-pregnancy outcome (phone, home or clinic as needed per local standard of care)
<b>Mothers exit</b> →	Approximately 6 weeks post-pregnancy outcome
	Approximately 6 months post-delivery
	Approximately 12 months post-delivery

**Figure 3: Study Visit Schedule – Cohort 3**

<b>Cohort 3</b>	Screening
Enrollment Window	Enrollment
	12 0/7 weeks of gestation – 29 6/7 weeks of gestation
	1-week (phone, home or clinic as needed per local standard of care)
	2-week
	3-week (phone, home or clinic as needed per local standard of care)
	4-week and every 4 weeks until 36th week of gestation
	Every odd-numbered week after 36th week of gestation (e.g., follow-up weeks 19, 21, 23) until pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Every even-numbered week including and after 36th week of gestation (e.g., follow-up weeks 20, 22, 24) until pregnancy outcome
<b>Infants enroll</b> →	Post-pregnancy outcome visit (delivery hospital/facility or clinic)
	1-week post-pregnancy outcome (phone, home or clinic as needed per local standard of care)
<b>Mothers exit</b> →	Approximately 6 weeks post-pregnancy outcome
	Approximately 6 months post-delivery
	Approximately 12 months post-delivery

**Primary Objectives:**

**Maternal and Infant Safety:** To describe the maternal and infant safety profile associated with study product exposure during pregnancy

**Pregnancy Outcomes:** To describe the pregnancy outcomes associated with study product exposure during pregnancy

**Primary Endpoints:**

**Maternal Safety (composite)**

- All serious adverse events, including maternal deaths
- All Grade 3 or higher adverse events (AE) as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])

**Infant Safety (composite)**

- All serious adverse events, including infant deaths and congenital anomalies
- All Grade 3 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017

**Pregnancy Outcomes**

- Frequency of the following pregnancy outcomes:
  - Full term live birth ( $\geq 37$  0/7 weeks)
  - Premature live birth ( $< 37$  0/7 weeks)
  - Pregnancy loss ( $\geq 20$  0/7 weeks)
  - Pregnancy loss ( $< 20$  0/7 weeks)

**Secondary Objectives:**

**Pregnancy Complications:** To describe pregnancy complications associated with study product exposure during pregnancy

**Infant Drug Levels:** To describe infant levels of study drugs associated with study product exposure during pregnancy

**Adherence:** To characterize adherence to open label use of the DPV VR (25 mg) and oral Truvada in pregnant women

**Acceptability:** To characterize acceptability of open label use of the DPV VR (25 mg) and oral Truvada in pregnant women

**Secondary Endpoints:**

**Pregnancy Complications**

- Frequency of the following pregnancy complications:
  - Hypertensive disorders of pregnancy
  - Chorioamnionitis
  - Puerperal sepsis and endometritis
  - Antepartum, intrapartum and postpartum hemorrhage
  - Preterm premature rupture of membranes (PROM)
  - Fever of unclear etiology

**Infant Drug Levels**

- Infant blood tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) concentrations
- Infant plasma DPV concentrations

**Adherence**

- Maternal blood TFV-DP and FTC-TP concentrations
- Maternal plasma DPV concentrations
- Participant report of frequency of study product use (e.g., missed doses for oral Truvada and VR removal/expulsions [voluntary and involuntary] and duration without VR in vagina)
- Residual drug levels in returned VRs

**Acceptability**

- Self-reported attitudes about study product attributes and willingness to use study products during pregnancy
- Proportion of participants who find the study products to be at least as acceptable as other HIV prevention methods

**Exploratory Objectives:**

**Genital Microenvironment:** To describe changes in the genital microenvironment associated with study product exposure during pregnancy

**Exploratory Endpoints:****Genital Microenvironment**

- Genital microflora characteristics in Gram stain and quantitative polymerase chain reaction (PCR)
- Biomarker expression in vaginal secretions

## 1 KEY ROLES

### 1.1 Protocol Identification

Protocol Title: Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

Protocol Number: MTN-042

Date: May 20, 2021

### 1.2 Sponsor and Monitor Identification

Funding Agencies: US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID)  
National Institutes of Health (NIH)

5601 Fishers Lane  
Rockville, MD 20852 USA

US National Institute of Mental Health (NIMH)  
6001 Executive Boulevard  
Rockville, MD 20852 USA

US *Eunice Kennedy Shriver* National Institute of Child Health and  
Human Development (NICHD)  
6100 Executive Boulevard  
Bethesda, MD 20892 USA

Pharmaceutical Company  
Collaborators:

Gilead Sciences, Inc.  
333 Lakeside Drive  
Foster City, CA 94404 USA

International Partnership for Microbicides (IPM)  
8401 Colesville Road, Suite 200  
Silver Spring, MD 20910 USA

IND Sponsor:

DAIDS/NIAID/NIH  
5601 Fishers Lane  
Rockville, MD 20852 USA

Monitor:

Pharmaceutical Product Development, Inc. (PPD)  
929 North Front Street  
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### **1.3 Medical Officer**

Medical Officer:

Jeanna M. Piper, MD  
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### **1.4 Clinical Laboratories**

Laboratory Center:

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204 Craft Avenue  
Pittsburgh, PA 15213 USA

Pharmacology:

MTN Pharmacology Core  
Johns Hopkins University; 600 N. Wolfe Street, Osler 527  
Baltimore, MD 21287 USA

MTN Pharmacology Core  
Clinical Pharmacology Analytical Laboratory (CPAL)/Marzinke Lab  
4940 Eastern Avenue  
Mason F. Lord (MFL) Center Tower Suite 6000, Room 621  
Baltimore, Maryland 21224 USA

MTN Pharmacology Core  
University of Colorado School of Pharmacy  
12850 E. Montview Blvd. V20-4101; Mail Stop C238  
Aurora, CO 80045 USA

## **1.5 Data Centers**

Data Center: MTN Statistical Data and Management Center (SDMC) Statistical Center for HIV/AIDS Research & Prevention (SCHARP)/Fred Hutchinson Cancer Research Center (FHCR) Center (FHCR)  
1100 Fairview Avenue N., LE-400  
PO Box 19024  
Seattle, WA 98109-1024 USA

Qualitative Data Center: Women's Global Health Imperative, RTI International  
2150 Shattuck Avenue, Suite 800  
Berkeley, CA 94704 USA

## **1.6 Study Operations**

Study Operations: MTN LOC - FHI 360  
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PO Box 21059  
Durham, NC 27701 USA

## 2 INTRODUCTION

### 2.1 Pregnancy and HIV in Sub-Saharan Africa

Reproductive-age women are disproportionately affected by HIV-1, accounting for 56% of adults living with HIV-1 in sub-Saharan Africa.<sup>1</sup> In eastern and southern Africa, for example, young women (aged 15–24 years) accounted for 26% of new HIV infections in 2016 despite making up just 10% of the population.<sup>2</sup> AIDS-related illnesses remain the second leading cause of death for young women aged 15–24 years in Africa.<sup>2</sup> These data clearly show reproductive women in sub-Saharan Africa are at high risk of HIV acquisition.

Furthermore, findings suggest that biological and behavioural changes during and after pregnancy may further increase a woman's HIV risk. Gray et al have shown that pregnancy produces a two-fold increase in susceptibility to HIV acquisition<sup>3</sup>, and a recent analysis found that the per-sexual act probability of HIV acquisition increased steadily throughout pregnancy and into the postpartum period.<sup>4,5</sup> Potentially relevant biological changes/factors include elevated hormone levels and changes in the vaginal microbiome associated with genital or cervical inflammation, as well as nutritional deficiency and lowered immunity. Social and behavioral factors during pregnancy and breastfeeding may also increase exposure and susceptibility to HIV infection; for example, untreated sexually transmitted infections (STIs), reduced condom use, changes in extra-primary partnerships, and increased intimate partner violence (IPV). In addition, incident HIV infection during pregnancy has been demonstrated to increase the odds of mother-to-child transmission (MTCT) by 15-fold.<sup>5</sup> A woman's seroconversion during pregnancy imparts a significant risk of transmitting HIV to her infant due to high levels of HIV viremia during acute infection. In one study representing nearly 10,000 mother and infant pairs, the 3% of women infected with HIV during pregnancy accounted for over 25% of all MTCT cases of HIV.<sup>6</sup>

In sub-Saharan African countries, the estimated fertility rates are high – 5.1 births per woman.<sup>7</sup> Also, the prevalence of breastfeeding in many of these countries is relatively high and of long duration. In 2017, in Eastern and Southern Africa, 55% of children were exclusively breastfed the first six months of life, compared with 43% of children globally; 87% of children continued breastfeeding at one year, compared with 74% of children globally; and 53% of children continued breastfeeding at two years, compared with 45% of children globally.<sup>8</sup> These data, plus the fact that pregnant women remain sexually active, strongly suggest that these women represent a key target group for HIV prevention efforts.<sup>9</sup>

Prior clinical trials of antiretroviral (ARV) drug use during pregnancy have primarily been in the context of treatment and/or prevention of mother-to-child transmission (PMTCT) in women known to have acquired HIV. However, unintended pregnancy is common, as high as 40% globally, thereby highlighting the need to characterize the consequences of HIV prevention agents during pregnancy.<sup>10</sup> Although medication use (and fetal exposure) during pregnancy is common, the standard regulatory approach has in the past limited research efforts during pregnancy.<sup>11</sup> The ethical imperative to investigate medication during pregnancy is a well-recognized concept with documented justification. Informed use of medical therapies during pregnancy is necessary to optimize care (principle of beneficence) and there is a large societal cost from the lack of safety data and the resulting reticence to use indicated therapies during pregnancy.<sup>11</sup> Studies of HIV prevention agents in pregnancy and lactation are ethically justifiable based on the concept of “prospect of direct benefit” to the mother, without a requirement for statistical power solely in studies of pregnant and lactating women to detect this benefit.<sup>11</sup> With the increased risk of HIV acquisition during pregnancy and increased

transmission risk to the infant with new infection during pregnancy and lactation, careful investigation into identifying safe and effective ARV-based prevention interventions during pregnancy is warranted.

While pregnant women are among those most in need of safe and effective HIV prevention and treatment, research during pregnancy has been limited. Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) was a seven-year project funded by the National Institute of Allergy and Infectious Diseases (NIAID) with the primary aim of developing concrete guidance to address these evidence gaps, delays and inequities. The project's extensive research, much of it conducted in sub-Saharan Africa, was published in July 2020<sup>12</sup>. The study team together with a multidisciplinary working group of 26 international experts recommended the advancement of timely, needed and responsible research with pregnant women because without fair representation and inclusion in research, women are bound to face decisions about the use of medications during pregnancy with little or no scientific evidence on which to base those decisions. Of note, the PHASES report mentions the MTN-042/DELIVER study as an example of a study that will provide critically needed evidence about the safety of the dapivirine (DPV) vaginal ring (VR) and oral pre-exposure prophylaxis (PrEP) during pregnancy.

Two ARV-based prevention interventions, the DPV VR (25 mg) and once-daily Truvada (200 mg emtricitabine [FTC]/300 mg tenofovir disoproxil fumarate [TDF]), have been evaluated in individuals at high risk for HIV infection and have shown *in vitro* and *in vivo* efficacy and favorable safety profiles.<sup>13,14</sup>

## **2.2 Description of DPV VR and Truvada Tablet**

### **2.2.1 DPV VR**

The Dapivirine Vaginal Ring-004 is an off-white matrix ring, containing 25 mg of DPV dispersed in a platinum-catalyzed silicone elastomer. The DPV molecule was originally developed as an oral ARV agent by Janssen Sciences Ireland UC, which conducted the early, non-clinical and clinical development. DPV, also known as TMC-120, a substituted di-aminopyrimidine derivative (DAPY), is a tight binding non-nucleoside reverse transcriptase inhibitor (NNRTI) with potent antiviral activity against HIV-1. DPV is chemically described as 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzotrile. DPV's ARV profile is superior to that of several other NNRTI drugs, including nevirapine (NVP), delavirdine (DLV), and efavirenz (EFV). Like other NNRTIs, *in vitro* tests have also shown that DPV is not active against HIV-2 and has little or no activity against common sexually transmitted infections (STIs), therefore, it is not intended for use against HIV-2 or other STIs. DPV does not have any contraceptive properties. DPV has potent activity against wild-type HIV-1 strains and strains harboring different resistance-inducing mutations. Detailed information on DPV is available in the DPV VR Investigator's Brochure (IB).<sup>13</sup>

Based on its proven *in vitro* and *in vivo* efficacy and favorable safety profile, as well as its physical and chemical properties, DPV has proven to be a promising microbicide candidate. Under a license agreement with Janssen Sciences Ireland UC, the International Partnership for Microbicides (IPM) has developed different non-oral pharmaceutical forms (either as a gel or VR delivery system) of DPV for prevention of infection with human immunodeficiency virus type 1 (HIV-1) through male-to-female vaginal intercourse. The Dapivirine Vaginal Ring-004 was designed to provide sustained release of DPV for a minimum of one month to provide for a convenient dosing schedule. The *in vitro* release from the DPV VR (25 mg) in isopropyl alcohol (IPA):water (1:1) over 28 days was approximately 12 mg. Data from post-use analysis of DPV

residual levels in used rings indicate that approximately 4 mg of DPV is released over a one month period of VR use. When delivered in this manner, DPV has demonstrated favorable safety and pharmacokinetic (PK) profiles.<sup>13</sup>

On July 23, 2020, the DPV VR received a positive scientific opinion from the European Medicines Agency (EMA) under Article 58 for its use in HIV prevention by cisgender women ages 18 and older in low- and middle-income countries.<sup>15</sup> The World Health Organization (WHO) has since included the DPV VR on its prequalification list of medicines.<sup>16</sup> The WHO has also formulated a conditional recommendation which states the DPV VR “may be offered as an additional prevention choice for women at substantial risk of HIV infection (defined as HIV incidence >3 per 100 person-years in the absence of PrEP) as part of combination prevention approaches”.<sup>17</sup> The recommendation comes after a recent Guideline Development Group meeting assessed the benefits of the DPV VR outweighed the harms based on a systematic review and meta-analysis of the scientific evidence presented to them, including the DPV VR’s cost-effectiveness, acceptability, demonstrated feasibility, and its potential to increase equity.<sup>16,17</sup> The Group noted some variability in DPV VR effectiveness in younger age groups and limited data regarding DPV VR use among pregnant and breastfeeding women. IPM is currently seeking regulatory approval of the ring’s use in several African countries through a collaborative process led by the WHO that accelerates country regulatory reviews for products that have received a positive opinion from the EMA or other stringent regulatory authority. The first of these decisions could occur by mid-2021. The ring is also under review by the US Food and Drug Administration.

### **2.2.2 Truvada Tablet**

Truvada (200 mg FTC/300 mg TDF) is a fixed-dose combination of the antiviral drugs emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). The chemical name of FTC is 5-fluoro-1-(2R,5S)-[2(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. TDF is a fumaric acid salt of the bis-isopropoxycarbonyloxymethyl ester derivative of tenofovir (TFV). The chemical name of TDF is 9-[(R)-2 [[bis[[[(isopropoxycarbonyl)oxy]methoxy] phosphinyl]methoxy]propyl]adenine fumarate (1:1).<sup>14</sup>

Truvada was originally approved by the US Food and Drug Administration (FDA) in 2004 in combination with other ARV agents as a treatment for HIV-1 infection in adults. Gilead Sciences, Inc. received US FDA approval in 2012 for once-daily Truvada (FTC and TDF), in combination with safer sex practices, to reduce the risk of sexually acquired HIV-1 infection in adults at high risk. Truvada, known as PrEP, is the first agent to be approved for HIV prevention in uninfected adults.<sup>18</sup> Truvada for oral PrEP has also been approved for use by adults at high risk of sexually acquiring HIV-1 infection in a number of other countries, including South Africa, Malawi, Kenya and Zimbabwe.<sup>19</sup> Furthermore, a Technical Working Group convened in April 2017 at the Ugandan Ministry of Health following the release of WHO’s 2016 guidance. Due to the high cost of Truvada, they recommended use of the TDF/lamivudine (3TC) 300/300mg tablet for PrEP instead, although private health care providers (HCPs) or non-governmental organizations (NGOs) would be allowed to give Truvada or other TFV-containing drugs for PrEP if available and affordable. The World Health Organization recommends use of Truvada in pregnant and lactating women at risk of HIV; guidelines regarding use in pregnancy and lactation differ by country.

Truvada does not protect against common STIs such as gonorrhea, syphilis or chlamydia; therefore, it is recommended that it be used in conjunction with condoms.<sup>20</sup> However, a secondary analysis<sup>21</sup> within the Partners PrEP study for HIV-1 prevention among 4,747 highly-

adherent serodiscordant couples found that daily oral TDF-based PrEP reduced herpes simplex virus (HSV)-2 acquisition by 30% compared to placebo among initially HSV-2-seronegative participants. Truvada does not have any contraceptive properties, and animal studies have not found evidence that Truvada alters female fertility.<sup>14</sup> Detailed information on Truvada is available in the package insert.<sup>14</sup>

### **2.2.3 Mechanism of Action**

#### **DPV VR**

DPV is an NNRTI; NNRTIs bind to the HIV reverse transcriptase (RT) enzyme thereby preventing viral replication and therefore the production of an infectious virus.<sup>13</sup>

#### **Truvada Tablet**

Truvada is a fixed-dose combination of antiviral drugs FTC and TDF. FTC and TDF are nucleoside reverse transcriptase inhibitors (NRTIs), which act by blocking RT enzyme, preventing HIV replication and therefore the production of an infectious virus.<sup>14</sup>

### **2.2.4 Strength of Study Products**

#### **DPV VR**

The Dapivirine Vaginal Ring-004 contains 25 mg of DPV as active ingredient. It is a matrix VR in which the drug substance is dispersed in a platinum-catalyzed cured silicone.<sup>13</sup>

#### **Truvada Tablet**

The once-daily film-coated Truvada oral tablet contains 200 mg of FTC and 300 mg of TDF, equivalent to 245 mg of tenofovir disoproxil, as active ingredients. Dosages used in MTN-042 are the same as licensed doses, and the safety profile has been assessed as part of FDA licensure.<sup>14</sup>

## **2.3 Nonclinical Studies – DPV**

### **2.3.1 *In vitro* and *In vivo* Studies of DPV**

#### **Anti-HIV-1 Activity**

The activity of DPV against wild-type HIV-1, African isolates of HIV-1 (including subtype C virus), and a panel of NNRTI-resistant viruses has been established using *in vitro* models. The 50% effective concentration (EC<sub>50</sub>) values ranged from 0.3 ng/mL (0.9 nM) against laboratory isolates to <33 ng/mL (<100 nM) against HIV-1 isolates encoding one or more known NNRTI resistance mutations.<sup>22,23</sup> The anti-HIV activity of DPV was also confirmed in an *ex vivo* model of human cervical explant cultures.<sup>22,23</sup> Pre-treatment of tissue with DPV for 2 or 24 hours inhibited HIV-1 infection when challenged with virus on Days 0, 2, 4 and 6 post drug removal. DPV was also able to inhibit virus dissemination by migratory cells up to 6 days post drug removal at concentrations as low as 10 µM (3.3 µg/mL) following treatment for 2 or 24 hours. In addition, DPV (32.9 ng/mL) was able to block transfer of free virus by migratory dendritic cells to indicator T-cells (IC<sub>50</sub>= 0.1 nM [0.03 ng/mL]). More information regarding HIV-1 activity can be found in the Dapivirine Investigator's Brochure (IB).<sup>13</sup>

#### **Resistance to DPV**

In wild-type HIV-1 laboratory strains (at a high multiplicity of infection and in the presence of increasing concentrations of DPV), at DPV [40 nM], [200 nM] and [1 µM], virus breakthrough occurred between 4 and 7 days; between 7 and 10 days; and up to 30 days, respectively. In all

cases, mutations were present. Virus with the Y181C mutation was resistant to DPV. More information regarding resistance activity can be found in the Dapivirine IB.<sup>13</sup>

In vitro, DPV has demonstrated reduced antiviral activity against subtype B virus with certain single NNRTI mutations. Low-level resistance to DPV occurred with virus containing K101E, K103N, or Y181C, 3 commonly transmitted NNRTI resistance mutations. Additionally, low-level resistance was seen with the E138K, F227C, and K103S mutations. Intermediate- or high-level DPV resistance was conferred by the L100V, L100I, M230L, Y188L, K101P, Y181I, and Y181V mutations.<sup>24</sup>

### **Cross-resistance of DPV**

In comparison with NVP, DLV, EFV and emvirine, DPV showed significantly better *in vitro* activity against laboratory and recombinant HIV strains resistant to one or more drugs of the same class. The EC<sub>50</sub> was below 32.9 ng/mL (100 nM) for 80% of the strains compared with only 56% of the strains for EFV.<sup>13</sup> When tested against 433 clinical isolates with phenotypic resistance to at least one of the NNRTIs (NVP, DLV, EFV, or DPV), DPV was able to inhibit 46% (202/433) of the samples, including 41% (142/350) of the strains resistant to EFV. In contrast, only 10% (24/231) of the DPV-resistant strains were inhibited by EFV.<sup>13</sup>

DPV cross-resistance was also evaluated using plasma samples derived from HIV-1 subtype C-infected individuals failing first-line nevirapine- or efavirenz-containing antiretroviral therapy (ART) regimens in South Africa. The majority of virus samples demonstrated cross-resistance to DPV. Although resistance levels (based on required inhibitory concentrations of DPV) were found to be greater than the expected plasma concentrations of DPV during VR use, researchers concluded that both wild type and resistant virus may be inhibited by high genital tract DPV concentrations.<sup>25</sup> More information regarding cross-resistance activity can be found in the Dapivirine IB.<sup>13</sup>

### **Carcinogenicity, reproductive toxicity and mutagenicity of DPV**

The DPV VR was investigated in a comprehensive nonclinical safety assessment program that included safety pharmacology studies, single dose and repeat dose toxicity studies of up to 39 weeks' duration, reproductive toxicity and mutagenicity studies, and a 2-year carcinogenicity study. Data from in vitro and in vivo mutagenicity studies indicate that DPV is non-genotoxic. The vaginal reproductive toxicity studies in rats and rabbits using gels containing DPV at concentrations up to 2.0 mg/mL (0.2%; 25 times higher than the maximum concentration measured in the vaginal fluid of women using the DPV VR) showed that there were no adverse effects on the maternal animals or the developing embryo/fetus. No treatment-related neoplastic or non-neoplastic findings were seen in a vaginal carcinogenicity study in rates at concentrations up to 5 mg/mL. In rat and dog, the NOAEL was considered to be 20 mg/kg/day, based on prior nonclinical toxicity studies using the oral route of administration. Results show there were no effects in rats at the maternally non-toxic dose of 20 mg/kg/day, or in rabbits at up to 90 mg/kg. These data suggest that the risk of any adverse effects in pregnant women exposed to DPV, when used as a microbicide, is low. These data fulfill one of the major recommendations of conducting research within a pregnant population – reliable non-clinical data, especially with respect to mutagenic and teratogenic effects.<sup>26-29</sup>

### **2.3.2 Condom Compatibility Studies (DPV Gel and Placebo VR)**

Chemical compatibility studies with different DPV-containing gel formulations have been conducted on the following types of condoms<sup>13</sup>: Non-lubricated latex condoms (male condom); Silicone lubricated latex condoms (male and female condoms); Aqueous lubricated latex

condoms (male condom); Silicone lubricated polyurethane condoms (male and female condoms); and Silicone lubricated nitrile condoms (female condom).

The results of condom compatibility testing indicate that DPV-containing vaginal gel formulations (0.05%) have no deleterious effects on the integrity of male or female condoms, as indicated by tensile condom properties tested pre- and post-treatment. Two clinical condom functionality studies (one with male condoms [IPM 029] and one with female condoms [IPM 033]) were conducted with a placebo VR (silicone elastomer VR containing no active ingredient). Results from both studies showed that the difference between the total clinical failure rate between condom use while using a VR and condom use while not using a VR was less than the pre-defined non-inferiority margins in both studies (3% for the male condom study and 8% for the female condom study). Condom use was safe and well tolerated during placebo VR use.<sup>13</sup>

## **2.4 Nonclinical Studies – Truvada**

### **Anti-HIV-1 Activity**

No antagonism was observed in combination studies evaluating the *in vitro* antiviral activity of Truvada. More information regarding anti-HIV-1 activity can be found in the Truvada package insert.<sup>14</sup>

### **Resistance**

HIV-1 isolates with reduced susceptibility to the combination of FTC and TDF have been selected *in vitro*. Genotypic analysis of these isolates identified the M184V/I and/or K65R amino acid substitutions in the viral RT. In addition, a K70E substitution in HIV-1 RT has been selected by TDF and results in reduced susceptibility to TDF. Individuals with K65R have increased susceptibility to other NRTIs such as zidovudine (ZDV). More information regarding resistance studies can be found in the Truvada package insert.<sup>14</sup>

### **Cross-Resistance**

Cross-resistance among certain NRTIs has been recognized. The M184V/I and/or K65R substitutions selected *in vitro* by the combination of FTC and unformulated TDF are also observed in some HIV-1 isolates from subjects failing treatment with TDF in combination with either lamivudine (3TC) or FTC, and other ARVs. More information regarding cross-resistance studies can be found in the Truvada package insert.<sup>14</sup>

### **Carcinogenicity, reproductive toxicity and mutagenicity of Truvada**

Both emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) were evaluated in nonclinical safety assessment programs inclusive of toxicity, pharmacology, reproductive toxicity, mutagenicity and long-term carcinogenicity studies. For FTC, the long-term oral carcinogenicity studies showed no drug-related increases in tumor incidence found in mice at doses up to 750 mg/kg/day (26 times the human systemic exposure at the therapeutic dose of 200 mg/day) or in rats at doses up to 600 mg/kg/day (31 times the human systemic exposure at the therapeutic dose). Also, FTC was not found to be genotoxic in mutagenicity studies. Finally, FTC did not affect fertility in male rats at approximately 140-fold or in male and female mice at approximately 60-fold higher exposures (AUC) than in humans given the recommended 200 mg daily dose. Fertility was normal in the offspring of mice exposed daily from before birth (in utero) through sexual maturity at daily exposures (AUC) of approximately 60-fold higher than human exposures at the recommended 200 mg daily dose in reproductive fertility testing.<sup>14</sup>

For TDF in long-term oral carcinogenicity studies in mice and rats, the results show that at the high dose in female mice, liver adenomas were increased at exposures 16 times that in humans. In rats, the study was negative for carcinogenic findings at exposures up to 5 times that observed in humans at the therapeutic dose. TDF was mutagenic in the in vitro mouse lymphoma assay and negative in an in vitro bacterial mutagenicity test (Ames test). In an in vivo mouse micronucleus assay, TDF was negative when administered to male mice. There were no effects on fertility, mating performance, or early embryonic development when TDF was administered to male rats at a dose equivalent to 10 times the human dose based on body surface area comparisons for 28 days prior to mating and to female rats for 15 days prior to mating through day 7 of gestation. There was, however, an alteration of the estrous cycle in female rats. In toxicology studies to rats, dogs, and monkeys, tenofovir exposure (based on AUCs) greater than or equal to 6-fold those observed in humans cause bone toxicity. In monkeys the bone toxicity was diagnosed as osteomalacia. Osteomalacia observed in monkeys appeared to be reversible upon dose reduction or discontinuation of tenofovir. In rats and dogs, the bone toxicity manifested as reduced bone mineral density. The mechanism(s) underlying bone toxicity is unknown. Evidence of renal toxicity was noted in four animal species. Increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calciuria and decreases in serum phosphate were observed to varying degrees in these animals. These toxicities were noted at exposures (based on AUCs) 2–20 times higher than those observed in humans. The relationship of the renal abnormalities, particularly the phosphaturia, to the bone toxicity is not known.<sup>14</sup> These data fulfill the one of the major recommendations of conducting research within a pregnant population - reliable non-clinical data, especially with respect to mutagenic and teratogenic effects.<sup>26-29</sup>

## **2.5 Clinical Studies – DPV**

To date, a total of 31 Phase 1 and Phase 2 clinical research studies of DPV have been completed: ten studies of DPV VRs (containing 25 mg, 503 subjects received DPV VRs); eight studies of DPV vaginal gel (491 subjects received DPV vaginal gel); eleven studies of oral DPV (211 subjects received oral DPV); two studies of DPV vaginal film (25 women received DPV vaginal film).<sup>13</sup>

Two Phase 3 studies, MTN-020 (ASPIRE) and IPM 027 (The Ring Study), evaluating the long-term safety and efficacy of the monthly use of the DPV VR (25 mg) have been completed. A total of 4588 participants were enrolled between the two studies, with 2620 assigned to receive DPV VRs.<sup>30,31</sup> Two Phase 3B open-label extension trials, IPM 032 (DREAM) and MTN-025 (HOPE), offering the extended use of the DPV VR to former participants of The Ring Study and ASPIRE, respectively, have also been completed. A total of 2309 participants were enrolled between the two Phase 3B studies, including 978 assigned to the placebo rings in the Phase 3 trials.<sup>13</sup>

To date, approximately 5350 adult women between 18 and 65 years of age have been exposed to the DPV VR across the clinical development program's completed Phase 1-3B studies.<sup>13</sup>

### **2.5.1 Clinical Pharmacokinetics (PK) of DPV**

In clinical trials evaluating the use of VRs and vaginal gels to date, DPV concentrations in plasma have been very low (less than 2 ng/mL) or undetectable up to 84 days after drug exposure. Maximum plasma levels of DPV after vaginal administration were 1000-fold lower than maximum plasma concentrations after oral administration of DPV (e.g., DPV C<sub>max</sub> after oral administration (300 mg b.i.d., for 14 days) was 2286 ng/mL).<sup>32</sup>

The clinical PK profile of the Dapivirine Vaginal Ring-004 formulation evaluated in IPM 013 showed a rapid increase in plasma and vaginal fluid concentrations of DPV after VR insertion.<sup>13</sup> Maximal DPV plasma concentrations were achieved in plasma by Day 7 of VR use and maximal DPV concentrations in cervicovaginal fluids (CVF) were achieved between Day 1 and Day 14 of VR use. DPV concentrations decreased steadily over the remainder of a 28-day or 35-day VR use period. Plasma DPV concentrations did not exceed 1 ng/mL, and were therefore well below concentrations at the maximum tolerated dose (MTD) for multiple oral DPV doses. For DPV in CVF, the highest DPV concentration was observed in the area where the VR was placed, followed by the cervix, with the lowest concentrations near the introitus.

Data from post-use analysis of residual DPV levels in the Dapivirine Vaginal Ring-004 (IPM 015, in which a VR containing DPV 25 mg was inserted once every 28 days over a 12-week period) indicate that, on average, 4 mg of DPV were released over approximately one month of VR use.<sup>13</sup> The mean remaining amounts of DPV in the used VRs returned at Weeks 4, 8 and 12 were 21.09 mg, 21.54 mg and 21.84 mg, respectively. No clear relationship (neither linear nor exponential) was observed between the residual amount of DPV and corresponding plasma concentrations (i.e., at scheduled VR removal). DPV plasma concentrations below approximately 200 pg/mL were generally associated with above-average VR residual amounts, while plasma concentrations above 200 pg/mL were generally associated with relatively constant residual levels (between approximately 20 and 22 mg).<sup>13</sup>

### **2.5.2 Phase 1 and 2 Studies of DPV**

Across all clinical trials conducted in healthy participants evaluating multiple VR formulations, the DPV VR was generally well-tolerated.<sup>13</sup>

The Dapivirine Vaginal Ring-004 has been evaluated in ten completed Phase 1 and Phase 2 clinical research studies, each demonstrating the relative safety of this VR.<sup>13</sup>

MTN-029/IPM 039 was a Phase 1, open-label clinical study designed to assess the presence of DPV in blood, breast milk, and CVF when delivered via a VR containing 25mg of DPV used continuously for 14 days by lactating women.<sup>33</sup> The study also evaluated the safety and tolerability of the DPV VR as well as adherence to the DPV VR during lactation. MTN-029/IPM 039 enrolled 16 healthy, HIV-negative women, aged 18 years or older, at least 6 weeks postpartum, who were lactating but not breastfeeding, at two U.S. sites. All participants had detectable DPV in milk and plasma, with median (interquartile range) peak concentration for milk and plasma at 676 pg/mL (443, 924.5) and 327 pg/mL (274.5, 378), respectively. Estimated daily infant exposure was 68.0 ng/kg/day (53.0, 85.1). Estimated terminal concentration half-life after VR removal was 39.0 hours (27.1, 53.4) and 35.2 hours (29.8, 46.4) for milk and plasma, respectively. Six of 16 (38%) participants experienced eight total AEs, most of which were mild and unrelated to study product.

### **2.5.3 Phase 3 Studies of DPV**

#### **IPM 027 (The Ring Study)**

IPM 027 (also known as The Ring Study), initiated in March 2012, was a randomized, double-blind, placebo-controlled efficacy and long-term safety study that enrolled 1959 healthy, HIV-uninfected women, ages 18-45. Participants were randomized in a 2:1 ratio to receive either a DPV VR or a placebo VR to be used every four weeks over approximately two years.<sup>32,36</sup>

The median age at enrollment was 25 years, and 91% were unmarried. At the data cut-off point, there were 2806 person-years of follow-up, and 761 women had completed the two-year follow-up period. A total of 139 post-randomization HIV-1 infections occurred: 80 among women assigned to DPV VR (incidence 4.23 per 100 person-years) and 59 among women assigned to placebo (incidence 6.43 per 100 person-years). The DPV VR reduced the risk of HIV-1 infection by 35.1% (95% CI: 9.05-53.64%;  $p=0.0114$ ) relative to placebo. A 38.6% (95% CI: 7.48-59.26%) reduction in HIV-1 infection was observed in a subgroup analysis of women older than 21 years at baseline and a 27.51% (95% CI: -31.30% to 59.98%) reduction was observed in the subgroup of women who were 18 to 21 years of age at baseline.<sup>30,34</sup> There is no apparent biological rationale for this difference between age groups, however the trial was not designed to explore efficacy by age group. The overall level of DPV VR efficacy observed in IPM 027 has been updated to 35% as a result of EMA review of the application submitted under Article 58.<sup>35</sup>

No clinically significant differences in the frequency of TEAEs were detected between the DPV and placebo treatment groups, and the majority (>80%) were assessed as moderate (Grade 2) or mild (Grade 1) in severity. Product-related AEs in both treatment groups included metrorrhagia, menometrorrhagia, pelvic discomfort/pain, suprapubic pain and application site pain, and all were assessed as mild (Grade 1) in severity by the Investigator. There were no statistically significant differences in the frequency of the primary safety endpoints between the study arms. Further, there was no overall difference between NNRTI resistance profiles.<sup>13</sup>

### **MTN-020 (ASPIRE)**

MTN-020, A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), was a Phase 3 clinical study designed to assess the efficacy and safety of the 25 mg DPV VR for the prevention of HIV-1 acquisition in women. The double-blind, randomized controlled study was conducted in HIV-uninfected women, ages 18-45. A total of 2629 women from Malawi, South Africa, Uganda, and Zimbabwe enrolled in the study. Participants replaced the VR monthly for a minimum of one year. Results were presented at the February 2016 CROI<sup>36</sup> and published that same month in the *New England Journal of Medicine*.<sup>31</sup>

A total of 168 HIV-1 infections occurred: 71 among those assigned the DPV VR and 97 among those assigned the placebo VR (incidence 3.3 and 4.5 per 100 person-years, respectively). DPV VR resulted in a 27% (95% CI: 1-46%,  $p=0.046$ ) relative reduction in HIV-1 incidence overall and a 37% (95% CI: 12-56%,  $p=0.007$ ) reduction in an analysis defined early in the study excluding data from two study sites with lower retention and adherence. In pre-defined as-randomized subgroup analyses, HIV protection differed significantly by age, with a 61% reduced risk of HIV for women  $\geq 25$  years (95% CI: 32-77%,  $p<0.001$ ), and 10% reduced risk for women  $< 25$  years (95% CI: -41-43%,  $p=0.64$ ). A post-hoc analysis was conducted to further explore this result, which indicated a 56% (95% CI: 31-71%,  $p<0.001$ ) reduction among women older than 21 years of age, and no HIV-1 protection for women aged 18-21; importantly, objective markers of adherence were lower in the 18-21 year-old subgroup compared to women older than 21.<sup>31</sup>

There were no statistically significant differences in the frequency of the primary safety endpoints between the study arms or in other AEs commonly detected in the study population. Incident STIs occurred at a similar rate in the two study arms. Product-related AEs included pelvic pain, application site pain, pelvic inflammatory disease (PID), cervix erythema, cervix edema, cervicitis, urinary tract infection (UTI), urinary incontinence, dyspareunia, headache, decreased neutrophil count, abnormal weight loss, and dysmenorrhea, and all were assessed as moderate (Grade 2) in severity. Finally, among those acquiring HIV-1, detection of NNRTI

mutations did not differ by study arm (8/68 assigned DPV and 10/96 assigned placebo,  $p=0.80$ ).<sup>13</sup>

### **MTN-025 (HOPE)**

MTN-025, the HIV Open-label Prevention Extension (HOPE) study, was a multi-site, open-label, randomized, Phase 3b study implemented in the ASPIRE clinical research sites.<sup>37</sup> Eligible HIV-uninfected ASPIRE participants received the same VR used in MTN-020, a silicone elastomer VR containing 25 mg of DPV, to be replaced monthly, for a total period of 12 months of use. Study follow-up visits occurred monthly for the first 3 months and quarterly thereafter, reflecting a transition to a more real-world type of follow-up (versus a clinical trial approach). The HOPE study enrolled 1456 former ASPIRE participants who were HIV- negative and otherwise eligible to enroll. As with ASPIRE, the HOPE study found no significant safety concerns with the ring, while ring use adherence was higher in HOPE. Furthermore, though the HOPE study lacked a comparison placebo group, HIV-1 incidence was lower than expected by weighted bootstrap sampling of the placebo arm of ASPIRE (matched by site, age, and presence of a curable STI at baseline).

Product-related AEs were minimal and similar in frequency and severity as those observed in ASPIRE, with no serious adverse events (SAE) related to ring use. At baseline, 1342 participants (92%) accepted the VR, and ring uptake remained high throughout the study: 90%, 89%, 87%, 83%, and 79% at Months 1, 2, 3, 6, and 9. Most (86%) returned rings had residual DPV levels consistent with some use during the prior month ( $>0.9$  mg released). A total of 35 HIV-1 infections were observed among enrolled participants between July 2016 and August 2018 for an observed incidence of 2.7 per 100 person-years (95% CI: 1.9-3.8) among all women in HOPE, regardless of ring acceptance or use. Expected HIV-1 incidence was 4.4 per 100 person-years (95% CI: 3.2-5.8) in the absence of access to the ring; an incidence of  $\leq 2.7$  would be expected to occur in fewer than 33 in 10,000 (0.33%) samplings. Lastly, no clear resistance pathway for resistance-associated mutations potentially selected by DPV was identified based on the pattern of NNRTI mutations observed among the 35 HOPE participants who acquired an HIV infection during the study.

### **IPM 032 (DREAM)**

IPM 032, the Dapivirine Ring Extended Access and Monitoring (DREAM) study, was a multi-site, open-label follow-on study to The Ring Study implemented in six of the IPM 027 sites.<sup>38</sup> In total, 941 eligible HIV-uninfected former Ring Study participants received the same DPV VR used in The Ring Study. Like the HOPE study, DREAM study participants were asked to use the DPV VR for a total period of 12 months, replacing it monthly, and to attend monthly study follow-up visits for the first 3 months and quarterly thereafter.

The ring was found to be well-tolerated in DREAM with a safety profile similar to The Ring Study. Most (95%) DREAM participants' returned rings had residual DPV levels which showed they had used the ring at least some of the time (ranging from intermittent to consistent use), up from 83% in The Ring Study. From July 2016 to November 2018, an HIV-1 incidence of 1.6 percent was observed, compared to an incidence rate of 4.3% in a simulated placebo group based on data from participants with similar characteristics in the placebo arm of The Ring Study, suggesting an estimated 63% reduction in HIV-1 risk for women who used the ring.

### **Studies of the DPV VR in Pregnancy**

The use of DPV VR has been shown to be well-tolerated for HIV-1 prevention in nonpregnant reproductive-aged women. Clinical data in pregnant women are limited, as pregnant women were excluded from participation in clinical trials. Participants who became pregnant

discontinued use of the DPV VR, and since pregnancy testing was conducted at monthly visits for MTN-020 and IPM 027, overall exposure of the developing embryo to DPV was limited.<sup>39</sup> However, limited data of DPV on pregnancy outcomes and infants are available. Of the 2629 women enrolled in ASPIRE, 169 became pregnant during follow-up, resulting in 179 incident pregnancies and 181 pregnancy outcomes. No difference in pregnancy incidence by study arm was observed (HR=0.93; 95% CI 0.68 – 1.26). The distribution of pregnancy outcomes was similar by study arm, and no difference was noted in the frequency or pattern of congenital anomalies or infant growth parameters by study arm.<sup>40</sup> In IPM 027, 53 pregnancies occurred among the 1959 participants with 38 known outcomes; the proportion of participants who reported adverse pregnancy outcomes was similar between the DPV and placebo groups.<sup>13</sup> In both IPM 027 and MTN-020, the rare congenital abnormalities reported were reported with similar frequencies between the DPV VR group and the placebo ring group.<sup>39</sup> No safety signals were found and no congenital anomalies or birth defects were observed in any of the 70 pregnancies that occurred among HOPE participants who may have used the ring early on in their pregnancy prior to discovery of the pregnancy and subsequent product use discontinuation.<sup>41</sup> Similarly, no safety signals were found in respect of pregnancy outcomes among DREAM participants who may have used the ring early on in their pregnancy prior to discovery of the pregnancy, and subsequent product use discontinuation. One congenital umbilical hernia was reported in the infant of a participant who became pregnant during the clinical trial. The congenital umbilical hernia was considered resolved after a duration of 102 days during follow up of the infant.<sup>38</sup>

## **2.6 Clinical Studies – Truvada**

### **2.6.1 Clinical Pharmacokinetics of Truvada**

Truvada may be administered with or without food.<sup>14</sup> *In vitro* and clinical PK drug-drug interaction studies have shown that the potential for CYP450 mediated interactions involving FTC and TFV with other medicinal products is low. FTC and TFV are primarily excreted renally by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of Truvada with drugs eliminated by active tubular secretion may increase concentrations of FTC, TFV, and/or the co-administered drug. Drugs that decrease renal function may increase concentrations of FTC and/or TFV.<sup>14</sup>

### **2.6.2 Phase 3 Studies of FTC with TDF**

#### **Clinical studies of FTC with TDF in HIV prevention**

A review<sup>42</sup> of seven completed PrEP randomized clinical trials with a combined 18,747 female and male participants, including the iPrEX (Iniciativa Profilaxis Pre-Exposición), Partners PrEP, the Bangkok Tenofovir Study, FEM-PrEP, VOICE (Vaginal and Oral Interventions to Control the Epidemic) and CAPRISA (Centre for the AIDS Programme of Research in South Africa) studies, evaluated safety, efficacy, adherence and potential barriers to ‘real-world’ uptake. Across all studies, reduction in HIV risk provided by oral TDF alone or in combination with FTC ranged from 0%–75%. While adherence to daily pill-taking assessed by pill counts and self-report was high at 84%–95%, the proportion of participants in the PrEP arms with detectable serum drug levels was lower, ranging from 24%–82%. Regarding safety, TDF-based oral PrEP did not increase rates of serious (grade 3 or 4) AEs in any studies. In some studies, the risk of nausea, vomiting, diarrhea, unexplained weight loss, fatigue, and dizziness was higher than with placebo. Side effects were generally mild, infrequent (affecting 1%–10% of participants), and disappeared after 1 to 2 months of use. Drug resistance was rare among participants who

acquired an HIV infection after starting PrEP (0%–12% of incident cases during follow-up), but was common among participants who were recently infected with HIV before starting PrEP (up to 100% of such cases).

### **iPrEx study**

The iPrEx trial was a randomized, double-blind, placebo-controlled multinational study evaluating Truvada in 2,499 HIV-seronegative men or transgender women who have sex with men and with evidence of high-risk behavior for HIV-1 infection.<sup>43</sup> All subjects received monthly HIV-1 testing, risk-reduction counseling, condoms, and management of sexually transmitted infections. Of the 2,499 enrolled subjects, 1,251 received Truvada and 1,248 received placebo. The mean age of subjects was 27 years; 5% were Asian, 9% Black, 18% White, and 72% Hispanic/Latino. Subjects were followed for 4,237 person-years. The primary outcome measure was the incidence of documented HIV seroconversion. At the end of treatment, emergent HIV-1 seroconversion was observed in 131 subjects, of which 48 occurred in the Truvada group and 83 occurred in the placebo group, indicating a 42% (95% CI: 18–60%) reduction in risk. Risk reduction was found to be higher (53%; 95% CI: 34–72%) among subjects who reported previous unprotected receptive anal intercourse (URAI) at screening (732 and 753 subjects reported URAI within the last 12 weeks at screening in the Truvada and placebo groups, respectively). In a post-hoc case control study of plasma and intracellular drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable intracellular tenofovir diphosphate concentrations. Efficacy was therefore strongly correlated with adherence.

TDF treatment is known to cause decreases in renal function, and there were trends toward more creatinine elevations in the Truvada group than in the placebo group. In testing for elevations in serum creatinine levels, there were 41 instances of elevations that were at least 1.1 times the upper limit of the normal range or more than 1.5 times the baseline level. Of these elevations, 26 (2%) were in the FTC–TDF group and 15 (1%) were in the placebo group (P=0.08). Two of these elevations increased in grade, accounting for a total of 43 creatinine adverse events. Overall, 18 creatinine elevations (44%) remained in the normal range, and 36 (88%) were not confirmed on the next test. A total of 10 elevations led to discontinuation of a study drug (7 in the Truvada group and 3 in the placebo group); study drugs were restarted in 9 subjects. Serum creatinine levels were elevated at more than one consecutive test in 5 subjects in the FTC–TDF group (<1%) and in none of the subjects in the placebo group. All elevations in the serum creatinine level resolved after the discontinuation of a study drug, within 4 weeks in 3 subjects, within 12 weeks in 1 subject, and within 20 weeks in 1 subject. Four of the subjects resumed taking FTC–TDF without recurrence of the elevation. Moderate nausea (grade 2 and above) was reported more frequently in the Truvada group than in the placebo group (22 vs. 10 events, P=0.04), as was unintentional weight loss of 5% or more (34 vs. 19 events, P=0.04).

### **Partners PrEP study**

The Partners PrEP study was a Phase 3 trial of TDF or Truvada in serodiscordant heterosexual couples in Kenya and Uganda; it found high efficacy against HIV acquisition, and the DSMB overseeing the study recommended stopping the placebo arm early.<sup>44</sup> The team enrolled a total of 4,758 HIV serodiscordant couples. Participants were randomized in a 1:1:1 ratio, to TDF, Truvada, and a matched placebo. Following 7,827 person-years of follow-up, 82 emergent HIV-1 seroconversions were reported, with an overall observed seroincidence rate of 1.05 per 100 person-years. Of the 82 seroconversions, 13 and 52 occurred in partner subjects randomized to Truvada and placebo, respectively. Two of the 13 seroconversions in the Truvada arm and 3 of the 52 seroconversions in the placebo arm occurred in women during treatment interruptions for pregnancy. Findings from this study revealed 67% (95% CI 44 to 81%, p<0.0001) and 75%

(95% CI 55 to 87%,  $p < 0.0001$ ) reductions in HIV acquisition compared to those who received placebo in the TDF and Truvada arms, respectively. Efficacy of daily oral PrEP was high in all women; among subgroups of higher-risk women (those with placebo-arm HIV-1 incidence  $>5.0$  per 100 person years), daily oral TDF and Truvada PrEP efficacy estimates ranged from 64% to 84%.<sup>45</sup> In a post-hoc case control study of plasma drug levels in about 10% of study subjects, risk reduction appeared to be greatest in subjects with detectable plasma tenofovir concentrations.

Additional analyses from the Partners PrEP data relevant to MTN-042 were findings for: the efficacy of TFV-containing PrEP in reducing HSV-2 incidence,<sup>21</sup> safety in early pregnancy,<sup>46</sup> the low incidence of drug resistance in PrEP users detected by sensitive assays,<sup>47</sup> and the low incidence and reversibility of renal glomerular changes.<sup>48</sup>

### **Other studies of Truvada in pregnancy and lactation**

Although there have been no adequate and well-controlled trials conducted in pregnant and/or lactating women, limited exposure data for Truvada in pregnant and postpartum women are available.<sup>49,50</sup> Results from the Antiretroviral Pregnancy Registry (APR) Interim Report, 1 January 1989 through 31 July 2017, showed exposures for pregnant women to emtricitabine- and tenofovir-containing regimens were: 1148 and 3777 in the first trimester; 120 and 984 exposures, respectively, in second trimester; and 61 and 488 exposures, respectively, in the third trimester. Birth defects occurred in 60 of 2614 (2.3%) live births for emtricitabine-containing regimens and 76 of 3342 (2.3%) live births for tenofovir-containing regimens among first trimester exposures. Compared to the background birth defect rate of 2.7% for pregnant women in the U.S. (reference population), there was no association between emtricitabine or tenofovir and overall birth defects.<sup>51</sup>

A recent systematic review<sup>52</sup> noted multiple research gaps, including limited data on: (1) accurately measured PrEP exposure within maternal and infant populations including drug levels needed for maternal protection; (2) uncommon perinatal outcomes (e.g., congenital anomalies); (3) infant outcomes such as bone growth beyond one year following PrEP exposure; and (4) outcomes in HIV-uninfected women who use PrEP during pregnancy and/or lactation. The authors concluded that early safety studies of PrEP among pregnant women without HIV infection are reassuring and ongoing/planned studies will contribute extensive new data to bolster the safety profile of PrEP use in pregnancy.

### **PROMISE trial**

The P1084s sub-study of the Promoting Maternal-Infant Survival Everywhere, or PROMISE, trial compared newborn bone mineral content (BMC), measured using dual-energy X-ray absorptiometry scans of whole body and lumbar spine obtained within 28 days of birth, in 425 infants by exposure to maternal antiretroviral regimens at gestational ages older than 14 weeks at 8 sites in 4 African countries. The women were randomly assigned to initiate 1 of 3 antiretroviral regimens during pregnancy: arm 1 (zidovudine with single-dose nevirapine plus one dose of TDF and emtricitabine); arm 2 (zidovudine, lamivudine, and ritonavir-boosted lopinavir); or arm 3 (TDF, emtricitabine, and ritonavir-boosted lopinavir). No adverse associations were found between infant whole-body and lumbar spine BMC measurements and maternal TDF use when arms 2 and 3 were directly compared.<sup>53</sup> This is in contrast to an earlier finding from a smaller cohort study that compared 74 tenofovir-exposed infants to 69 unexposed infants and found a statistically significant lower mean of 12% newborn BMC level following maternal TDF use.<sup>54</sup>

## **IMPAACT 2009**

IMPAACT (International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group) 2009: Feasibility, Acceptability and Safety of Oral PrEP for Primary HIV Prevention During Pregnancy and Breast Feeding in Adolescents and Young Women is a parallel, observational cohort study of HIV-uninfected pregnant adolescents and young women (aged 16-24). The study is designed to characterize adherence over time among women who initiate once-daily oral PrEP during pregnancy and continue in the first 6 months following delivery, and to compare pregnancy outcomes among participants who take PrEP and participants who decline PrEP during the antenatal period. Prior to initiation of the main study component, a PK study component was implemented to establish adherence benchmarks for tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) for pregnant (14-24 weeks gestation at Enrollment) and postpartum (6-12 weeks postpartum at Enrollment) adolescents and young women who took PrEP daily under direct observation, and to compare these benchmarks in the pregnant and postpartum groups. Twenty pregnant and twenty postpartum women enrolled in the PK study component and took PrEP daily for twelve weeks, with >99% of oral PrEP doses taken under direct observation. Consistent with other studies, TFV-DP in DBS was 31-37% lower in pregnant women compared with postpartum women.<sup>55</sup> As of Q1 2021, the study is pending initiation of accrual into the main study in Zimbabwe, Malawi, Uganda, and South Africa. No safety data will be available from this study prior to initiation of the last two MTN-042 Cohorts.

## **2.7 Cross-resistance to ART**

ART resistance is a serious emerging threat to HIV treatment access – particularly in sub-Saharan Africa where weak health systems and poor access to monitoring and diagnostics make managing HIV even more challenging considering the high incidence of HIV infections in the region.

### **2.7.1 DPV VR**

Virologic failure and ART resistance following initiation of ART was assessed among women who acquired HIV infection during participation in ASPIRE. All ASPIRE participants with incident HIV during product use and with at least one CD4 cell count and HIV RNA (viral load) measurement were included in the analysis. Virologic failure was defined as either lack of suppression of plasma HIV RNA to <200 copies/ml after 6 months of ART, or plasma HIV RNA rebound to  $\geq$ 200 copies/ml at any time after suppression. Of 168 participants with incident HIV infection observed in ASPIRE, 158 had at least one HIV RNA measurement and were included in the analysis. Virologic failure occurred in 14 participants with no significant difference between DPV and placebo recipients (17% vs 23%; Fisher's exact  $P=0.76$ ). Among the 14 virologic failure events, 8 were viral rebound and 6 never suppressed. 18/158 women with incident HIV infection on study product had one or more NNRTI resistance mutations, of which 10/18 initiated ART and had  $\geq$ 6 months post-ART follow-up: 2/10 (20%) with NNRTI mutations vs. 12/57 (21%) with no NNRTI mutations had virologic failure. Genotypic resistance test results were available for 9/14 participants with virologic failure. NNRTI drug resistance mutations occurred in 7/9 overall; 6/7 were treatment-emergent. The most common mutation was K103N, occurring in 4/9 participants. The use of the DPV VR in women acquiring HIV during the ASPIRE trial was thus not associated with significant differences in the virologic outcomes following initiation of NNRTI-containing ART. There was no significant difference in virologic response time or frequency of virologic failure among DPV recipients compared to placebo, and no evidence to suggest that the presence of NNRTI mutations at seroconversion impacted the rate of virologic failure.<sup>56</sup>

## 2.7.2 Truvada Tablet

Resistance in individuals seroconverting while taking Truvada has been assessed from 5 placebo-controlled, Phase 3 studies. All studies included an active arm in which participants were assigned a once daily regimen of oral TDF/FTC, and all participants underwent monthly rapid testing for HIV seroconversion.<sup>57-61</sup> Resistance to TFV and FTC was found to be infrequent (3%) from use of TDF/FTC tablet for oral PrEP if HIV-1 infection is not present at the time oral PrEP is started (5 cases in 160 seroconverters assigned to TDF/FTC in 5 PrEP studies). Resistance to TFV and FTC is much more common (41%) if TDF/FTC PrEP is started during undiagnosed acute HIV-1 infection (7 cases in 17 participants).<sup>47,62-66</sup> The risk of resistance with Truvada is low if acute HIV-1 infection is excluded before starting oral PrEP.<sup>67</sup>

## 2.8 Acceptability and Adherence

### 2.8.1 DPV VR

Multiple clinical trials have also evaluated adherence to the DPV VR among reproductive-aged women in Africa and the US.<sup>68-72</sup> Adherence was assessed either by self-report or by objective measures such as residual DPV concentrations in used VRs or blood plasma DPV levels. Self-reported adherence to VR use was very high overall, with >80% of participants across studies saying they used the VR every day. Blood plasma drug levels supported these findings, although adherence was likely overestimated in the ASPIRE study given that participants who used the VR for only a portion of the month would have been categorized as adherent as per the study definition of adherence.

The most commonly stated activities that led to voluntary removal of the VR were cleaning, menses and sexual intercourse, while the most commonly stated activities that led to involuntary expulsions of the VR were urination/defecation and sexual activity. Reasons for removing the VR included: male partner's wishes, menses, and perceived side effects. In ASPIRE, drug detection appeared to increase after the first months of VR use and become stable after the first year, which may indicate that some time was needed for participants to become comfortable with the VR.

Subgroup analyses of residual VR data suggest that the majority of women inconsistently used the VR throughout their participation in ASPIRE and that consistent VR use led to greater reductions in HIV-1 acquisition risk.<sup>73</sup> Residual dapivirine levels indicating at least some use (>0.9 mg released over a month) were associated with a 48% relative reduction in HIV-1 acquisition risk (95% CI: 21% to 66%;  $p = 0.002$ ) compared to placebo. Exploratory analyses accounting for potential misclassification in timing of HIV-1 acquisition estimated 75% to 91% HIV-1 risk reduction with >4 mg released when compared to placebo. Results for the subgroup of women <25 years of age, who tended to have lower adherence, were generally consistent with those overall.

Adherence was higher in the HOPE open-label study than in ASPIRE.<sup>37</sup> 89.3% of returned rings (12,530 of 14,034) had residual dapivirine amounts consistent with some use during the previous month (>0.9 mg released) and the mean dapivirine amount released was greater than in the ASPIRE trial (by 0.21 mg;  $p < 0.0001$ ). Similarly, adherence was higher in the DREAM open-label study than in IPM 027.<sup>38</sup> At all timepoints, most participants had dapivirine residual amounts in used rings of 23.5 mg or less, indicating at least some VR use, and mean dapivirine residual amounts in used rings were lower than in the IPM 027 trial (by 0.25 mg;  $p = 0.027$ ).

The VR was highly acceptable overall to participants in ASPIRE. Acceptability increased over time and varied by country, with participants in Uganda and Zimbabwe reporting higher likelihood of future use.<sup>74</sup> Participants with low overall acceptability were less likely to use the VR consistently based on objective adherence measurements. Some attributes of acceptability, including effects on sex, perceived negative change to the vaginal environment, and minding VR use during menses influenced adherence more strongly, whereas others like comfort and ease of insertion had no effect.

### **2.8.2 Truvada Tablet**

Multiple clinical trials have evaluated the acceptability of and adherence to the Truvada oral tablet among reproductive-aged women in Africa.<sup>57,60,68,75-81</sup> One study conducted with female sex workers in Kenya found the Truvada tablet a feasible and highly acceptable product regardless of dosing schedule (daily, twice weekly, or within two hours after sex); however, another study conducted with South African women found the pericoital dosing schedule to be a poor fit with their usual post-sex routines. The latter study, HPTN 067, found acceptability could be enhanced by interpersonal support, personal belief in PrEP's efficacy, cellphone and other reminders, and keeping pills at hand, and that a daily dosing regimen may lead to better habit formation and more forgiveness for missed doses.

Adherence was assessed by self-report, returned pill count, and/or blood plasma drug levels. Overall, Truvada tablet adherence tended to be high by self-report (>88% across studies) and returned pill counts (>75% across studies), but less consistently so by blood plasma drug levels (from <30% in VOICE to 86% in the Partners Demonstration Project). Most VOICE participants did not use the study products daily, a finding that is not consistent with pre-study assessments of the willingness of the target populations to use such products, adherence assessments based on clinic-based product counts and self-reporting, and the high rates of retention. Lower adherence in VOICE was associated with characteristics that predicted a higher risk of HIV acquisition. Results were consistent with those of the FEM-PrEP study, in which daily Truvada use did not reduce HIV-1 acquisition among women and in which study drug adherence was also low. However, VOICE results markedly differed from those of Partners PrEP, which displayed a significant reduction in risk of HIV-1 acquisition. Of note was that VOICE participants who were most likely to adhere were similar in terms of age and marital status to women in the Partners PrEP study. The VOICE study highlights the need for biomarker measures of adherence that do not rely solely on self-reporting and that are not easily manipulated by participants, such as real-time biologic monitoring of drug levels.

Barriers and facilitators to adherence were assessed in the HPTN 067 and FEM-PrEP studies. Facilitators included: participant's support for the research, HIV risk reduction, personal experiences with persons living with HIV/AIDS, strategies and tools such as adherence counseling and reminder alerts, social and emotional support (e.g., from partners and clinic staff), material support (e.g., financial reimbursement and clinical care). Barriers included: concerns about side effects, community stigma and distrust, privacy concerns (e.g., disclosure to partner, being identified as an HIV positive person), negative clinic or research participation experiences, and Truvada tablet characteristics (e.g., odor, size). Lastly, data from Partners PrEP and other Phase 3 PrEP studies like iPrEx and VOICE indicate that adherence at early time points predict adherence over the next one to two years, suggesting that adherence-focused interventions should occur as soon as possible after initiation of PrEP.

## 2.9 Rationale for Study Design

The purpose of MTN-042, a multicenter, prospective, open-label, randomized phase 3b is to characterize the safety, adherence, and acceptability of the DPV VR (25 mg), inserted every 4-weeks, and once-daily, Truvada (200 mg FTC/300 mg TDF) tablet used by African women during pregnancy. This study will further elucidate safety during pregnancy by testing the hypothesis that the administration of either study product will be safe and well-tolerated by women and their fetuses/infants so that women will experience similar rates of adverse pregnancy outcomes with either the DPV VR or Truvada compared to the general population.

Prior clinical trials of ARV drugs during pregnancy have primarily been in the context of treatment and/or PMTCT in women known to have acquired HIV. However, unintended pregnancy is common, as high as 40% globally, thereby highlighting the need to characterize the consequences of HIV prevention agents during pregnancy. Although there have not been adequate and well-controlled trials of DPV VR and Truvada conducted in pregnant and/or postpartum women, to date, limited exposure data suggests these agents could be safe for women and their fetuses/infants. The availability of these agents further supports the need for controlled studies during pregnancy to inform national programs as well as country regulators on conditions of licensure.

### **Ethical justification**

The FDA<sup>28</sup>, EMA<sup>26</sup>, and SAHPRA<sup>27</sup>, among other organizations, consider inclusion of pregnant women in clinical trials ethically justifiable when the trial holds the prospect of direct benefit to the mother and/or fetus, and adequate nonclinical studies have been completed on the investigational products. Development of accessible HIV prevention options for pregnant women in the study countries is a significant public health issue. MTN-042 affords the prospect of direct benefit to pregnant women and their infants in sub-Saharan Africa – a region where young women of reproductive age have high HIV acquisition rates<sup>2</sup> and limited access to HIV prevention options - with two products that have been shown to be well-tolerated and to reduce risk of HIV-1 infection in non-pregnant populations<sup>13,14,31,82</sup>. For the fetuses and infants of the participants, this study provides access to two products that have shown no significant risk of causing congenital abnormalities according to non-clinical data<sup>13,14</sup> and available clinical data from exposure during pregnancy<sup>39,51</sup>, and provides direct benefit by reducing the maternal risk of HIV infection during pregnancy which dramatically increases the odds of MTCT.<sup>5</sup>

As noted by the PHASES study team<sup>12</sup>, however, more research with pregnant women is needed to provide the necessary evidence for women to make informed choices about HIV prevention methods during pregnancy. Use of the DPV VR during pregnancy is currently considered missing information by the EMA due to limited available data. Acknowledging that some women may be at high risk of HIV-1 infection during pregnancy, allowance is made in the currently approved Summary of Product Characteristics<sup>35</sup> for clinical judgment on the part of healthcare professionals in deciding on its use during pregnancy. Given that health care providers will be allowed to use their best judgement when deciding whether to prescribe the DPV VR to pregnant women, it is inevitable that some pregnant women will use it, and it is in their best interest for the data to be available as early as responsibly possible.

### **Safeguards to mitigate risk**

Several safeguards have been implemented in the design and execution of the study to mitigate potential risks from exposure to the DPV VR and Truvada during pregnancy. Eligibility criteria for the study restricts enrollment to only healthy, HIV-uninfected pregnant females, 18-40

(inclusive) years of age, with an uncomplicated singleton pregnancy who are willing to be randomized to study product, and their newborn infants.

Additionally, a step-wise approach with pauses in accrual for interim safety reviews will be used to enroll subjects. Enrollment will begin with later gestational ages – i.e., later in pregnancy – then progress to earlier gestational ages once safety is confirmed. Participant accrual will be paused at all sites once accrual goals are met for the currently enrolling cohort. This will be done to allow all enrolled participants to give birth and to conduct interim safety analyses to determine if accrual into the next cohort can commence or if the study needs to be stopped early.

Criteria for MTN-042 site selection included provision of prenatal care at the site or a related clinic, and a relationship with local inpatient maternity units that participants would be anticipated to utilize for delivery. Study sites will have established relationships with hospitals and other facilities serving the study participants, and these facilities will represent the highest standard of care available in the study countries. This will mean faster and more comprehensive communication with study staff of any adverse events or complications observed during participants' prenatal care and delivery, and any subsequent response measures taken to address them, that may occur outside the study site clinics. In order to ensure that participants are receiving appropriate prenatal care during the course of the study, sites will collect documentation (certified copies of maternal records where possible) of antenatal visits from the participant herself and from her care provider once she has provided written permission during the screening process. In the event a problem with a pregnancy is suspected, an ultrasound can be ordered at the site or a referral will be provided.

Finally, subjects may voluntarily withdraw from the study for any reason and/or the investigator may withdraw the participant to protect their safety and/or for their unwillingness to comply with required study procedures.

Understanding cultural beliefs, societal norms and roles within the community is critically important for the success of a study involving pregnant women. In order to do so, MTN conducted a qualitative study, MTN-041 - Qualitative Assessment of Acceptability of Vaginal Ring and Oral Pre-exposure Prophylaxis Use during Pregnancy and Breastfeeding, in order to identify specific factors, belief systems and attitudes that may affect pregnant women's perceptions of the MTN-042 study and potential interest in using a monthly vaginal ring or daily PrEP during pregnancy and/or breastfeeding, and who within a woman's sphere of influence is most likely to support or discourage the use of either or both products. This study took place at the planned trial sites for MTN-042, and involved focus group discussions with women currently or recently pregnant and breastfeeding; men whose partners are or were recently pregnant or breastfeeding; and mothers and mothers-in-law of pregnant and breastfeeding women. In-depth interviews were conducted with community and traditional leaders, health providers, midwives and traditional birth attendants. Findings were utilized to inform recruitment, retention, community activities, data collection instruments, and study tools. The information gained from MTN-041 is helping the MTN-042 team to better understand the socio-cultural context of the participants' communities and be attentive to sensitivities and contextual considerations that may be important to understand for participant comfort and confidence in the study team. Increased trust may mitigate risk through improved communication between pregnant participants and the study team, bringing potential issues of concern to attention sooner than later.

### **Young women and adherence**

In the VOICE study, which examined use of daily Truvada and 1% tenofovir gel, women younger than 25 were least likely to use their assigned products.<sup>59</sup> ASPIRE<sup>31</sup> and The Ring Study<sup>13</sup> both found lower levels of HIV protection in young women aged 18-21; the rationale behind these data was that poor adherence observed in this age group resulted in decreased effectiveness of the DPV VR. In a study of a subset of ASPIRE participants, the non-adherence of young women was attributed to their tendency to be less serious about the future and about HIV prevention in general.<sup>83</sup>

Young women in sub-Saharan Africa represent one of the populations most vulnerable to HIV<sup>1,2</sup>, and in this region that has one of the highest birth rates in the world<sup>7</sup>, biological, social, and behavioral factors related to pregnancy increase the susceptibility of young, pregnant women in sub-Saharan Africa to HIV acquisition.<sup>3,4,5</sup> However, pregnancy is not only a time of increased risk in a woman's life, but it can also be a time of significant change. Altruistic motivations toward the unborn infant has been shown in expectant mothers<sup>84,85</sup>, and this can drive health-seeking behaviors that last beyond pregnancy. The data from prior DPV VR and Truvada trials suggest that HIV risk reduction is correlated with adherence to product use; MTN-042 seeks to investigate whether changing motivations in pregnant women may mean greater adherence to HIV prophylaxis. Pregnant HIV-infected women, for example, have been found to have greater adherence to ARVs than non-pregnant women.<sup>86</sup>

### **Investigation of microbiota as biomarkers for HIV risk**

With bacterial targets serving as biomarkers of HIV risk or protection, data on the description of the possible impact of product use on participants' vaginal microenvironment, will be an important contribution to this area of HIV research.

### **Community support**

At the MTN-042 Stakeholders' Consultation held April 2018 in Johannesburg, South Africa, organized by MTN and AVAC, regional and international experts joined stakeholders with expertise in bioethics, maternal and fetal health, HIV prevention clinical trial design, regulatory affairs and health policy, as well as civil society and community representatives to share views about the study's design and objectives and opinions about specific aspects of the study.<sup>87</sup> Stakeholders were very supportive of the study; there was consensus that pregnant women deserve safe, effective and equitable access to prevention.<sup>87</sup> Stakeholders supported further study of the DPV VR and were unanimous in their view that the time is right to move forward with this agenda.<sup>87</sup> And though IMPAACT 2009 (which recently completed its initial PK component) will be evaluating the safety of PrEP in adolescent and young women during pregnancy, stakeholders felt that, together, both studies would contribute much needed data about the safety of PrEP in pregnant women.<sup>87</sup> Consideration was given to the challenges in and ethical and regulatory framework for conducting research among pregnant women, and the socio-cultural barriers and belief structures within communities.<sup>87</sup> The stakeholders' input and enthusiastic support has shaped the development of MTN-042.

### **Justification for design change: Merging Cohorts 3 and 4 and 4:1 randomization in merged Cohort 3**

The HIV prevention landscape has changed substantially since the MTN-042 study protocol was approved. Recent years have seen an increased call for better drug safety data during pregnancy and for ethical inclusion of pregnant women in clinical research.<sup>88</sup> Furthermore, the DPV VR has received a positive scientific opinion from the EMA under Article 58 for use as an HIV prevention method by cisgender women ages 18 and older in low- and middle-income countries,<sup>15</sup> and the WHO has included the DPV VR on its prequalification list of medicines as

well as formulated a conditional recommendation supporting offering of the DPV VR as an HIV prevention option.<sup>16</sup> IPM is seeking regulatory approval of the ring in several African countries through WHO's Stringent Regulatory Authorities Collaborative Review process, and the first in-country decisions are likely to be issued as early as mid-2021. Prescribing information for the DPV VR will likely indicate a preference to avoid the use of the DPV VR during pregnancy, but still allow the healthcare provider to exercise their discretion if they consider that the woman and/or her unborn child are at high risk of HIV-1 infection.

Should the ring be approved, there will likely be women exposed to the DPV VR during pregnancy due to not yet realizing they are pregnant or because they are at high risk of HIV acquisition and they and their providers agree the benefits of ring use outweigh the potential risks. Providing safety data on DPV VR use by pregnant women is therefore more urgent, and the long pause between Cohorts 3 and 4 is a concern. While the 4-step design was optimal when the protocol was first developed, it is now unnecessarily complex, and if the DPV VR is approved, the delay between Cohorts 3 and 4 will needlessly postpone the availability of data during DPV VR rollout in African countries. Recently published results from the DPV VR open-label studies<sup>37,38</sup> and MTN-023<sup>89</sup> have added to the existing literature on its use for HIV prevention, providing further evidence of its favorable safety profile.

This protocol modification will collapse Cohorts 3 and 4 into a new combined Cohort 3, with 200 participants randomized to the DPV VR and 50 participants randomized to oral Truvada. This combined Cohort 3 would encompass the gestational ages at enrollment (12-29 6/7 weeks) originally included in both Cohorts 3 and 4 so would provide safety data covering all of the initially planned gestational ages. Efforts will be made to ensure that entire gestational age range is represented among the enrollments. There are no changes to safety monitoring included in this modification. The proposed changes should allow the study to enroll and complete follow-up for all participants through delivery by early 2023. This will expedite the availability of safety data for DPV VR use by pregnant women, which will be critical to inform product rollout should the DPV VR be approved for HIV prevention. To further that goal, the team also proposes publishing safety data from each of the two earlier Cohorts as soon as they are available.

### 3 OBJECTIVES

#### 3.1 Primary Objectives

**Maternal and Infant Safety:** To describe the maternal and infant safety profile associated with study product exposure during pregnancy

**Pregnancy Outcomes:** To describe the pregnancy outcomes associated with study product exposure during pregnancy

#### 3.2 Secondary Objectives

**Pregnancy Complications:** To describe pregnancy complications associated with study product exposure during pregnancy

**Infant Drug Levels:** To describe infant levels of study drugs associated with study product exposure during pregnancy

**Adherence:** To characterize adherence to open label use of the DPV VR (25 mg) and oral Truvada in pregnant women

**Acceptability:** To characterize acceptability of open label use of the DPV VR (25 mg) and oral Truvada in pregnant women

### 3.3 Exploratory Objectives

**Genital Microenvironment:** To describe changes in the genital microenvironment associated with study product exposure during pregnancy

## 4 STUDY DESIGN

### 4.1 Identification of Study Design

MTN-042 is a multi-site, two-arm, randomized (2:1 in Cohorts 1-2 and 4:1 in Cohort 3), open-label Phase 3b study evaluating the safety, adherence and acceptability profiles of the monthly DPV VR and daily oral Truvada tablet when used by HIV-uninfected pregnant women in Africa. The MTN-042 study will take a step-wise approach to dosing starting at later gestational ages, then progressing to earlier gestational ages. The following gestational age ranges will determine eligibility for each study cohort:

Cohort 1: 36 0/7 weeks – 37 6/7 weeks

Cohort 2: 30 0/7 weeks – 35 6/7 weeks

Cohort 3: 12 0/7 weeks – 29 6/7 weeks

### 4.2 Summary of Major Endpoints

#### Primary Endpoints:

##### **Maternal Safety (composite)**

- All serious adverse events, including maternal deaths
- All Grade 3 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])

##### **Infant Safety (composite)**

- All serious adverse events, including infant deaths and congenital anomalies
- All Grade 3 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017

##### **Pregnancy Outcomes**

- Frequency of the following pregnancy outcomes:
  - Full term live birth ( $\geq 37$  0/7 weeks)
  - Premature live birth ( $< 37$  0/7 weeks)
  - Pregnancy loss ( $\geq 20$  0/7 weeks)

- Pregnancy loss (<20 0/7 weeks)

## **Secondary Endpoints:**

### **Pregnancy Complications**

- Frequency of the following pregnancy complications:
  - Hypertensive disorders of pregnancy
  - Chorioamnionitis
  - Puerperal sepsis and endometritis
  - Antepartum, intrapartum and postpartum hemorrhage
  - Preterm premature rupture of membranes (PROM)
  - Fever of unclear etiology

### **Infant Drug Levels**

- Infant blood TFV-DP and FTC-TP concentrations
- Infant plasma DPV concentrations

### **Adherence**

- Maternal blood TFV-DP and FTC-TP concentrations
- Maternal plasma DPV concentrations
- Participant report of frequency of study product use (e.g., missed doses for oral Truvada and VR removal/expulsions [voluntary and involuntary] and duration without VR in vagina)
- Residual drug levels in returned VRs

### **Acceptability**

- Self-reported attitudes about study product attributes and willingness to use study products during pregnancy
- Proportion of participants who find the study products to be at least as acceptable as other HIV prevention methods

## **Exploratory Endpoints:**

### **Genital Microenvironment**

- Genital microflora characteristics in Gram stain and quantitative PCR
- Biomarker expression in vaginal secretions

## **4.3 Description of Study Population**

The MTN-042 study population will consist of approximately 550 healthy, HIV-uninfected, pregnant females 18-40 (inclusive) years of age who have an uncomplicated singleton pregnancy and are willing to be randomized to study product, and their infants, who meet eligibility criteria as described in [Sections 5.2](#) to [5.4](#). Cohorts 1-2 will each consist of approximately 150 women and their infants, and Cohort 3 will consist of approximately 250 women and their infants.

## **4.4 Time to Complete Accrual**

Time to complete accrual will be approximately 4 to 9 months for recruitment and enrollment of each Cohort, with accrual pauses of approximately 3 to 8 months between Cohorts to allow all

enrolled participants to give birth and for interim safety analyses to be conducted before continuing to the next Cohort, for a study duration of approximately 37-45 months.\* Also, infants born to MTN-042 participants will be followed for approximately one year, for a total study duration of approximately 48-56 months including the one year of infant follow-up for the last study Cohort. See [Section 10.5](#) for additional details.

*\* Overall study duration – from first enrollment through closure of all follow-up – may be longer than planned if temporary site closures due to the COVID-19 pandemic cause delays or pauses in enrolling participants at one or more research sites.*

#### **4.5 Expected Duration of Participation**

The total duration of study participation for each participant will vary depending on gestational age at time of enrollment and length of pregnancy prior to pregnancy outcome, and will range from approximately 12 weeks or less for Cohort 1 to approximately 36 weeks or less for Cohort 3. Participants who become infected with HIV will continue in study follow-up with a modified study visit/procedure schedule for a minimum of twelve months. In addition, infants born to MTN-042 participants will be followed for approximately one year.

#### **4.6 Sites**

MTN-042 participants will be recruited from clinical research sites (CRS) selected by the MTN Executive Committee.

## **5 STUDY POPULATION**

### **5.1 Selection of the Study Population**

Approximately 550 women and their infants will be enrolled in this study. Inclusion and Exclusion Criteria, [Sections 5.2](#) and [5.3](#), respectively, are used to ensure the appropriate selection of study participants for MTN-042.

#### **5.1.1 Recruitment**

Participants will be recruited from a variety of sources across sites including, but not limited to, antenatal clinics, primary care health clinics, HIV testing facilities, gynecology clinics, and community-based organizations. It is anticipated that all participating MTN-042 sites will have established relationships with hospitals and other facilities serving pregnant women. Participants may also be referred to the study from other local research projects and other health and social service providers serving the target study population. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs) prior to use. Site community representatives should advise on these materials before they are submitted to the IRB/EC for review. Community education strategies, including group sessions, may be employed as part of participant and significant other (e.g., partner) outreach.

### 5.1.2 Retention

Once a participant is enrolled into the study, the study site will make every effort to retain the participant in follow-up to minimize possible bias associated with loss-to-follow-up. An average retention rate of 95% will be targeted across sites.

## 5.2 Inclusion Criteria

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

1. Age 18 through 40 years (inclusive) at Enrollment, verified per site standard operating procedures (SOPs).
2. At Enrollment, evidence of a viable, intrauterine, singleton pregnancy with sonographic confirmation, including for gestational age assessment.

*Note: If adequate (per judgment of Investigator of Record [IoR]/designee) sonographic results are not available from medical records at Screening, an ultrasound must be performed and results be available for review at Enrollment for all Cohorts. The ultrasound should be performed no later than the 36<sup>th</sup> week of gestation for Cohort 1 or the 28<sup>th</sup> week of gestation for Cohort 2.*

3. At Enrollment, pregnancy within gestational age limits of the currently enrolling cohort (per [Section 7.13](#)).
4. HIV-uninfected based on testing performed at Screening and Enrollment (per protocol algorithm in [Appendix III](#)).
5. At Screening and Enrollment, intending to continue her pregnancy until delivery.
6. At Screening and Enrollment, intending to deliver at a health center or hospital where adequate records may be obtained, as defined in site SOPs.

*Note: Plans to deliver at a health center or hospital where adequate records may be obtained is inclusionary due to logistical challenges related to collection of VRs, specimens and delivery outcome data outside of those settings.*

7. At Screening and Enrollment, willing to be randomized at time of enrollment to either of the two study arms, and to continue study product use until delivery.
8. Able and willing to comply with all study requirements and complete all study procedures.
9. Able and willing to provide the following:
  - a. Informed consent for her and her infant to be screened for and to enroll in MTN-042, as defined in site SOPs.
  - b. Adequate locator information, as defined in site SOPs.
  - c. Adequate documentation of registration for antenatal care, as defined in site SOPs.
  - d. Permission to contact participant's antenatal and postpartum care provider(s) and to obtain copies of antenatal and postpartum care records.

10. At Screening and Enrollment, agrees not to participate in other research studies involving drugs, medical devices, vaginal products, or vaccines for the duration of study participation, unless approved by the PSRT.

### 5.3 Exclusion Criteria

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

1. Per participant report at Screening and/or Enrollment, intends to do any of the following during the study participation period:
  - a. Use oral PrEP outside the context of study participation.
  - b. Relocate away from the study site.
  - c. Travel away from the study site for a time period that would interfere with study participation.
2. At Screening or Enrollment, has a positive HIV test.
3. At Screening or Enrollment, diagnosed with urinary tract infection (UTI), cervicitis, STI or reproductive tract infection (RTI) requiring treatment per WHO guidelines.

*Note: Detection of BV or candida in the absence of symptoms is not exclusionary. Otherwise eligible participants diagnosed during screening with a UTI, cervicitis, or STI/RTI requiring treatment per WHO guidelines are offered treatment consistent with WHO recommendations. If treatment is completed and symptoms have resolved within 35 days of obtaining informed consent for screening, the participant may be enrolled.*

4. At Enrollment, has a clinically apparent Grade 2 or higher pelvic exam finding.\*

*Note: Cervical friability bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the Investigator of Record (IoR)/designee is considered expected bleeding and is not exclusionary.*

5. Participant report, clinical evidence and/or antenatal/medical care record of any of the following:
  - a. Currently breastfeeding at Enrollment.
  - b. Known adverse reaction to any of the study products (ever).
  - c. Known adverse reaction to latex and polyurethane (ever).
  - d. Symptoms suggestive of acute HIV infection at Screening or Enrollment.
  - e. Non-therapeutic injection drug use in the 12 months prior to Enrollment.
  - f. Use of HIV post-exposure prophylaxis (PEP) and/or PrEP during the current pregnancy.
  - g. Participation in any other research study involving drugs, medical devices, vaginal products, or vaccines during the current pregnancy.
  - h. At Screening or Enrollment, known to have any of the following during the current pregnancy:
    - Multiple gestation
    - Placenta previa
    - Cervical cerclage

- Abnormal fetal anatomy (in the opinion of the IoR or designee)
  - Intrauterine growth restriction
  - Pre-existing or gestational diabetes
  - Hypertensive disorder of pregnancy
  - Severe malaria
  - Treatment for preterm labor
  - Abnormal quantity of amniotic fluid (oligohydramnios or polyhydramnios)
- i. At Screening, known to have had any of the following in a previous pregnancy:
    - Intrauterine growth restriction
    - Gestational diabetes
    - Hypertensive disorder of pregnancy
    - Intrauterine fetal demise (estimated gestational age  $\geq 20$  weeks)
    - Delivery prior to 37 0/7 weeks
  - j. At Enrollment, as determined by the IoR/designee, has any significant obstetrical complication (e.g., premature rupture of membranes, any abnormal placentation) or uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease that would make study participation unsafe.
6. At Screening, has any of the following laboratory abnormalities:
    - a. Positive for hepatitis B surface antigen (HBsAg).
    - b. Aspartate aminotransferase (AST) or alanine transaminase (ALT)  $\geq$  Grade 1.\*\*
    - c. Hemoglobin  $\geq$  Grade 2.\*\*
    - d. Platelet count  $\geq$  Grade 1.\*\*
    - e. Creatinine  $\geq$  Grade 1.\*\*
    - f. Estimated creatinine clearance  $\geq$  Grade 2 (Cockcroft Gault formula).\*\*
    - g. Glycosuria  $\geq$  Grade 2.\*\*
    - h. Proteinuria  $\geq$  Grade 2.\*\*

*Note: Otherwise eligible participants with an exclusionary test (other than HBsAg) may be re-tested during the screening process; re-testing procedure details can be found in the MTN-042 Study Specific Procedures (SSP) Manual. If improvement to a non-exclusionary grade or resolution is documented within 35 days of providing informed consent for screening, the participant may be enrolled.*

7. Has any 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.

*\*Female Genital Grading Table for Use in Microbicide Studies Addendum 1 (Dated November 2007) to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017.*

*\*\*DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017.*

#### **5.4 Infant Enrollment**

Infants are prospectively selected for inclusion in MTN-042 when their mothers enroll in the study. Infants enter the study when they are born, without set inclusion or exclusion criteria. If an infant is deemed too ill to undergo study procedures, the IoR/designee may opt to omit

specific study procedures. Participant mothers will be strongly encouraged to complete one year of follow-up for their infants, but can decline further participation at any time.

## **5.5 Co-enrollment Guidelines**

As indicated in [Sections 5.2](#) and [5.3](#), participants should not take part in other research studies involving drugs, medical devices, vaginal products or vaccines after the Screening Visit and while taking part in this study. Each site will be responsible for defining procedures for management and prevention of co-enrollment prior to initiation.

Exceptions to this guideline may be made for participants to co-enroll in the following types of studies at the discretion of the IoR/designee:

- Participants may take part in ancillary studies approved by the MTN-042 Protocol Chair.
- Participants who acquire HIV may take part in observational and/or interventional studies for HIV-positive persons.
- Participants may take part in observational studies, including pregnancy registries if available.

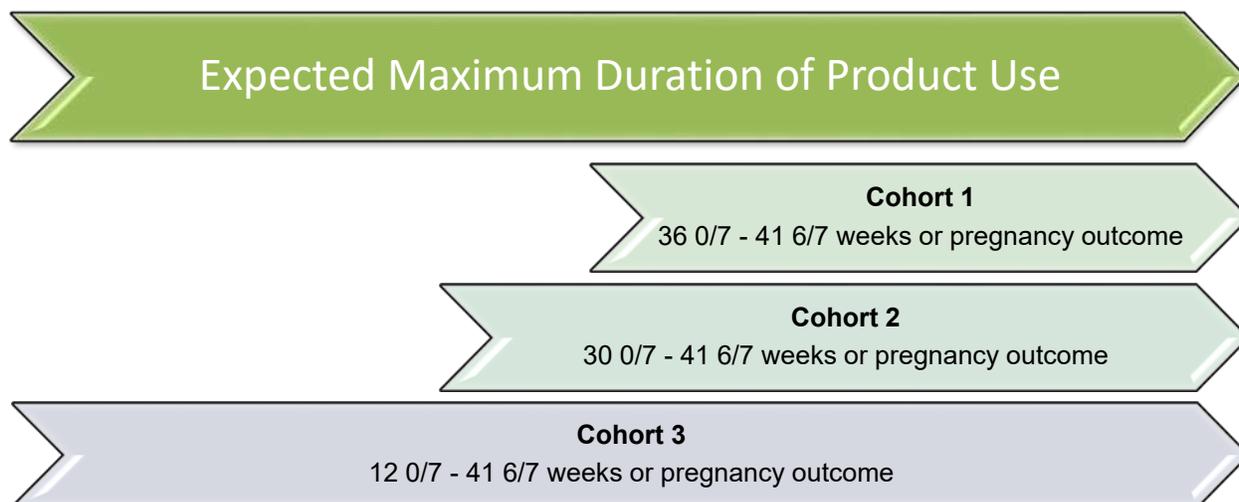
Should any participant report or should study staff discover concurrent participation in any other study after enrolling in MTN-042, the IoR/designee will consult the PSRT regarding ongoing product use and other potential safety considerations associated with co-enrollment.

## **6 STUDY PRODUCT**

### **6.1 Regimen**

Each participant will be randomized (2:1 in Cohorts 1 and 2 and 4:1 in Cohort 3) to one of two study products: a VR containing 25 mg of DPV to be inserted monthly or a Truvada oral tablet containing 200 mg FTC/300 mg TDF taken daily. Participants will use one of the two study products up to 41 6/7 weeks of gestation, i.e., for a maximum of approximately six (6) to thirty (30) weeks depending on their gestational age cohort and time to pregnancy outcome. Figure 4 illustrates the increasing duration of study product exposure for later enrolled groups.

**Figure 4: Expected Maximum Duration of Product Use by Study Cohort**



## **6.2 Administration**

### **6.2.1 DPV VR (25 mg)**

The participant will insert the study VR at the clinic monthly, and if needed, a study clinician/designee will check that the VR is properly placed. Study participants will be given detailed instructions in the clinic on proper VR insertion and removal procedures. Hands should be thoroughly washed before and after study VR insertion and/or removal. Additional details on the use of the DPV VR (VR insertion, removal, procedures in the event of expulsion or loss) will be provided in the MTN-042 SSP.

### **6.2.2 Truvada Tablet**

Study participants will be instructed to take one Truvada oral tablet daily for their assigned study period, and will take the first tablet at the clinic under direct observation. Truvada should be taken close to the same time each day. If a participant misses a dose, the missed dose should be taken as soon as possible, unless the next dose is estimated to be due within 6 hours. If the next dose is estimated to be due within 6 hours, the missed dose must be skipped. The next dose must be taken as originally scheduled.

## **6.3 Study Product Formulation**

### **6.3.1 DPV VR (25 mg)**

The study VR is an off-white, flexible ring containing 25 mg of DPV dispersed in a platinum-catalyzed-cured silicone matrix. The VR dimensions are as follows: 56 mm and 7.7 mm, outer diameter and cross-sectional diameter, respectively. The VR is designed to provide sustained release of drug over a minimum period of one month. DPV 0.3125% (w/w) is dispersed in a flexible, opaque, cured silicone VR delivery device. The DPV VR optimally should be stored in

the site pharmacy at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

### **6.3.2 Truvada Tablet**

Truvada is a fixed dose combination oral tablet containing FTC and TDF. One Truvada tablet contains 200 mg FTC plus 300 mg of TDF. Truvada should be stored at 25°C (77°F). Excursions are permitted between 15°C and 30°C (59°F and 86°F).

## **6.4 Supply and Accountability**

### **6.4.1 Supply**

#### DPV VR (25 mg)

IPM (Silver Spring, MD, USA) will supply and oversee the manufacture of the study VRs and analyze/release the rings under Good Manufacturing Practices (GMP).

#### Truvada Tablet

Truvada tablets are supplied by Gilead Sciences, Inc. (Foster City, CA, USA).

### **6.4.2 Accountability**

Each CRS Pharmacist of Record (PoR) is required to maintain a complete record of all study products received and subsequently dispensed. All study products not dispensed must be returned to the MTN Pharmacist after the study is completed or terminated unless otherwise instructed by the MTN Pharmacist. The procedures to be followed are provided in the MTN-042 Pharmacy Study Product Management Procedures Manual.

All study product dispensed to a participant must be documented by the clinic staff when it is returned. This includes VR(s) brought back to the clinic by the participant and any VR removed at the clinic visit as well as any unused tablets. Any study products not returned must also be documented by the clinic.

### **6.4.3 Study Product Dispensing**

Study VRs and tablets are dispensed only to enrolled study participants or clinic staff on behalf of the participant, upon receipt of a written prescription from an authorized prescriber. An authorized prescriber includes the IoR or a licensed clinician directly responsible to the IoR as noted on the FDA Form 1572.

Dispensing takes place on the day of enrollment and at each scheduled monthly follow-up visit until the participant's pregnancy outcome is ascertained. The pharmacist will dispense one VR per month or one bottle of 30 tablets per month.

During study product use, participants will receive a new VR or a supply of tablets monthly. Product will be dispensed in quantities sufficient to last until the next scheduled monthly study visit. In the event that additional study products between visits are needed, participants will be instructed to contact the study site. If the participant is unable to attend their next scheduled visit, it is up to the discretion of the IoR/designee to allow the provision of additional study product. The IoR/designee will document approval of this additional dispensation.

## 6.5 Retrieval of Study Product

Study participants will be instructed to return all study products (unused Truvada oral tablets or unused/used VR) to the clinic at each scheduled monthly study visit. Clinic staff should forward all unused study products to the site pharmacy. In the event that study products are not returned at the end of each study visit, site staff members will make every effort to encourage participants to return study product as soon as possible. If study product is not returned within the time frames outlined below for permanent discontinuations or temporary holds, the MTN-042 PSRT must be notified.

**Table 1: Retrieval of Study Product**

Condition	Timeframe for Retrieval
Permanent discontinuation due to potential HIV infection or Grade 3 or higher renal or hepatic toxicity	Within 24 hours
Permanent discontinuation for any other reason or IoR discretion	Within 5 working days
Temporary hold for reasons with expected duration of at least 7 days	Within 7 working days
Pregnancy outcome (e.g., delivery)	Within 10 working days

Participants will be instructed to return all study product (used or unused) prior to exiting the study. Specifically, for each participant, all VRs or oral tablets remaining in the participant's possession should be retrieved at the Post-Pregnancy Outcome (PPO) visit. If the participant does not bring her study product to this visit, or if the participant delivers outside of a hospital or health center, study staff must arrange to retrieve the VR or oral tablets within 10 business days of her pregnancy outcome.

## 6.6 Concomitant Medications and Practices

With the exception of those listed below as prohibited, enrolled participants may use concomitant medications during study participation. Throughout the course of the study, prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations will be recorded as concomitant medications on a case report form (CRF) designated for that purpose. Intravaginal product use and practices will also be recorded.

The use of vaginal products, including, spermicides, lubricants, contraceptive VRs, douches, vaginal medications, etc., is prohibited. Receptive sexual activity (including penile-vaginal intercourse, anal intercourse, receptive oral intercourse, finger stimulation) and inserting any non-study objects into the vagina (including tampons, pessaries, sex toys, female condoms, diaphragms, menstrual cups, cervical caps or any other vaginal barrier method, etc.), is permitted, except for 24 hours prior to clinic visits.

## 6.7 Prohibited Medications

Concomitant use of medications for PEP and PrEP outside the context of study participation is prohibited (see [Section 9.3](#) for product hold details).

## 6.8 Condoms

All participants will be offered condoms. The condoms will be made available in the clinic and will be dispensed by the clinic staff.

## 7 STUDY PROCEDURES

An overview of the study visit and evaluations schedules are provided in [Appendices I](#) and [II](#). Presented below is additional information on visit-specific study procedures. With approved SOPs and participant permission, appropriate components of some study visits may be completed off-site. Detailed instructions to guide and standardize operating procedures across sites as well as information regarding the study visit windows are provided in the MTN-042 SSP Manual available at <http://www.mtnstopshiv.org/research/studies>.

**Figure 5: Study Visit Schedule – Cohort 1**

<b>Cohort 1</b>	
	Screening
Enrollment Window	Enrollment
36 0/7 weeks of gestation – 37 6/7 weeks of gestation	Every odd-numbered week after Enrollment (e.g., follow-up weeks 1, 3, 5) until pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Every even-numbered week after Enrollment (e.g., follow-up weeks 2, 4, 6) until pregnancy outcome
<b>Infants enroll</b> →	Post-pregnancy outcome (delivery hospital/facility or clinic)
	1-week post-pregnancy outcome (phone, home or clinic as needed per local standard of care)
<b>Mothers exit</b> →	Approximately 6 weeks post-pregnancy outcome
	Approximately 6 months post-delivery
	Approximately 12 months post-delivery

**Figure 6: Study Visit Schedule – Cohort 2**

<b>Cohort 2</b>	Screening
Enrollment Window 30 0/7 weeks of gestation – 35 6/7 weeks of gestation	Enrollment
	1-week (phone, home or clinic as needed per local standard of care)
	2-week
	3-week (phone, home or clinic as needed per local standard of care)
	4-week
	Every odd-numbered week after 36th week of gestation (e.g., follow-up weeks 5, 7, 9) until pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Every even-numbered week including and after 36th week of gestation (e.g., follow-up weeks 6, 8, 10) until pregnancy outcome
	Post-pregnancy outcome visit (delivery hospital/facility or clinic)
	1-week post-pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Approximately 6 weeks post-pregnancy outcome
<b>Infants enroll</b> →	Approximately 6 months post-delivery
	Approximately 12 months post-delivery
<b>Mothers exit</b> →	

**Figure 7: Study Visit Schedule – Cohort 3**

<b>Cohort 3</b>	Screening
Enrollment Window 12 0/7 weeks of gestation – 29 6/7 weeks of gestation	Enrollment
	1-week (phone, home or clinic as needed per local standard of care)
	2-week
	3-week (phone, home or clinic as needed per local standard of care)
	4-week and every 4 weeks until 36th week of gestation
	Every odd-numbered week after 36th week of gestation (e.g., follow-up weeks 19, 21, 23) until pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Every even-numbered week including and after 36th week of gestation (e.g., follow-up weeks 20, 22, 24) until pregnancy outcome
	Post-pregnancy outcome visit (delivery hospital/facility or clinic)
	1-week post-pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Approximately 6 weeks post-pregnancy outcome
<b>Infants enroll</b> →	Approximately 6 months post-delivery
	Approximately 12 months post-delivery
<b>Mothers exit</b> →	

## 7.1 Pre-Screening

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants either on-site or at off-site locations. Study staff will consult with their local IRBs/ECs regarding pre-screening potential pregnant participants. If deemed acceptable, during pre-screening interactions study staff may explain the study to potential participants and ascertain elements of presumptive eligibility, to be confirmed at clinic screening visits. A key

element of presumptive eligibility, gestational age, will be confirmed by ultrasound conducted prior to enrollment for all Cohorts but no later than the potential participant’s 36<sup>th</sup> week of gestation for Cohort 1 or 28<sup>th</sup> week of gestation for Cohort 2. This may occur during pre-screening as part of standard of care, especially for Cohorts 1 and 2. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded 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 potential participant identifiers. Whenever de-identified process information is recorded, it will be stored at the study site. At each site, procedures and documentation will comply with local IRB/EC requirements. Potential participants may be pre-screened for the currently enrolling group or for the subsequent group not yet open for enrollment, with attention to the participant’s gestational age and the screening window. Any participant who at any time expresses an interest in involving her current sexual partner and/or family members in discussions about study participation will be encouraged to bring them to the clinic, where a staff member can explain the study and answer any questions they may have.

## 7.2 Visit 1: Screening Visit

A Screening Visit may take place up to 35 days prior to the Enrollment Visit (Day 0). Multiple visits may be conducted to complete all required screening procedures, if necessary, including sonographic confirmation of gestational age. Potential participants will be instructed to bring antenatal records (e.g., antenatal care card) with them to the Screening Visit, if possible, to expedite the screening process. Participants will also provide permission for the study site to obtain copies of their antenatal records, including laboratory and ultrasound results, for review prior to final confirmation of eligibility. If required per local laws and regulations, signed record release forms will be obtained. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined.

*NOTE: Participants who fail their first screening attempt may be re-screened once.*

**Table 2: Visit 1 – Screening Visit**

<b>Visit 1 – Screening Visit</b>	
<b>Component</b>	<b>Procedures</b>
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Obtain informed consent for screening and enrollment</li> <li>• Obtain signed medical records release and antenatal care provider information (if required per local laws/regulations)</li> <li>• Obtain planned location for delivery</li> <li>• Schedule ultrasound (if adequate records not available at Screening)</li> <li>• Assign a unique Participant Identification (PTID) Number</li> <li>• Assess eligibility</li> <li>• Collect demographic information</li> <li>• Collect locator information</li> <li>• Provide reimbursement</li> <li>• Schedule next visit*</li> </ul>
<b>Behavioral/Counseling</b>	<ul style="list-style-type: none"> <li>• HIV pre- and post-test counseling</li> <li>• HIV/STI risk reduction counseling</li> </ul>

Visit 1 – Screening Visit		
Component	Procedures	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>Review medical history and obstetric symptoms</li> <li>Review available ultrasound results and antenatal care records</li> <li>Review concomitant medications and vaginal products</li> <li>Physical exam</li> <li>Pelvic exam*</li> <li>Obstetric abdominal exam</li> <li>Calculate gestational age</li> <li>Treat RTI/UTI/STIs*</li> <li>Disclose available test results</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>Dipstick urinalysis (UA) (and/or culture**)</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>HIV-1 testing</li> <li>HBsAg</li> <li>AST/ALT</li> <li>Creatinine</li> <li>Complete blood count (CBC) with platelets</li> <li>Syphilis serology</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>Nucleic acid amplification test (NAAT) for <i>Neisseria gonorrhoeae</i> (GC)/<i>Chlamydia trachomatis</i> (CT)/<i>Trichomonas vaginalis</i> (Trich)</li> <li>Wet prep/potassium hydroxide (KOH) wet mount for candidiasis and/or BV*</li> <li>Vaginal pH*</li> </ul>
<b>Study Product/Supplies</b>		<ul style="list-style-type: none"> <li>Offer condoms</li> </ul>

\* if indicated and/or per local standard of care

\*\* Per local standard of care

### 7.3 Visit 2: Enrollment Visit (Day 0)

The Enrollment Visit must be completed within 35 days of the Screening Visit.

**Table 3: Visit 2 – Enrollment Visit**

Visit 2 – Enrollment Visit	
Component	Procedures
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>Re-assess and confirm eligibility</li> <li>Review/confirm informed consent</li> <li>Randomization</li> <li>Review/update locator information</li> <li>Provide reimbursement</li> <li>Schedule next visit/contact*</li> </ul>
<b>Behavioral/Counseling</b>	<ul style="list-style-type: none"> <li>Baseline behavioral assessment</li> <li>Baseline product acceptability assessment (Cohorts 2-3 only)</li> <li>HIV pre- and post-test counseling</li> <li>HIV/STI risk reduction counseling</li> <li>Protocol adherence counseling</li> </ul>

Visit 2 – Enrollment Visit		
Component	Procedures	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical history and obstetric symptoms</li> <li>• Review/update available ultrasound results and antenatal care records</li> <li>• Review/update concomitant medications and vaginal products</li> <li>• Targeted physical exam*</li> <li>• Pelvic exam</li> <li>• Obstetric abdominal exam</li> <li>• Confirm calculation of gestational age</li> <li>• Treat RTI/UTI/STIs*</li> <li>• Disclose available test results</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Dipstick UA (and/or culture**)</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• HIV-1 testing</li> <li>• Creatinine</li> <li>• AST/ALT</li> <li>• CBC with platelets</li> <li>• Syphilis serology*</li> <li>• Plasma archive</li> <li>• Dried blood spot (DBS) for baseline TFV-DP and FTC-TP drug levels</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>• NAAT for GC/CT/Trich*</li> <li>• Wet prep/KOH wet mount for candidiasis and/or BV*</li> <li>• Vaginal pH</li> <li>• Vaginal swab(s) for microbiota</li> <li>• Vaginal Gram stain</li> <li>• Vaginal swab(s) for biomarkers</li> </ul>
<b>Study Product/Supplies</b>	<ul style="list-style-type: none"> <li>• Provide study VR or study tablets</li> <li>• Insertion of study VR at the clinic (clinician to check VR placement if inserted by participant) (for DPV group) or DOD of first study tablet (for Truvada group)</li> <li>• Provide product use instructions</li> <li>• Offer condoms</li> </ul>	

\* if indicated and/or per local standard of care

\*\* Per local standard of care

## 7.4 Follow-up Visits/Contacts Prior to Pregnancy Outcome

### 7.4.1 Phone Contacts Prior to Pregnancy Outcome

This phone contact (or visit, if needed per local standard of care) will occur 1 week (i.e., approximately 7 days) and 3 weeks (i.e., approximately 21 days) following enrollment for all participants. The 1-week phone contact can occur no earlier than 6 days before the target date and no later than 2 days following the target date. The 3-week phone contact can occur no earlier than 2 days before the target date and no later than 2 days following the target date. Beginning on their 36<sup>th</sup> week of gestation until pregnancy outcome, this phone contact (or visit, if needed) will also occur every odd-numbered week of study participation. These contacts can occur no earlier than 2 days before the target date and no later than 2 days following the target

date. This phone contact may not occur for Cohort 1 participants due to proximity of delivery. Participants contacted over the phone who show a need for counseling and/or treatment for RTI/UTI/STIs can have these procedures conducted as part of an interim visit if scheduling allows.

**Table 4: Phone Contacts Prior to Pregnancy Outcome**

Phone Contacts Prior to Pregnancy Outcome	
Component	Procedures
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Review/update planned location for delivery</li> <li>• Provide reimbursement (sites to reference SOPs)</li> <li>• Schedule next visit/contact</li> </ul>
<b>Behavioral/Counseling</b>	<ul style="list-style-type: none"> <li>• Protocol adherence counseling*</li> <li>• HIV/STI risk reduction counseling*</li> </ul>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical history and obstetric symptoms</li> <li>• Review/update concomitant medications and vaginal products</li> <li>• Collect AEs</li> <li>• Treat RTI/UTI/STIs*</li> <li>• Disclose available test results</li> </ul>

\* if indicated and/or per local standard of care

#### 7.4.2 Bi-weekly Visits After 36<sup>th</sup> Week of Gestation

This visit will occur for all participants every two weeks (i.e., approximately 14 days) following their 36<sup>th</sup> week (inclusive – the visit should occur in the 36<sup>th</sup> week) of gestation until pregnancy outcome. This means that participants in Cohort 1 will have bi-weekly follow-up visits every two weeks (i.e., approximately 14 days) following their Enrollment Visit until pregnancy outcome. Beginning on their 36<sup>th</sup> week of gestation until pregnancy outcome, participants in Cohorts 2-3 will have bi-weekly follow-up visits every even-numbered week of study participation. Participants in Cohorts 2-3 will also have a follow-up visit two and four weeks following their Enrollment Visit, but those will be called the 2-week and 4-week Visits (see Sections [7.4.3](#) and [7.4.4](#)). These visits can occur no earlier than 4 days before the target date and no later than 4 days following the target date. Participants in the DPV VR group will be instructed to remove the VR if they believe they are going into labor and bring it with them to the PPO Visit. This follow-up visit may not occur for all participants due to proximity of delivery (especially Cohort 1).

**Table 5: Bi-weekly Visits After 36<sup>th</sup> Week of Gestation**

Bi-weekly Visits After 36 <sup>th</sup> Week (inclusive) of Gestation	
Component	Procedures
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Review/update planned location for delivery</li> <li>• Provide reimbursement</li> <li>• Schedule next visit/contact</li> </ul>
<b>Behavioral/Counseling</b>	<ul style="list-style-type: none"> <li>• HIV pre- and post-test counseling ▲</li> <li>• HIV/STI risk reduction counseling ▲</li> <li>• Protocol adherence counseling</li> <li>• Contraceptive counseling ▲</li> <li>• In-depth interview (subset) ◆</li> </ul>

Bi-weekly Visits After 36 <sup>th</sup> Week (inclusive) of Gestation		
Component	Procedures	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical history and obstetric symptoms</li> <li>• Review/update available ultrasound results and antenatal care records</li> <li>• Review/update concomitant medications and vaginal products</li> <li>• Targeted physical exam*</li> <li>• Pelvic exam*</li> <li>• Obstetric abdominal exam</li> <li>• Collect AEs</li> <li>• Treat RTI/UTI/STIs*</li> <li>• Disclose available test results</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Dipstick UA (and/or culture**) *</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• HIV-1 testing ▲</li> <li>• Creatinine (Cohort 1 only) ▲</li> <li>• Creatinine (Cohorts 2-3)*</li> <li>• AST/ALT*</li> <li>• CBC with platelets*</li> <li>• Syphilis serology*</li> <li>• DBS for TFV-DP and FTC-TP drug levels (Truvada group)</li> <li>• Plasma for DPV drug levels (DPV group)</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>• NAAT for GC/CT/Trich*</li> <li>• Wet prep/KOH wet mount for candidiasis and/or BV*</li> <li>• Vaginal pH*</li> <li>• Vaginal swab(s) for microbiota</li> <li>• Vaginal Gram stain</li> <li>• Vaginal swab(s) for biomarkers</li> </ul>
	<b>Study Product</b>	<ul style="list-style-type: none"> <li>• Adherence assessment: Returned study VR *</li> </ul>
<b>Study Product/Supplies</b>	<ul style="list-style-type: none"> <li>• Remove and/or collect study VR or study tablets *</li> <li>• Provide study VR or study tablets *</li> <li>• Provide product use instructions *</li> <li>• Insertion of study VR at the clinic (clinician to check VR placement, as needed) (for DPV group) or DOD of first study tablet (for Truvada group)<sup>†</sup></li> <li>• Offer condoms</li> </ul>	

\* if indicated and/or per local standard of care, \*\* Per local standard of care, ▲ Required at second Bi-weekly Visit and if indicated at all others, <sup>†</sup> Required if product resupply occurs during visit, ♦ May be scheduled any time between 1st Bi-weekly Visit and study exit to accommodate participant availability

### 7.4.3 2-week Visit (Cohorts 2-3)

This visit will occur 2 weeks (i.e., approximately 14 days) following enrollment for participants in Cohorts 2-3. This visit can occur no earlier than 4 days before the target date and no later than 4 days following the target date. Participants in Cohort 1 will also have follow-up visits two weeks following their Enrollment Visit if they are still pregnant at that time, but those are called the Bi-weekly Visits After 36<sup>th</sup> Week of Gestation (see [Section 7.4.2](#)).

**Table 6: 2-week Visit (Cohorts 2-3)**

2-week Visit (Cohorts 2-3)		
Component	Procedures	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>Review/update locator information</li> <li>Provide reimbursement</li> <li>Schedule next visit/contact</li> </ul>	
<b>Behavioral/Counseling</b>	<ul style="list-style-type: none"> <li>HIV pre- and post-test counseling*</li> <li>HIV/STI risk reduction counseling*</li> <li>Protocol adherence counseling</li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>Review/update medical history and obstetric symptoms</li> <li>Review/update concomitant medications and vaginal products</li> <li>Targeted physical exam*</li> <li>Pelvic exam*</li> <li>Obstetric abdominal exam</li> <li>Collect AEs</li> <li>Treat RTI/UTI/STIs*</li> <li>Disclose available test results</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>Dipstick UA (and/or culture**) *</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>HIV-1 testing*</li> <li>Creatinine*</li> <li>AST/ALT*</li> <li>CBC with platelets*</li> <li>Syphilis serology*</li> <li>DBS for TFV-DP and FTC-TP drug levels (for Truvada group)</li> <li>Plasma for DPV drug levels (for DPV group)</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>NAAT for GC/CT/Trich*</li> <li>Wet prep/KOH wet mount for candidiasis and/or BV*</li> <li>Vaginal pH*</li> <li>Vaginal swab(s) for microbiota</li> <li>Vaginal Gram stain</li> <li>Vaginal swab(s) for biomarkers</li> </ul>
<b>Study Product/Supplies</b>		<ul style="list-style-type: none"> <li>Offer condoms</li> </ul>

\* if indicated and/or per local standard of care

\*\* Per local standard of care

### 7.4.4 4-week Visit(s) (Cohorts 2-3)

This visit will occur 4 weeks (i.e., approximately 28 days) following enrollment for participant Cohorts 2-3. For Cohort 3, this visit will also occur every 4 weeks after their first 4-week Visit until their 36<sup>th</sup> week (inclusive – this visit should occur in the 36<sup>th</sup> week) of gestation. These visits

can occur no earlier than 4 days before the target date and no later than 4 days following the target date. Participants in Cohort 1 will also have follow-up visits four weeks following their Enrollment Visit if they are still pregnant at that time, but those are called the Bi-weekly Visits After 36<sup>th</sup> Week of Gestation (see [Section 7.4.2](#)).

**Table 7: 4-week Visit(s) (Cohorts 2-3)**

<b>4-week Visit(s) (Cohorts 2-3)</b>		
<b>Component</b>	<b>Procedures</b>	
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>Review/update locator information</li> <li>Provide reimbursement</li> <li>Schedule next visit/contact</li> </ul>	
<b>Behavioral/Counseling</b>	<ul style="list-style-type: none"> <li>Behavioral assessment <math>\phi</math></li> <li>Product acceptability assessment <math>\phi</math></li> <li>Social harms assessment <math>\phi</math></li> <li>In-depth interview (IDI) (subset) <math>\diamond</math></li> <li>HIV pre- and post-test counseling</li> <li>HIV/STI risk reduction counseling</li> <li>Protocol adherence counseling</li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>Review/update medical history and obstetric symptoms</li> <li>Review/update available ultrasound results and antenatal care records</li> <li>Review/update concomitant medications and vaginal products</li> <li>Targeted physical exam</li> <li>Pelvic exam*</li> <li>Obstetric abdominal exam</li> <li>Collect AEs</li> <li>Treat RTI/UTI/STIs*</li> <li>Disclose available test results</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>Dipstick UA (and/or culture**) <math>\nabla</math></li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>HIV-1 testing (or confirmation of testing)</li> <li>Creatinine <math>\pi</math></li> <li>AST/ALT <math>\nabla</math></li> <li>CBC with platelets <math>\nabla</math></li> <li>Syphilis serology*</li> <li>DBS for TFV-DP and FTC-TP drug levels (for Truvada group)</li> <li>Plasma for DPV drug levels (for DPV group)</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>NAAT for GC/CT/Trich*</li> <li>Wet prep/KOH wet mount for candidiasis and/or BV*</li> <li>Vaginal pH*</li> <li>Vaginal swab(s) for microbiota</li> <li>Vaginal Gram stain</li> <li>Vaginal swab(s) for biomarkers</li> </ul>
	<b>Study Product</b>	<ul style="list-style-type: none"> <li>Adherence assessment: Returned study VR</li> </ul>

4-week Visit(s) (Cohorts 2-3)	
Component	Procedures
Study Product/Supplies	<ul style="list-style-type: none"> <li>Remove and/or collect study VR or study tablets</li> <li>Provide study VR or study tablets</li> <li>Provide product use instructions</li> <li>Insertion of study VR at the clinic (clinician to check VR placement, as needed) (for DPV group) or DOD of first study tablet (for Truvada group)</li> <li>Offer condoms</li> </ul>

\* if indicated and/or per local standard of care, \*\* Per local standard of care, ♦ May be scheduled any time between 1st 4-week Visit and study exit to accommodate participant availability, ϕ Required at 1st 4-week Visit for Cohorts 2-3, and also at the 4-week visit corresponding to, or immediately before, the 36th week of gestation for Cohort 3, ▽ Required at 1st 4-week Visit for Cohorts 2-3, and also for Cohort 3 at the visit corresponding to, or immediately following, the 28th week of gestation, π Required at 1<sup>st</sup> 4-week Visit and every 12 weeks thereafter

## 7.5 Follow-up Visits After Pregnancy Outcome

### 7.5.1 Post-Pregnancy Outcome (PPO) Visit

All participants will have a follow-up visit as soon after their pregnancy outcome as possible but no later than two weeks (i.e., 14 days) of their pregnancy outcome. If the PPO Visit is missed, a subset of these procedures will be made up as part of an interim visit as outlined in the MTN-042 SSP Manual.

**Table 8: PPO Visit – Mothers**

PPO Visit – Mothers		
Component	Procedures	
Administrative and Regulatory	<ul style="list-style-type: none"> <li>Review/update locator information</li> <li>Review/update signed medical records release and delivery care provider information (if required per local laws/regulations)</li> <li>Obtain actual location of delivery</li> <li>Provide reimbursement</li> <li>Schedule next visit/contact*</li> </ul>	
Behavioral/Counseling	<ul style="list-style-type: none"> <li>Contraceptive counseling*</li> <li>HIV pre- and post-test counseling*</li> <li>HIV/STI risk reduction counseling*</li> <li>Protocol adherence counseling</li> <li>Behavioral assessment (Cohorts 2-3 only)</li> </ul>	
Clinical	<ul style="list-style-type: none"> <li>Review/update medical history and obstetric symptoms</li> <li>Review/update available delivery and antenatal care records</li> <li>Review/update concomitant medications and vaginal products</li> <li>Targeted physical exam</li> <li>Collect AEs</li> <li>Treat RTI/UTI/STIs*</li> <li>Disclose available test results</li> </ul>	
Laboratory	Urine	<ul style="list-style-type: none"> <li>Dipstick UA (and/or culture**) *</li> </ul>

PPO Visit – Mothers		
Component		Procedures
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• HIV-1 testing*</li> <li>• Creatinine*</li> <li>• AST/ALT*</li> <li>• CBC with platelets*</li> <li>• Syphilis serology*</li> <li>• DBS for TFV-DP and FTC-TP drug levels (for Truvada group)</li> <li>• Plasma for DPV drug levels (for DPV group)</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>• NAAT for GC/CT/Trich*</li> <li>• Wet prep/KOH wet mount for candidiasis and/or BV*</li> </ul>
	<b>Study Product</b>	<ul style="list-style-type: none"> <li>• Adherence assessment: Returned study VR</li> </ul>
<b>Study Product/Supplies</b>		<ul style="list-style-type: none"> <li>• Remove and/or collect study VR or study tablets (if final VR or tablets not already collected)</li> <li>• Offer condoms</li> </ul>

\* if indicated and/or per local standard of care

\*\* Per local standard of care

**Table 9: PPO Visit – Infants**

PPO Visit – Infants		
Component		Procedures
<b>Administrative and Regulatory</b>		<ul style="list-style-type: none"> <li>• Obtain consent for infant if not already obtained</li> <li>• Collect/review/update locator information</li> <li>• Provide reimbursement</li> <li>• Schedule next visit/contact*</li> </ul>
<b>Clinical</b>		<ul style="list-style-type: none"> <li>• Review infant health, anthropometry, feeding history</li> <li>• Review/update delivery records</li> <li>• Review/update infant health records</li> <li>• Review/update concomitant medications</li> <li>• Physical exam</li> <li>• Collect AEs</li> <li>• Disclose available test results</li> </ul>
<b>Laboratory</b>	<b>Blood</b>	<ul style="list-style-type: none"> <li>• HIV-1 testing*</li> <li>• Creatinine</li> <li>• AST/ALT*</li> <li>• CBC with platelets*</li> <li>• DBS for TFV-DP and FTC-TP drug levels (for infants born to mothers in the Truvada group)</li> <li>• Plasma for DPV drug levels (for infants born to mothers in the DPV group)</li> </ul>

\* if indicated and/or per local standard of care

### 7.5.2 1-week PPO Phone Contact

This phone contact (or visit, if needed) will occur 1 week (i.e., approximately 7 days) following pregnancy outcome for all participants, and may be skipped if the PPO Visit occurs within the visit window for this phone contact. This visit can occur no earlier than 7 days before the target

date and no later than 7 days following the target date. All participants will be asked about the outcome of their pregnancy, including the status of their infant at the time of delivery. No infant procedures will occur during the phone contact unless the infant has already been enrolled. Participants who show a need for counseling and/or treatment for RTI/UTI/STIs can have these procedures conducted as part of an interim visit if scheduling allows.

**Table 10: 1-week PPO Phone Contact – Mothers**

1-week PPO Phone Contact – Mothers	
Component	Procedures
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Provide reimbursement (sites to reference SOPs)</li> <li>• Schedule next visit/contact</li> </ul>
<b>Behavioral/Counseling</b>	<ul style="list-style-type: none"> <li>• Protocol adherence counseling*</li> <li>• HIV/STI risk reduction counseling*</li> </ul>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical history and obstetric symptoms</li> <li>• Review/update concomitant medications and vaginal products</li> <li>• Collect AEs</li> <li>• Treat RTI/UTI/STIs*</li> <li>• Disclose available test results</li> </ul>

\* if indicated and/or per local standard of care

**Table 11: 1-week PPO Phone Contact – Infants**

1-week PPO Phone Contact – Infants	
Component	Procedures
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Collect/review/update locator information</li> <li>• Provide reimbursement</li> <li>• Schedule next visit/contact</li> </ul>
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update infant health, anthropometry, feeding history</li> <li>• Review/update concomitant medications</li> <li>• Collect AEs</li> <li>• Disclose available test results</li> </ul>

### 7.5.3 6-week PPO/Study Exit Visit (SEV)/Early SEV

All participants, including infants, will have follow-up visits six weeks (i.e., approximately 42 days) following pregnancy outcome. This visit can occur no earlier than 13 days before the target date and no later than 13 days following the target date. This will be the Study Exit Visit (SEV) for all participant mothers. This set of visit procedures will also be performed as the Early SEV for participants who are withdrawn from the study for any reason, if they are willing to complete a final study visit.

**Table 12: 6-week PPO/SEV/Early SEV – Mothers**

6-week PPO/SEV/Early SEV – Mothers	
Component	Procedures
<b>Administrative and Regulatory</b>	<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Provide reimbursement</li> <li>• Schedule next visit/contact*</li> </ul>

6-week PPO/SEV/Early SEV – Mothers		
Component	Procedures	
<b>Behavioral/Counseling</b>	<ul style="list-style-type: none"> <li>• Behavioral assessment</li> <li>• Social harms assessment</li> <li>• Social benefits assessment</li> <li>• Contraceptive counseling</li> <li>• Protocol adherence counseling</li> <li>• HIV pre- and post-test counseling</li> <li>• HIV/STI risk reduction counseling</li> </ul>	
<b>Clinical</b>	<ul style="list-style-type: none"> <li>• Review/update medical history and obstetric symptoms</li> <li>• Review/update available delivery and postpartum care records</li> <li>• Review/update concomitant medications and vaginal products</li> <li>• Targeted maternal physical exam*</li> <li>• Pelvic exam*</li> <li>• Collect AEs</li> <li>• Treat RTI/UTI/STIs*</li> <li>• Disclose available test results</li> </ul>	
<b>Laboratory</b>	<b>Urine</b>	<ul style="list-style-type: none"> <li>• Dipstick UA (and/or culture**)</li> <li>• Offer pregnancy testing</li> </ul>
	<b>Blood</b>	<ul style="list-style-type: none"> <li>• HIV-1 testing</li> <li>• Creatinine</li> <li>• AST/ALT</li> <li>• CBC with platelets</li> <li>• Syphilis serology</li> </ul>
	<b>Pelvic</b>	<ul style="list-style-type: none"> <li>• NAAT for GC/CT/Trich</li> <li>• Wet prep/KOH wet mount for candidiasis and/or BV*</li> <li>• Vaginal pH</li> <li>• Vaginal swab(s) for microbiota</li> <li>• Vaginal Gram stain</li> <li>• Vaginal swab(s) for biomarkers</li> </ul>
<b>Study Product/Supplies</b>		<ul style="list-style-type: none"> <li>• Offer condoms</li> </ul>

\* if indicated and/or per local standard of care

\*\* Per local standard of care

**Table 13: 6-week PPO Visit – Infants**

6-week PPO Visit – Infants		
Component		Procedures
Administrative and Regulatory		<ul style="list-style-type: none"> <li>• Collect/review/update locator information</li> <li>• Provide reimbursement</li> <li>• Schedule next visit/contact</li> </ul>
Clinical		<ul style="list-style-type: none"> <li>• Review/update infant health, anthropometry, feeding history</li> <li>• Review/update infant health records</li> <li>• Review/update concomitant medications</li> <li>• Targeted infant physical exam</li> <li>• Collect AEs</li> <li>• Disclose available test results</li> </ul>
Laboratory	Blood	<ul style="list-style-type: none"> <li>• HIV-1 testing*</li> <li>• Creatinine</li> <li>• AST/ALT*</li> <li>• CBC with platelets*</li> </ul>

\* if indicated and/or per local standard of care

## 7.6 Semi-annual PPO Visits/Early SEV for Infants

All participants who deliver live births will bring their infant for a follow-up visit 6 months (i.e., approximately 26 weeks) and 12 months (i.e., approximately 52 weeks) following delivery. These visits can occur no earlier than 28 days before the target date and no later than 28 days following the target date. This set of visit procedures will also be performed as the Early SEV for infants who are withdrawn from the study for any reason, if their mothers are willing to bring them in for a final study visit.

**Table 14: Semi-annual PPO Visits/Early SEV**

Semi-annual PPO Visits/Early SEV for Infants		
Component		Procedures
Administrative and Regulatory		<ul style="list-style-type: none"> <li>• Review/update locator information</li> <li>• Provide reimbursement</li> <li>• Schedule next visit/contact (if indicated at Month 12)</li> </ul>
Clinical		<ul style="list-style-type: none"> <li>• Review/update infant health, anthropometry, feeding history</li> <li>• Review/update infant health records</li> <li>• Review/update concomitant medications</li> <li>• Targeted infant physical exam</li> <li>• Collect AEs</li> <li>• Disclose available test results</li> </ul>
Laboratory	Blood	<ul style="list-style-type: none"> <li>• HIV-1 testing*</li> <li>• Creatinine*</li> <li>• AST/ALT*</li> <li>• CBC with platelets*</li> </ul>
Study Product/Supplies		<ul style="list-style-type: none"> <li>• Offer condoms to mother</li> </ul>

\* if indicated and/or per local standard of care

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

Participants who permanently discontinue study product use due to an AE must continue to be followed until resolution or stabilization of the AE is documented.

Guidance related to permanent discontinuation of study product, including additional information regarding consultation with the PSRT, is included in [Section 9](#).

### 7.7.1 Participants Who Become Infected with HIV

If a participant acquires HIV-1 after the Enrollment Visit, she will be referred to local care and treatment services that have capacity to provide ART services. Participants who acquire an HIV infection will continue in study follow-up with a modified study visit/procedure schedule for a minimum of twelve months. Protocol-specified procedures for MTN-042 will continue except the following:

- HIV-1 testing
- Provision of study VR or study tablets, provision of product use instructions, and retrieval and collection of study VR or study tablets
- Collection of drug level and biomarker specimens
- Behavioral and product acceptability assessments
- Provision of HIV pre- and post-test, and product adherence counseling

Upon documentation of the first positive rapid HIV test, the following procedures must be performed regardless of whether or not they are scheduled to be completed:

- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR
- CBC with platelets
- AST/ALT
- Blood creatinine and calculation of creatinine clearance
- Collection of drug level and biomarker specimens

Upon confirmation of HIV infection per the algorithm in [Appendix IV](#), the following procedures are performed on the mother at the following time points:

- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR will be performed at the clinic visit immediately following confirmation of an HIV-infection and every three months thereafter for a minimum of twelve months. (See MTN-042 SSP for other procedures to be completed during these quarterly visits.)
- HIV-1 genotyping will be performed on the stored plasma closest to the time of HIV-1 infection.
- HIV-1 RNA PCR or HIV-1 genotyping may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center (LC).

Upon delivery of a live infant by an HIV-infected participant, or upon HIV seroconversion of a participant between the birth of her infant and her infant's first birthday (whether found via study testing or report from external testing), the following procedures are performed on the infant if consented to by the participant:

- Infant HIV-1 testing will be performed at the PPO Visit or as soon as possible after delivery for infants born to HIV-positive participants. For infants whose mothers seroconverted after they were born, HIV-1 testing will be performed as soon as possible after discovery of the mother's HIV-positive status. Infant HIV-1 testing (including confirmation of HIV infection) will be done per local standard of care and may occur at a scheduled visit or an interim visit.

The following procedures are performed on HIV-positive infants if consented to by the participant:

- Immediately following confirmation of HIV infection, perform plasma collection, CD4+ T cell count, HIV-1 RNA PCR test, and HIV-1 genotyping.
- Facilitate rapid referral of the infant for appropriate further management including necessary blood tests, urgent ART initiation, and adherence counselling and follow up for the mother/guardian.
- At all subsequent scheduled clinic visits until the infant is one year old, perform plasma collection, CD4+ T cell count and HIV-1 RNA PCR. HIV-1 RNA PCR or HIV-1 genotyping may be performed at additional/alternate time points as requested by site IoR or at the discretion of the Laboratory Center (LC).

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

### **7.7.2 Participants Who Experience a Pregnancy Loss**

If a participant experiences a pregnancy loss after the Enrollment Visit, she will discontinue product use (as a scheduled end of use due to pregnancy outcome) and attend routine post-pregnancy outcome visits with the following procedures performed at her next clinic visit:

- CBC with platelets
- AST/ALT
- Blood creatinine and calculation of creatinine clearance
- Collection of drug level and biomarker specimens

### **7.7.3 Participants Who Permanently Discontinue Study Product Use for Reasons other than Seroconversion or Loss of Pregnancy**

Participants who permanently discontinue study product use for any reason (clinician-initiated or self-initiated) other than seroconversion or loss of pregnancy will continue follow-up visits with a modified study visit/procedure schedule until their originally scheduled study exit date. Infants born to participants who are permanently discontinued from study product use will continue follow-up visits with their original study visit/procedure schedule until their originally scheduled study exit date.

Upon documentation of the product discontinuation, the following procedures must be performed regardless of whether or not they are scheduled to be completed:

- CBC with platelets
- AST/ALT
- Blood creatinine and calculation of creatinine clearance
- Collection of drug level and biomarker specimens

For those participants who permanently discontinue study product use for reasons other than seroconversion or loss of pregnancy and who remain in MTN-042 follow-up, protocol-specified procedures for MTN-042 will continue except the following:

- Provision of study VR or study tablets, provision of product use instructions, and retrieval and collection of study VR or study tablets
- Collection of drug level and biomarker specimens
- Behavioral and product acceptability assessments
- Provision of product adherence counseling

#### **7.7.4 Participants Who Temporarily Hold Study Product Use**

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

- Provision of study VR or tablet, product use instructions, and protocol adherence counseling.

Drug level and biomarker specimens must be collected at the visit in which the study product is temporarily held, regardless of whether or not they were scheduled; however, they are to be discontinued at subsequent visits.

The aforementioned protocol procedures are to be resumed at follow-up visits once study product use has been resumed.

#### **7.7.5 Interim Visits**

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

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visit or to perform missed procedures.
- For product-related reasons, including to provide participants with a replacement or additional VR or tablets.
- In response to AEs and/or SAEs. When interim contacts or visits are completed in response to participant reports of AEs and/or SAEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see [Sections 8](#) and [9](#)).
- For interim STI counseling and testing in response to STI symptoms.
- For interim HIV counseling and testing in response to participant report of symptoms consistent with acute infection or presumed exposure to HIV.
- To provide participants with the results of confirmatory HIV test results, per the algorithm in [Appendix IV](#).
- To capture pregnancy outcome and/or infant health information (e.g., if a participant misses her PPO Visit).
- For other reasons at participant request, e.g., to report a social harm.

Given the specification of visit windows for this study, interim contacts and visits will occur when more than one visit takes place within an allowable visit window. All interim contacts and visits will be documented in participants' study records and on CRFs, if applicable.

## 7.8 Final Contact

Since participant mothers' final study visit includes laboratory testing for HIV and other conditions, additional contacts after this visit may be required to provide her additional study test results and post-test counseling, if needed. Since participant infants' final study visit includes medical exams and may include laboratory testing, additional contacts after this visit may be required to provide these test results and for AE follow-up. Study sites may complete these contacts at the study clinic or at community-based locations, depending on site capacities and site and participant preferences. All final contacts will be documented in participant study records.

## 7.9 Behavioral Evaluations

Behavioral endpoints will be assessed via CRFs.\* A Baseline Behavioral Questionnaire will be administered in the clinic at the Enrollment Visit to all participants in Cohorts 1-3. All participants will be asked about the context of HIV prevention and study product use, while participants in Cohorts 2-3 will be asked more detailed questions about sexual behavior, HIV prevention method use and intravaginal practice history, and about their attitudes towards the attributes of the study product, their attitudes and perceptions about using the study product during pregnancy, and other preliminary acceptability measures of the study product. At their first 4-week Visit, participants in Cohorts 2-3 will be asked to complete the Follow-up Behavioral Questionnaire which will include participant reports of their use of study product, coital frequency, HIV prevention method use and intravaginal practices, acceptability questions similar to those from the Enrollment Visit, and additional questions about their experiences using the study product, including reasons for non-use, if applicable, willingness to use in the future, beliefs around use of vaginal products and/or oral medications during pregnancy, and any perceived effect on the fetus/infant. Participants in Cohort 3 will also complete the Follow-up Behavioral Questionnaire at the 4-week Visit corresponding with their 36<sup>th</sup> week of gestation. Participants in Cohorts 2-3 will complete a brief Post-PPO Behavioral Questionnaire at their PPO Visit and all participants will complete a Behavioral Questionnaire at their SEV, which may include follow-up questions about the context of study product use.

IDIs will also be conducted with a subset of all participants in Cohort 1 at the Bi-weekly Visit(s) after the 36<sup>th</sup> week of gestation (these may be scheduled any time between the first bi-weekly visit and study exit to accommodate participant availability), and with a subset of all participants in Cohorts 2-3 at the 4-week Visit (these may be scheduled any time between the first 4-week Visit and study exit to accommodate participant availability). All IDIs will be conducted by trained and experienced facilitators to gain further insight on the social and behavioral issues described above.\* Additional IDIs may be conducted at undetermined time points during study follow-up with a subset of participants representing unexpected and/or interesting examples of experiences and behaviors relevant to the study endpoints. Interviews will be audio-recorded. Depending on participant availability and visit length, it may be necessary to conduct these IDIs as a separate visit.

*\* At Enrollment (for new participants) or at their next scheduled study visit (for already enrolled participants) and at one or more timepoints during the study, additional questions may be asked related to COVID-19's potential influence on the context of participants' HIV prevention and study product use, in order to explore the impact of the pandemic on study product adherence and acceptability.*

## 7.10 Counseling

HIV testing and risk reduction counseling will be provided to all participants upon study screening. Protocol adherence counseling, including product use adherence counseling during the product use period, will be provided to all participants upon enrollment into the study. Contraception counseling will be provided to all participants at specific study visits prior to and after their pregnancy outcome. Counseling will be provided in accordance with standard methods using a participant-centered approach to frame discussions around their experiences with the study and the prevention products. Counseling sessions may be audio-recorded to ensure the quality and consistency of the counseling across study sites, and to allow the counseling session content to be analyzed to understand participant experiences and concerns about study participation. Cognitive behavioral and motivational strategies will be incorporated into the counseling sessions as desired by participants to address adherence barriers. Lastly, sites may offer additional support strategies (e.g., text messages, phone calls, peer support groups) for participants to complement their protocol adherence counseling.

Participants will be monitored for symptoms of depression throughout their participation in the study. A validated depression scale designed for use with pregnant and postpartum women will be administered in the antenatal period and in the postpartum period. Participants will be referred to additional counseling and/or mental health services if clinically indicated.

## 7.11 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- General appearance
- Weight
- Abdomen\*
- Head, eye, ear, nose and throat (HEENT)\*
- Height\*
- Lymph nodes\*
- Neck\*
- Heart\*
- Lungs\*
- Extremities\*
- Skin\*
- Neurological\*

*\*May be omitted after the Screening Visit.*

Obstetric abdominal exams will include the following assessments:

- Appearance
- Palpation of abdomen
- Fundal height

- Auscultation of fetal heart tones (by Doppler, fetoscope or ultrasound), including rate per minute (not measured if fetus already known to be deceased but has not yet been delivered)

If a problem with the pregnancy is suspected, an ultrasound can be ordered, or a referral will be provided.

Once born, clinical evaluation of infants will include the following assessments (including assessment for and documentation of any anomalies, and photograph[s] of the infant if permitted by the mother/guardian):

- Vital signs
  - Temperature
  - Pulse
  - Blood pressure (if indicated)
  - Respirations
  - Oxygen saturation (if indicated at sites with capacity)
- General appearance
- Weight
- Length
- Head circumference
- Anterior fontanel closure/posterior fontanel closure
- Heart
- Lungs
- Abdomen\*
- Head, eye, ear, nose and throat (HEENT)\*
- Lymph nodes\*
- Neck\*
- Extremities\*
- Skin\*
- Neurological\*
- Ages and stages assessment (at 6- and 12-month visits only)

*\*May be omitted after the PPO Visit.*

### **Pelvic examination and specimen collection**

Pelvic examinations will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at [https://apps.who.int/iris/bitstream/handle/10665/69748/WHO\\_RHR\\_04.02\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/69748/WHO_RHR_04.02_eng.pdf).

Additional clinical assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam. Speculum exams will be required at the Enrollment Visit; at all other visits they will be performed only as indicated (e.g., abnormal discharge, pain) per the local standard of care.

The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the MTN-042 SSP Manual.

## 7.12 Laboratory Evaluations

### Local Laboratory

- Urine
  - Dipstick UA and/or culture
  - Pregnancy testing
- Blood
  - Plasma archive and storage (kept at site until notified by MTN LC)
  - Syphilis serology
  - HIV-1 testing
  - CD4+ T cell count
  - HIV-1 RNA PCR
  - CBC with platelets
  - AST/ALT
  - Creatinine and calculation of creatinine clearance
    - Weight will be captured each time creatinine is measured in all participants in order to calculate creatinine clearance
  - HbsAg
- Pelvic
  - NAAT for GC/CT/Trich\*
  - Vaginal pH
  - Wet prep/KOH wet mount for candidiasis and/or BV

*\*In the event of laboratory supply issues, the MTN Laboratory Center can approve an alternate methodology to be used as backup.*

### Laboratory Center

- Blood
  - TFV-DP and FTC-TP concentrations in maternal and infant blood
  - DPV concentrations in maternal and infant plasma
  - HIV-1 confirmatory testing as needed (see [Appendix IV](#))
  - HIV-1 drug resistance
  - COVID-19 infection testing
    - Testing related to COVID-19 infection would only be performed retrospectively on stored plasma samples if such testing is available and deemed necessary to better understand the impact of COVID-19 infection on the study safety endpoints.
- Pelvic
  - Vaginal Gram stain
  - Vaginal swabs for microbiota
  - Vaginal swabs for biomarkers

### Designated Laboratory:

- VR for residual DPV levels

Infant blood draw volume amounts planned for this study fall within the limits recommended by the U.S. National Institutes of Health (NIH) Guidelines for Limits on Blood Drawn for Research Purposes for pediatric patients:  $\leq 5$  mL/kg in a single day and  $\leq 9.5$  mL/kg over any eight-week period.<sup>90</sup> The maximum amount required to be drawn for research purposes from infants in the Truvada arm is 6 mL over 12 months of study participation (with  $\leq 4$  mL in a single day and  $\leq 6$

mL in any given eight-week period). The maximum amount required to be drawn for research purposes from infants in the DPV VR arm is 6 mL over 12 months of study participation (with  $\leq 4$  mL in a single day and  $\leq 6$  mL in any given eight-week period). See Table 15 below for a summary of infant blood volumes to be drawn for research purposes by clinic visit and by study arm. Additional blood may be drawn if clinically indicated, including: HIV testing (3-4 mL); creatinine, AST and ALT (1-2 mL); and CBC (1 mL). In instances of clinical need, it is the responsibility of the infant's attending physician to determine if phlebotomy in excess of the stated limits may be permitted, particularly for patients with significant anemia or compromised cardiac output.

**Table 15. Protocol-required Infant Blood Draw Volumes by Study Arm and by Clinic Visit**

Clinic Visit	Truvada Group	DPV VR Group
PPO Visit	4 mL	4 mL
6-week PPO Visit	2 mL	2 mL
6-month PPO Visit	0 mL	0 mL
12-month PPO Visit	0 mL	0 mL
TOTAL	6 mL	6 mL

Once all required study analyses of collected specimens are complete, any remaining samples may be shipped to the MTN LC for use in study-related quality assurance and quality control testing. If study samples will be used for assay validation or proficiency testing that is not study related, all participant identifiers will be removed from the samples prior to use. Specimens obtained from participants who do not consent to long term storage will not be used for assay validation or proficiency testing purposes.

### 7.13 Calculation of Gestational Age

The best obstetric estimate should be used as the measure for gestational age, rather than estimates based on the LMP alone. Per site SOPs and as needed to confirm gestational age of potential participants, ultrasound measurement of the fetus will be conducted prior to enrollment but no later than the 36<sup>th</sup> week of gestation for Cohort 1 or the 28<sup>th</sup> week of gestation for Cohorts 2 and 3. Gestational age confirmation by ultrasound may occur between the Screening and Enrollment Visits if available medical and/or antenatal care records do not contain this evaluation.

Ultrasound measurement of the fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age. Gestational age assessment based on measurement of the crown–rump length (CRL) has an accuracy of  $\pm 5$ –7 days in the first trimester. However, it may not be possible to ensure that participants have a first-trimester ultrasound, particularly for Cohorts 1 and 2, given these are not routinely performed in the study countries. The range of second-trimester gestational ages (14 0/7 weeks to 27 6/7 weeks of gestation) introduces greater variability and complexity, which can affect revision of LMP dating and assignment of a final estimated delivery date (EDD). Table 16 includes guidelines for redating based on ultrasonography.

**Table 16. Guidelines for Redating based on Ultrasonography**

Gestational Age Range	Discrepancy between Ultrasound Dating and LMP that Supports Redating
≤ 8 6/7 weeks	More than 5 days
9 0/7 weeks to 15 6/7 weeks	More than 7 days
16 0/7 weeks to 21 6/7 weeks	More than 10 days
22 0/7 weeks to 27 6/7 weeks	More than 14 days
28 0/7 weeks and beyond	More than 21 days

If the estimated gestational age by the participant's LMP differs from the ultrasound estimate by more than these accepted variations, the ultrasound estimate of gestational age should be used instead of the participant's LMP estimate.

#### **7.14 Specimen Management**

Each study site will adhere to the standards of good clinical laboratory practice in accordance with DAIDS Laboratory Policy (<https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf>), MTN-042 SSP Manual (<http://www.mtnstopshiv.org/research/studies>) and site SOPs for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures. 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. Further, as part of quality control, researchers may need to look at short pieces of non-coding repetitive deoxyribonucleic acid (DNA) sequence (3-7 base pairs) from blood in the event of sample mix-up. This test will only let researchers know the number of times this short segment is repeated and not specific genes or specific sequences of base pairs. This sequence element does not contain any information about genes, therefore researchers will not be able to identify if participants are predisposed to specific diseases or any other genetic information based on this information. This test will be an important tool for distinguishing whether two samples collected at the same or different time points are likely from the same person. The test will only be used as part of a sample investigation with the knowledge of the site in situations where a known or suspected sample mix-up has occurred. No genetic testing (limited or genome-wide) is planned on leftover samples that are stored for the purposes of future research.

#### **7.15 DAIDS Laboratory Oversight**

All laboratories participating in DAIDS Sponsored and/or Funded Laboratories in Clinical Trials will adhere to the DAIDS Laboratory Policy (<https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf>).

#### **7.16 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 U.S. Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH). All biological specimens will be transported using packaging mandated by US Code of Federal Regulations (CFR) 42 Part 72. All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to instructions detailed in the International Air Transport Association

(IATA) Dangerous Goods Regulations. Biohazard waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

## **8 ASSESSMENT OF SAFETY**

### **8.1 Safety Monitoring**

Site IoRs/designees are responsible for continuous close safety monitoring of all study participants, and for alerting the PSRT if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Chair(s), DAIDS MO, NICHD MO, Protocol Safety Physician(s), IPM Representative, and Gilead Representative will serve as the PSRT. The MTN Statistical Data and Management Center (SDMC) prepares routine AE and clinical data reports for review by the PSRT, which meets via conference call approximately once per month or as needed throughout the period of study implementation to review safety data, discuss product use management, and address any potential safety concerns.

### **8.2 Clinical Data Safety Review**

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are the first layer of this tiered system and are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise.

Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC staff, the PSRT, and study sponsor.

During the study, the PSRT will review safety reports and conduct calls to review the data once a month. The content and format of the monthly safety reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to these routine safety data reviews, the PSRT will convene on an ad hoc basis to make decisions regarding the handling of any significant safety concerns. If necessary, experts external to the MTN with expertise in the fields of microbicides, biostatistics, or medical ethics may be invited to join the PSRT safety review.

The PSRT and an Interim Review Panel (IRP) will be charged with reviewing participant safety data as no DSMB is planned for this study. See [Section 10.7](#) for additional details.

### **8.3 Adverse Events Definitions and Reporting Requirements**

#### **8.3.1 Adverse Events**

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study participants at the time of enrollment. This definition is applied to all study groups, and is applied beginning at the time of enrollment

(i.e., once a participant is randomized). The term “investigational products” for this study refers to the DPV VR and Truvada oral tablet.

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

Study site staff will document in source documents and in the study database all AEs reported by or observed in enrolled study participants, regardless of severity and presumed relationship to study product. Study staff will also report on CRFs all SAEs for infants (first year of life) born from pregnancies followed during MTN-042 participation.

AE severity and laboratory tests will be graded per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies; dated November 2007). In cases where a genital AE is covered in both tables, the Female Genital Grading Table for Use in Microbicide Studies will be the grading scale utilized.

The following will not be reportable as AEs:

- Asymptomatic BV and asymptomatic candida.
- Bleeding at the time of speculum insertion/removal or cervicovaginal specimen collection that is judged by the clinician to be within the range normally anticipated for that procedure; however, bleeding of greater quantity or longer duration than typical will still be reported.
- Uterine cramping that is judged by the clinician to be within the range normally anticipated post-delivery.
- Perineal pain that is judged by the clinician to be within the range normally anticipated post-delivery.
- Lower extremity edema that is judged by the clinician to be within the range normally anticipated during pregnancy.
- Decreased fetal movement; however, AEs identified in the course of clinical evaluation of decreased fetal movement will be captured.
- Findings on electronic fetal monitoring strips.
- Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths).
  - However, untoward maternal conditions that either result in or result from fetal losses will be reported as AEs.
  - All fetal losses will be reported by sites on pregnancy outcome CRFs to the SDMC and will be considered during safety reviews conducted by the SDMC, the DAIDS MO, the NICHD MO, PSRT, and IRP.
- Physiologic discharge associated with pregnancy.
- Lochia during the postpartum period.
- Vaginal bleeding that is judged by the clinician to be within the range normally anticipated in the postnatal period.
- HIV acquisition

- All instances of HIV acquisition will be reported by sites on HIV Confirmatory Results CRFs to the SDMC and will be considered during safety reviews conducted by the SDMC, the DAIDS MO, the NICHD MO, PSRT, and IRP.

Protocol-specific grading scales will be used for the following AEs:

- Bleeding during pregnancy, prior to the onset of labor
  - Grade 0: None
  - Grade 1: Spotting or bleeding less than menses
  - Grade 2: Bleeding like menses or heavier, no intervention indicated
  - Grade 3: Profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated
  - Grade 4: Potentially life-threatening profuse bleeding and/or shock
- Hypertensive disorders of pregnancy
  - Grade 0: None
  - Grade 1: Pregnancy-induced hypertension
  - Grade 2: Mild preeclampsia
  - Grade 3: Severe preeclampsia
  - Grade 4: HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, eclampsia, or life-threatening sequelae of preeclampsia (e.g., pulmonary edema)
- Gestational diabetes
  - Grade 0: None
  - Grade 1: Diet-controlled, no or minimal interference with usual social and functional activities
  - Grade 2: Medication prescribed
  - Grade 3: Evidence of adverse effects on pregnancy secondary to diabetes
  - Grade 4: N/A
- Chorioamnionitis
  - Grade 0: None
  - Grade 1: Fever of 100.4°F -100.9°F with more than one of the following: FHR > 160 BPM, maternal HR > 120, uterine tenderness between contractions, purulent AF, or preterm labor
  - Grade 2: Grade 1 plus fever of 101°F -104°F
  - Grade 3: Grade 2 plus fetal distress or fever > 104°F
  - Grade 4: Grade 3 plus fetal demise or maternal symptoms of shock
- Puerperal sepsis and endometritis
  - Grade 0: None
  - Grade 1: Low grade fever and uterine tenderness, resolved with oral antibiotics
  - Grade 2: Moderate symptoms, treated by ≤ 3 days of parenteral antibiotics
  - Grade 3: Severe symptoms treated with > 3 days of IV antibiotics or addition of heparin
  - Grade 4: Severe infection or infection for which operative intervention is indicated
- Postpartum hemorrhage
  - Grade 0: Estimated blood loss (EBL) < 500 mL for vaginal delivery or < 1000 mL after caesarian section (CS) or reported as normal

- Grade 1: EBL 500-1000 mL for vaginal delivery or 1000-1500 mL for CS or reported as slightly increased
  - Grade 2: EBL > 1000 mL or vaginal delivery or > 1500 mL for CS, with or without mild dizziness, no transfusion required
  - Grade 3: Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products indicated
  - Grade 4: Hemorrhage with shock or coagulopathy, for which transfusion of > 2 units of packed cells or any amount of other blood components is indicated
- Preterm PROM
    - Grade 0: None
    - Grade 1: N/A
    - Grade 2: Preterm rupture with hospitalization but not resulting in delivery at less than 37 weeks' gestation
    - Grade 3: Delivery at 33-36 weeks' gestation or 1501-2500 grams birth weight
    - Grade 4: Delivery < 33 weeks' gestation or ≤ 1500 grams birth weight
- Axillary measured fever
    - Grade 0: None
    - Grade 1: 99.3°F to <100.4°F (37.4°C to <38°C)
    - Grade 2: 100.4°F to <101.7°F (38°C to <38.7°C)
    - Grade 3: 101.7°F to <102.9°F (38.7°C to <39.4°C)
    - Grade 4: ≥102.9°F (≥39.4°C)
- Creatinine (neonates 0-28 days old)
    - Grade 0: None
    - Grade 1: 1.1 mg/dL to <1.6 mg/dL
    - Grade 2: 1.6 mg/dL to <2.1 mg/dL
    - Grade 3: 2.1 mg/dL to 3.0 mg/dL
    - Grade 4: >3.0 mg/dL
- Creatinine (infants >28 days old)
    - Grade 0: None
    - Grade 1: 0.5 mg/dL to <0.7 mg/dL
    - Grade 2: 0.7 mg/dL to <0.9 mg/dL
    - Grade 3: 0.9 mg/dL to 1.2 mg/dL
    - Grade 4: >1.2 mg/dL

For any serious or expedited adverse events (EAEs) that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE. At a minimum, the SAE or EAE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit, or any new ≥ Grade 3 AEs uncovered at the last visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis. For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will

be recorded in source documents only — no updates should be made to AE Log CRFs based on the re-assessments.

### **8.3.2 Serious Adverse Events**

SAEs will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010) as AEs occurring at any dose that:

- Result in death
- Are life-threatening
- Require inpatient hospitalization or prolongation of existing hospitalization
- Result in persistent or significant disability/incapacity
- Are congenital anomalies/birth defects
- Are important medical events 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

### **8.3.3 Adverse Event Relationship to Study Product**

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
- *Not Related*: There is not a reasonable possibility that the AE is related to the study agent

## **8.4 Expedited Adverse Event Reporting Requirements**

### **8.4.1 Adverse Event Reporting to DAIDS**

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the Regulatory Support Center (RSC) website at <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>. For each study participant, EAE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of Enrollment through study termination.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Management System (CRMS) Support at [CRMSSupport@niaid.nih.gov](mailto:CRMSSupport@niaid.nih.gov). Site queries may also be sent from within the DAERS application itself.

The DAIDS EAE Form is available on the RSC website, <https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting>.

For questions about EAE reporting, please contact the RSC ([DAIDSRSCSafetyOffice@tech-res.com](mailto:DAIDSRSCSafetyOffice@tech-res.com)).

#### **8.4.2 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 requiring expedited reporting are the dapivirine vaginal ring (DPV VR) and Truvada oral tablet.

#### **8.4.3 Grading Severity of Events**

The grading of severity of events and the reporting period will be the same as for all AEs, as described in [Section 8.3.1](#). The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1, dated November 2007), will be used and is available on the RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

#### **8.4.4 Expedited AE Reporting Period**

The EAE reporting period for this study begins once the participant is enrolled and continues up through the participant's final study visit. After the protocol-defined AE reporting period, unless otherwise noted, only suspected, unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

#### **8.5 Social Harms Reporting**

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others and that social harms – non-medical adverse consequences – may result. For example, participants could be treated unfairly, or could have problems being accepted by their families, partners and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site IRBs/ECs according to their individual requirements beginning at the time of enrollment (i.e., after a participant signs the informed consent and eligibility is confirmed) until study participation is complete. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant as needed. Each site will provide such care and counseling in accordance with standardized guidance provided in the MTN-042 SSP Manual. While maintaining participant confidentiality, study sites may engage their community advisory boards (CABs) in exploring the social context surrounding instances of social harm.

#### **8.6 Regulatory Requirements**

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

## 9 CLINICAL MANAGEMENT

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

### 9.1 Grading System

AE severity grading is described in [Section 8.3.1](#).

### 9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

### 9.3 General Criteria for Temporary/Permanent Discontinuation of Study Product

Participants will be permanently discontinued from study product by the IoR/designee for any of the following reasons:

- Acquisition of HIV-1 infection.
- Acquisition of hepatitis B infection (for Truvada group only).
- Confirmation of  $\geq$  Grade 2 creatinine clearance (for Truvada group only).
- Confirmation of  $\geq$  Grade 2 glycosuria or proteinuria (for Truvada group only).
- Allergic reaction to the study product.
- Reported use of PrEP for HIV prevention prior to pregnancy outcome.
- Non-therapeutic injection drug use.

*NOTE: Pregnancy loss and admission to care for labor and delivery management, including induction of labor and cesarean delivery, are scheduled reasons for end of product use.*

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

- A reactive rapid HIV test. The study product must be held beginning immediately upon recognition of the first reactive rapid HIV test. If, via the algorithm in [Appendix IV](#), the participant is determined to be HIV-uninfected, she may resume product use. The IoR/designee must permanently discontinue the study product if HIV-1 infection is confirmed.
- Reported use of PEP for potential HIV exposure.
- Suspected onset of labor or rupture of membranes. If labor and rupture of membranes are subsequently ruled out, study product should be resumed. The IoR/designee must permanently discontinue the study product if labor or rupture of membranes is confirmed.
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to her/her infant's safety and well-being by continuing product

use, according to the judgment of the IoR/designee. The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation. If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

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

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

In general, a participant who develops a Grade 1 or 2 AE not specifically addressed in [Section 9.5](#) below, regardless of relatedness to study product, may continue product use.

##### **Grade 3**

Participants who develop a Grade 3 AE that is not specifically addressed in [Section 9.5](#) below and is judged by the IoR/designee to be not related to study product may continue product use.

In general, for participants who develop a Grade 3 AE not specifically addressed below, judged by the IoR/designee to be related to study product, and unless otherwise decided in consultation with the PSRT, the IoR/designee should:

- Temporarily hold the study product.
- Re-evaluate the participant at least weekly for up to 2 weeks.
- Resume study product if improvement to  $\leq$  Grade 2 is documented within 2 weeks.
- Consult PSRT regarding further study product management if improvement to severity  $\leq$  Grade 2 cannot be documented within 2 weeks.

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

##### **Grade 4**

Participants who develop a Grade 4 AE (including a complication of pregnancy and regardless of relationship to study product) should have the study product held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT.

#### **9.5 Other Clinical Findings**

A thorough evaluation of participant complaints is expected in the context of this study; however, management of the following side effects common with Truvada oral tablet use should be done according to the following guidelines if such practice is in line with the local standards of care:

##### **$\geq$ Grade 2 creatinine clearance**

- Oral study product should be held.
- The PSRT should be notified.
- The test should be repeated within one week.

- If a level of  $\geq$  Grade 2 is confirmed, study product will be permanently discontinued.
- If retesting cannot occur within one week, the IoR/designee must consult the PSRT for further guidance on resuming product use.

*NOTE: Absolute values for creatinine and creatinine clearance will be used to grade these AEs instead of changes from baseline due to absence of a true pre-pregnancy baseline measurement in this study population and due to normal fluctuations in these measurements during pregnancy.*

#### **$\geq$ Grade 2 glycosuria or proteinuria**

- Oral study product should be held.
- The PSRT should be notified.
- The test should be repeated within one week.
  - If a level of  $\geq$  Grade 2 is confirmed, study product will be permanently discontinued.
  - If either retesting cannot occur within one week or if retesting yields a result of Grade 1, the IoR/designee must consult the PSRT for further guidance on resuming product use.

Syndromic management of genital symptoms is acceptable while awaiting laboratory results if such practice is in line with the local standards of care. Observed single dose treatment should be provided whenever possible, per clinician discretion. When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible.

#### **STI/RTI requiring treatment**

- Study VR or tablet need not be held unless other temporary product hold/permanent discontinuation guidelines apply.
- Should the IoR/designee determine that a temporary hold is warranted, consultation with the PSRT is required.

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

Management of vaginal bleeding and chorioamnionitis events observed at scheduled or interim visits for all participants will be in accordance with the following:

#### **$\geq$ Grade 2 genital bleeding**

- Temporarily hold study product.
- Perform naked eye evaluation.
- If determined to be due to deep epithelial disruption, refer to guidelines below; otherwise study product will be permanently discontinued.

#### **$\geq$ Grade 2 chorioamnionitis**

- Participants who develop Grade 2 or higher chorioamnionitis will be referred for delivery per local standard of care; therefore, study product will be permanently discontinued.

Management of genital events observed at scheduled or interim visits for participants using the VR will be in accordance with the following:

**Superficial epithelial disruption (abrasion/peeling)**

- Continue study product use.
- Perform naked eye evaluation.
- Re-evaluate by speculum examination in 3-5 days.
- If condition worsens, temporarily hold study product use and consult the PSRT; otherwise continue study product use.

**Deep epithelial disruption (ulceration)**

- Temporarily hold study product for deep epithelial disruption confirmed by site investigator.
- Re-evaluate in 3-5 days and resume study product use if resolved.
- If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time, may resume study product use. If unresolved at this second reevaluation, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard.
- If there is reoccurrence with no identified etiology, continue temporary product hold and consult the PSRT regarding permanent discontinuation.

**Localized erythema or edema: area of less than 50% of vulvar surface or combined vaginal and cervical surface**

- Continue study product use.
- Perform naked eye evaluation.
- If asymptomatic, re-evaluate at next regularly scheduled visit.
- If symptomatic, re-evaluate by speculum examination in 3-5 days.
- If worsened significantly, temporarily hold study product use and consult the PSRT; otherwise continue study product use.

**Generalized erythema or severe edema: area of more than 50% of vulvar surface or combined vaginal and cervical surface affected by erythema**

- Temporarily hold study product.
- Perform naked eye evaluation.
- Re-evaluate in 3-5 days and resume study product use if resolved.
- If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time may resume study product use. If unresolved at this second reevaluation, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard.
- If there is reoccurrence with no identified etiology, continue temporary product hold and consult the PSRT regarding permanent discontinuation.

**Unexpected Grade 1 genital bleeding**

- Continue study product use (at study clinician's discretion).
- Perform naked eye evaluation.
- If determined to be due to deep epithelial disruption, refer to guidelines above; otherwise continue study product use.

**Cervicitis (including findings on exam such as inflammation and/or friability)**

- Temporarily hold study product.
- Evaluate for GC/CT; consider syndromic management, pending results of testing and per clinician discretion.

- If GC/CT detected, provide or prescribe treatment.
- Reevaluate in 3-5 days. If all symptoms and signs are resolved at that time, regardless of etiology, resume study product use.
- If unresolved at 3-5 days, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard.

#### **Genital petechiae**

- Continue study product use.
- Perform naked eye evaluation.
- Further evaluation or treatment per clinician discretion.

#### **Genital ecchymosis**

- Continue study product use.
- Perform naked eye evaluation.
- Further evaluation or treatment per clinician discretion.

### **9.6 HIV Infection**

A participant who has a positive test for HIV must have study product held, but will not be withdrawn from the study. If the participant is subsequently determined to be HIV-uninfected according to the algorithm in [Appendix IV](#), study product may be resumed. If HIV infection is confirmed, study product will be permanently discontinued by the IoR/designee. Participants identified as infected with HIV (and their infants once they are born, if also infected with HIV) are managed or referred for management according to the local standard of care. These participants will also be offered the option to continue in study follow-up with a modified study visit/procedure schedule, as per [Section 7.7.1](#), for at least 12 months after seroconversion.

The care provided at the referral sites is at a level that meets or exceeds the community standard for HIV care, and will include testing and prophylaxis for infants exposed to HIV infection. Written SOPs for referral for HIV care and treatment are in place at each study site. All study site investigators have identified facilities offering psychological and social services and medical care, including ART, to people infected with HIV-1 in the study countries. Some of the research sites are part of health care institutions that provide HIV care and support, and can refer pregnant women to those services. Other sites have established referral agreements with programs to expand access to ART.

At every study visit, study staff will actively follow-up on prior referrals to HIV 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. All follow-up actions, outcomes, counseling, and plans for next steps are documented in participant study records. Results of study laboratory testing may be helpful in clinical management, and these results are provided to the participant and her medical provider (with her permission) as soon as they are available.

### **9.7 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 a participant from the study to protect her/her infant's safety and/or if she is unwilling or unable to comply with required study procedures. The PSRT must be notified of all terminations conducted per IoR discretion. Participants also may be withdrawn if NIAID, IPM,

Gilead Sciences, Inc., government or regulatory authorities including the FDA and Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Participants will also be asked permission for study staff to contact them up to one year after their pregnancy outcome to obtain information about their pregnancy outcome and their infant's health. 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. In the event that participants who voluntarily withdraw from the study wish to keep their infants in study follow-up for one year postpartum, they may resume follow-up after giving birth until their originally scheduled study exit date.

## **10 ANALYTICAL CONSIDERATIONS**

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

The MTN-042 study is a multi-site, two-arm, randomized, open-label Phase 3b study evaluating the safety, adherence and acceptability profiles of two HIV-1 prevention products, the monthly DPV VR and daily oral Truvada tablet, when used by pregnant African women. Participants (aged 18-40 years) will be randomized in a 2:1 ratio (100 VR: 50 tablet) for Cohorts 1-2 and in a 4:1 ratio (200 VR: 50 tablet) for Cohort 3. The total length of follow-up for participant mothers will vary depending on gestational age at time of enrollment and length of pregnancy prior to pregnancy outcome, and will range from approximately 12 weeks or less for Cohort 1 to approximately 36 weeks or less for Cohort 3. Also, infants born to MTN-042 participants will be followed for approximately 52 weeks (i.e., one year).

Local background pregnancy outcome data will be an important component of analyses; these data will be compiled from the proposed MTN-042B study, a multi-site, cross-sectional chart review of pregnancy outcome data from four African sites. The objectives include determination of frequencies of full-term live birth and premature live birth (<37 weeks), important pregnancy and newborn complications, mean birth weight, and method of delivery.

### **10.2 Study Endpoints**

#### **10.2.1 Primary Endpoints**

##### **Maternal Safety (composite)**

- All serious adverse events, including maternal deaths
- All Grade 3 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])

**Infant Safety (composite)**

- All serious adverse events, including infant deaths and congenital anomalies
- All Grade 3 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017

**Pregnancy Outcomes**

- Frequency of the following pregnancy outcomes:
  - Full term live birth ( $\geq 37$  weeks)
  - Premature live birth ( $< 37$  weeks)
  - Pregnancy loss ( $\geq 20$  weeks)
  - Pregnancy loss ( $< 20$  weeks)

**10.2.2 Secondary Endpoints****Pregnancy Complications**

- Frequency of the following pregnancy complications:
  - Hypertensive disorders of pregnancy
  - Chorioamnionitis
  - Puerperal sepsis and endometritis
  - Antepartum, intrapartum and postpartum hemorrhage
  - Preterm premature rupture of membranes (PROM)
  - Fever of unclear etiology

**Infant Drug Levels**

- Infant blood TFV-DP and FTC-TP concentrations
- Infant plasma DPV concentrations

**Adherence**

- Maternal blood TFV-DP and FTC-TP concentrations
- Maternal plasma DPV concentrations
- Participant report of frequency of study product use (e.g., missed doses for oral Truvada and VR removal/expulsions [voluntary and involuntary] and duration without VR in vagina)
- Residual drug levels in returned VRs

**Acceptability**

- Self-reported attitudes about study product attributes and willingness to use study products during pregnancy
- Proportion of participants who find the study products to be at least as acceptable as other HIV prevention methods

**10.3 Primary Study Hypotheses**

- It is hypothesized that daily use of Truvada oral tablet or DPV vaginal matrix ring (25 mg) inserted once every 4 weeks will be generally safe and well-tolerated by the participants and their fetuses/infants.
- It is hypothesized that participants who use Truvada oral tablet daily or insert the DPV vaginal matrix ring (25 mg) once every 4 weeks will experience similar distributions of pregnancy outcomes to the general population.

## 10.4 Sample Size and Power Calculations

The proposed total sample size is N=550 pregnant women, which is comprised of 3 cohorts:

- Cohort 1: 150 women between 36 0/7 weeks – 37 6/7 weeks gestation
- Cohort 2: 150 women between 30 0/7 weeks – 35 6/7 weeks gestation
- Cohort 3: 250 women between 12 0/7 weeks – 29 6/7 weeks gestation

Eligible women enrolled in Cohorts 1-2 will be randomized into 2 arms in a 2:1 ratio (100 VR: 50 tablet). Eligible women enrolled in Cohort 3 will be randomized into 2 arms in a 4:1 ratio (200 VR: 50 tablet).

### 10.4.1 Primary Endpoints – Maternal and Infant Safety

To characterize the statistical properties of this study, Table 17 below presents the probability of observing zero, at least one, ten or more, and fifty or more safety endpoints in each group by cohort size and among the total study population for various “true” event rates, ranging from low to high:

**Table 17. Probability (%) of observing an event given different “true” event rates by cohort size**

“True” event rate	P (0 events)		P ≥ 1 event		P (≥ 10 events)		P (≥ 50 events)	
	n=100	n=50	n=100	n=50	n=100	n=50	n=100	n=50
<b>Cohorts 1-2<sup>a</sup></b>								
1%	36.6	60.50	63.40	39.50	0.00	0.00	0.00	0.00
5%	0.59	7.69	99.41	92.31	1.15	0.00	0.00	0.00
10%	0.00	0.52	100.00	99.48	41.68	0.94	0.00	0.00
15%	0.00	0.03	100.00	99.97	90.06	11.99	0.00	0.00
25%	0.00	0.00	100.00	100.00	99.99	73.78	0.07	0.00
<b>Cohort 3<sup>a</sup></b>	<b>n=200</b>	<b>n=50</b>	<b>n=200</b>	<b>n=50</b>	<b>n=200</b>	<b>n=50</b>	<b>n=200</b>	<b>n=50</b>
1%	13.4	60.50	86.6	39.50	0.00	0.00	0.00	0.00
5%	0.00	7.69	100.00	92.31	41.69	0.00	0.00	0.00
10%	0.00	0.52	100.00	99.48	99.19	0.94	0.00	0.00
15%	0.00	0.03	100.00	99.97	100.00	11.99	0.01	0.00
25%	0.00	0.00	100.00	100.00	100.00	73.78	46.21	0.00
<b>Overall<sup>a</sup></b>	<b>n=400</b>	<b>n=150</b>	<b>n=400</b>	<b>n=150</b>	<b>n=400</b>	<b>n=150</b>	<b>n=400</b>	<b>n=150</b>
1%	1.80	22.15	90.95	44.30	0.27	0.00	0.00	0.00
5%	0.00	0.05	100.00	99.59	99.06	13.22	0.00	0.00
10%	0.00	0.00	100.00	100.00	100.00	89.40	4.36	0.00
15%	0.00	0.00	100.00	100.00	100.00	99.86	91.06	0.00
25%	0.00	0.00	100.00	100.00	100.00	100.00	100.00	0.85

<sup>a</sup> Sample sizes in the table based on the proposed cohort sizes and study design. For example, Cohort 1 will include approximately 150 participants, with 2:1 randomization, there will be 100 participants in the VR arm and 50

participants in the Truvada arm.

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval for the “true” rate based on the observed data. Table 18 below shows the exact 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate. For example, if none of the 400 participants receiving the VR regimen experience a safety event, the 95% exact 2-sided upper confidence bound for the true rate of such events in a particular arm of the study is 0.92%.

**Table 18. Confidence intervals for endpoint rate (proportion of participants with endpoint) given number of endpoints (rows) in with number of participants (columns)**

Number of events	Number of participants <sup>a</sup>				
	n=50	n=100	n=150	n=200	n=400
0	0.00, 7.11	0.00, 3.62	0.00, 2.43	0.00, 1.83	0.00, 0.92
1	0.05, 10.65	0.03, 5.45	0.00, 3.66	0.01, 2.75	0.00, 1.38
2	0.49, 13.71	0.24, 7.04	0.16, 4.73	0.12, 3.57	0.06, 1.79
3	1.25, 16.55	0.62, 8.52	0.41, 5.73	0.31, 4.32	0.15, 2.18
4	2.22, 19.23	1.10, 9.93	0.73, 6.69	0.55, 5.04	0.27, 2.54
5	3.33, 21.81	1.64, 11.28	1.09, 7.61	0.82, 5.74	0.41, 2.89
6	4.53, 24.31	2.23, 12.60	1.48, 8.50	1.11, 6.42	0.55, 3.24
8	7.17, 29.11	3.52, 15.16	2.33, 10.24	1.74, 7.73	0.87, 3.90
10	10.03, 33.72	4.90, 17.62	3.24, 11.92	2.42, 9.00	1.21, 4.55
12	13.06, 38.17	6.36, 20.02	4.20, 13.56	3.14, 10.25	1.56, 5.18
15	17.86, 44.61	8.65, 23.53	5.71, 15.96	4.26, 12.07	2.11, 6.11
20	26.41, 54.82	12.67, 29.18	8.34, 19.84	6.22, 15.02	3.08, 7.62
30	45.18, 73.59	21.24, 39.98	13.92, 27.30	10.35, 20.72	5.12, 10.53

<sup>a</sup> Sample sizes in the table based on the proposed cohort sizes and study design.

#### 10.4.2 Primary Endpoints – Pregnancy Outcomes

Based on pregnancy outcome data from VOICE<sup>91</sup> and ASPIRE<sup>40</sup>, we expect certain pregnancy outcomes such as premature live birth and pregnancy loss  $\geq 20$  weeks to occur at a low frequency (5% and 2-3%, respectively). Among all women who became pregnant in VOICE and ASPIRE, pregnancy loss  $< 20$  weeks was between 19-22%. Given the enrollment criteria for this study, it is expected that the frequency of pregnancy loss  $< 20$  weeks will be lower in enrolled MTN-042 participants. As such, the probability and confidence interval estimates presented in Table 16 and Table 17 also apply to estimates of the frequency of pregnancy outcomes. For example, if there was one stillbirth among the 100 participants in Cohort 1 receiving the VR regimen, the stillbirth frequency would be 1.00% and the 95% exact 2-sided confidence interval would be (0.03, 5.45).

#### 10.5 Participant Accrual, Follow-up and Retention

Approximately 550 participants and their infants will be enrolled across three cohorts. The accrual period for Cohorts 1-2 will be approximately 4-5 months, while the accrual period for Cohort 3 will be approximately 7-9 months; Cohort 3 was designed to be larger in order to accumulate more person-years of observation and to better evaluate less frequent outcomes, such as pregnancy loss in the second trimester, after comprehensive evaluation of safety in the preceding Cohorts.\* Participant accrual will be paused at all sites once accrual goals are met for the currently enrolling Cohort. This will be done to allow all enrolled participants to give birth and, for Cohorts 1-2, to conduct interim safety analyses to determine if accrual into the next

Cohort can commence. The duration of these accrual pauses will vary depending on the Cohort and on the quantity and quality of data collected, and likely will resemble the following: approximately 3-4 months after Cohort 1 and approximately 4-6 months after Cohort 2. Cohort 1 accrual began in February 2020 and is expected to finish in May 2021. Therefore, it is expected that the Cohort 1 phase of the study will last approximately 16-17 months, Cohort 2 approximately 8-11 months, and Cohort 3 approximately 13-17 months, for a study duration of approximately 37-45 months.\* In addition, infants born to MTN-042 participants will be followed up for approximately one year, though this will not be part of the interim safety analyses after Cohorts 1-2. Therefore, total study duration including infant follow-up for all cohorts will be approximately 48-56 months.

*\* Overall study duration – from first enrollment through closure of all follow-up – may be longer than planned if temporary site closures due to the COVID-19 pandemic cause delays or pauses in enrolling participants at one or more research sites.*

## **10.6 Randomization**

Participants will be randomized in a 2:1 ratio (or a 4:1 ratio in Cohort 3) to the two arms of the study stratified by study site. The randomization scheme will be generated and maintained by the MTN SDMC.

## **10.7 Data and Safety Monitoring Procedures**

No DSMB oversight is planned for this study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and study or laboratory issues. These reviews will take place approximately every 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. Safety monitoring will be done by the PSRT.

It is not expected that MTN-042 will predispose pregnant women to higher frequencies of untoward pregnancy outcomes, given the favorable safety profile demonstrated for both study products among non-pregnant women and among pregnant women who enrolled in MTN-016. However, an interim review of the safety data by the IRP is planned after each cohort completes scheduled participation and prior to beginning accrual in the next scheduled cohort.

The IRP will consist of a multidisciplinary group of subject matter experts from the US and SSA that will likely include one or more obstetricians, pediatricians, statisticians, ethicists and/or public health professionals, among others. The IRP will review safety data collected in each cohort to look for higher frequencies for the primary outcomes compared to baseline estimates or when comparing between study drugs. In addition, a full safety review of secondary outcomes related to pregnancy will be conducted. If this were noted at interim review, serious consideration would be given as to the prudence of enrolling women in subsequent cohorts. Interim review results will be relayed to site IRBs/IECs and to study participants as appropriate.

The IRP will review frequencies of the following primary and secondary safety endpoints for each cohort:

- SAEs, including maternal and infant deaths and congenital anomalies
- Grade 3 and higher AEs for mother and infant
- Pregnancy outcomes:

- Full term live birth ( $\geq 37$  0/7 weeks)
- Premature live birth ( $< 37$  0/7 weeks)
- Pregnancy loss ( $\geq 20$  weeks)
- Pregnancy loss ( $< 20$  weeks)
- Pregnancy complications:
  - Hypertensive disorders of pregnancy
  - Chorioamnionitis
  - Puerperal sepsis and endometritis
  - Antepartum, intrapartum and postpartum hemorrhage
  - Preterm PROM
  - Fever of unclear etiology

## 10.8 Analyses

When the use of descriptive statistics to assess group 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). Within-treatment group assessment of the change from the baseline measurement to a follow-up measurement will be analyzed using McNemar's test (for categorical response variables) or the paired t-test or Wilcoxon signed-ranks test (for continuous variables). To assess the adequacy of the randomization, participants in each of the two arms will be compared using descriptive statistics for baseline characteristics including demographics and laboratory measurements. No formal statistical comparisons will be performed.

### 10.8.1 Primary Analyses

An intent to treat analysis will be performed to summarize the frequency of primary endpoints (maternal safety, infant safety and pregnancy outcome) by study arm. A secondary analysis will be conducted including only visits in which a participant has been exposed to the study product. Analyses will be conducted separately for each of the three cohorts, with a final aggregate analysis that will include all enrolled participants from each of the three cohorts. The number and the percentages of participants experiencing each primary endpoint (see [Section 10.2](#)) will be tabulated by study arm. Each participant will contribute once in each category (i.e., only for highest severity AE for each participant) for the calculation of event rates. Exact binomial confidence intervals will be calculated for each primary endpoint. Primary endpoint event rates will be compared to baseline estimates as described in [Section 10.7](#). A secondary analysis will be performed to summarize the total number of primary and secondary safety endpoints reported per participant by study arm.

### 10.8.2 Analysis of Secondary Endpoints

#### **Pregnancy Complications**

Pregnancy complications will be analyzed using the same approach as the primary endpoints (see [Section 10.8.1](#)).

#### **Infant Drug Levels**

The concentrations of study product and number and percentages of infants with detectable concentrations of study product will be summarized by study arm.

### **Adherence**

For women randomized to the VR arm, a combination of measures (maternal plasma DPV concentration and residual DPV levels in returned VRs) will be used to characterize use of study product. For women randomized to Truvada, maternal plasma concentrations will be used to quantify study product use. The number and proportion of participants with concentrations indicative of study product use will be compared by study arm. Trends over time in study product use will be explored using generalized estimating equations (GEE). Reasons for study product non-use (i.e. VR removal, missed pills) will be tabulated by arm.

### **Acceptability**

To assess acceptability of the study products, information will be obtained from questionnaires in which the participants will rate acceptability on a combination of categorical and continuous scales. Continuous measures of acceptability will be compared across arms using a t-test while categorical measures will be compared using chi-squared tests or Fisher's exact test, as appropriate. The number and percentages of participants who report the study products to be at least as acceptable as other HIV prevention methods will be summarized by study arm. These binomial proportions will be used to assess the acceptability of the study products along with the corresponding 95% confidence intervals and will be compared using chi-squared tests or Fisher's exact test, as appropriate.

#### **10.8.3 Missing Data**

We expect little to no missing data. Data will be considered missing (no data on outcome measures) if a participant does not return for a follow-up visit. However, if the probability of missing measurements depends on either covariates or on the measurement outcomes of participants, then the methods described above may give biased inferences and point estimates. If a substantial amount of endpoint data is missing (e.g., follow-up data missing in at least 10% of participants), then secondary analyses of the endpoints will be conducted using methods that relax the missing completely at random assumption to a missing at random assumption. For a univariate binary and quantitative outcome, respectively, a generalized linear model with a binomial or Normal error distribution will be used for estimation and testing.

## **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 will be generated routinely 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. Study data is entered into the electronic CRFs in the MTN-042 Medidata Rave study database, a data management system compliant with International Council on Harmonization (ICH) Good Clinical Practices (GCP) and CFR guidelines, which is maintained by the MTN SDMC.

Interview files generated in the field will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be uploaded and managed using a qualitative software package. RTI International will act as a hub, and manage all qualitative data for the study. A convention for file naming will be developed, and all data will be labeled

according to this process. Transcripts will be transferred to RTI International as they are completed. RTI International will save all versions of all files on a secure, password-protected server.

## **11.2 Source Documents and Access to Source Data/Documents**

All study sites will maintain source data/documents in accordance with the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual (<https://www.niaid.nih.gov/research/daids-score-manual>).

Each IoR/designee will maintain, and store securely, complete, accurate and current study records throughout the study. In accordance with U.S. regulations, for the investigational products tested, the IoR/designee will maintain all study documentation for at least two years following the date of marketing approval 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 the DAIDS SCORE Manual (<https://www.niaid.nih.gov/research/daids-score-manual>).

## **12 CLINICAL SITE MONITORING**

Study monitoring will be carried out by Pharmaceutical Product Development, Inc. (PPD) (Wilmington, NC) in accordance with current DAIDS policies. Study monitors will:

- Review informed consent forms (ICFs), procedures, and documentation.
- Assess compliance with the study protocol, GCP guidelines, and applicable regulatory requirements (US and non-US), including 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.
- Verify that current license/certification is available on site for study staff listed on the current FDA Form 1572, DAIDS IoRs, and Delegation of Responsibilities Log/Form.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of or in addition to onsite visits to ensure the safety of study participants and data integrity.<sup>92</sup> The site will make available study documents for site

monitors to review utilizing a secure platform. Selected platforms must be confirmed with the DAIDS Office of Clinical Site Oversight (OCSO) in advance.

For on-site visits, the IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., ICFs, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of certain study procedures. The IoR/designee will also allow inspection of all study-related documentation by authorized representatives of the MTN Leadership and Operations Center (LOC), SDMC, LC, NIAID, FDA, IPM, Gilead Sciences, Inc., OHRP and other local, US, and international regulatory entities. A site visit log will be maintained at the study site to document all visits.

## **13 HUMAN SUBJECTS PROTECTIONS**

### **13.1 Institutional Review Boards/Ethics Committees**

Site investigators will make every effort 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, IPM, Gilead Sciences, Inc., the FDA, OHRP, any of their appointed agents, and other local, US, and international regulatory entities.

*\* Changes to this protocol may be implemented by investigators prior to IRB/IEC approval, if those changes are required to eliminate apparent immediate hazards to the study participant. [See 45 CFR 46.108(a)(3)(iii) under the 2018 Requirements and 45 CFR 46.103(b)(4)(iii) under the pre-2018 Requirements.] These changes must be documented as Protocol Deviations and reported to the Protocol Team and IRB/IEC as soon as possible. [See ICH E6(R2), Good Clinical Practice, Section 4.5.4.] In the event of a public health emergency, investigators should adhere to the recommendations of their local institutions, IRB/IEC and local health departments. When conflicts exist between local directives, MTN, Protocol Team and/or DAIDS policies or guidance, sites should follow the requirement that is most protective of study participants and site staff. [See DAIDS Guidance, Coronavirus Disease (COVID-19) and DAIDS HIV/AIDS Network Clinical Research Studies, Page 3, dated March 13, 2020.]*

### **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 ICFs approved, as appropriate, by their local IRB/EC and any other applicable regulatory entities (REs). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (PRO) at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific ICFs *will* be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification 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 Investigational New Drug (IND) application for this study. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement (CTA) executed by NIAID, IPM, and Gilead Sciences, Inc.

Study implementation will also be guided by the MTN-042 SSP 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 product and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN LOC, SDMC, LC and other designated members of the Protocol Team.

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

### **13.4 Risk Benefit Statement**

#### **13.4.1 Risks**

##### General

It is not expected that this study will expose human subjects to unreasonable risk.

Pelvic examination and procedures may cause mild discomfort, pressure and/or vaginal bleeding or spotting. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Disclosure of HIV and STI status may cause worry, sadness or depression. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained counselors will be available to help participants deal with these feelings.

Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual behaviors. Participation in this study also includes the disclosure of protected health information (e.g., medical and antenatal care

records) to study staff. Participants will be counseled regarding potential confidentiality issues, including keeping any study materials (e.g., study products, handouts) and communications (e.g., text messages, phone calls, health records) confidential.

Participants at sites where local regulatory authorities require 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 of study product.

Participants will be asked questions about their study product use and vaginal and sexual practices. These questions may make some participants uncomfortable.

### Dapivirine

Use of the study VR may lead to urinary tract infections, vaginal discharge, vulvovaginal pruritus, vulvovaginitis, and pelvic pain. Less common side effects include: cervicitis, cystitis, vaginal odor, cervix erythema, cervix ecchymosis, cervix edema, cervical discharge, vulvovaginal pain/discomfort, pelvic discomfort, vaginal/uterine cervical erosion, genital itching/discomfort, dysuria, pollakiuria, bladder pain, abdominal pain/discomfort, suprapubic pain, application site pain/discomfort, and vaginal laceration. It is possible that a participant may have an allergic reaction to the study product. Symptoms of an allergic reaction include rash or other skin irritation, itching, joint pain, or difficulty in breathing. As with any vaginally retained product, the possibility of toxic shock syndrome, although rare, exists.

Safety data were evaluated from two Phase 3 studies, MTN-020 (ASPIRE) and IPM 027 (The Ring Study), which enrolled a total of 4588 women, and results were reported in February 2016. No safety concerns were noted in DPV VR users as compared to placebo VR users. There were no new safety concerns noted in the two DPV VR open-label extension trials, MTN-025 (HOPE) and IPM 032 (DREAM), which enrolled a total of 2309 women, and results were reported in July 2019 and June 2019, respectively. No prospective data is available for DPV VR use during pregnancy, and therefore there may be some risk to pregnant women from using a product whose full safety profile is unknown. However, the benefits of using this HIV prevention method are anticipated to outweigh the risks for the pregnant women targeted for this study, who live in regions with high HIV incidence. Furthermore, the study was designed to minimize risk from product exposure by taking a carefully monitored, step-wise approach to dosing starting at later gestational ages, then progressing to earlier gestational ages only once safety is confirmed via interim safety review.

Based on *in vitro* data, HIV-infected participants who have prolonged exposure to low concentrations of DPV by continuing to use the VR after infection may have a risk of selecting viruses carrying NNRTI resistance-associated mutations. Clinical relevance has yet to be established, however, as no clear resistance pathway has emerged. All NNRTI mutations observed in women using DPV VRs have also been observed in women using placebo rings, and it is unclear if the observed mutations were transmitted or arose due to DPV selective pressure given the increasing prevalence of NNRTI resistance mutations in the study communities and the absence of data on the transmitting partner's virologic profile.

### Truvada (FTC/TDF)

Truvada may have side effects, some of which are listed below. This list includes the more serious or common side effects with known or possible relationship. Participants taking Truvada

will be monitored closely for any side effects, and are asked to report all side effects to the study clinician.

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

- Gastrointestinal intolerance (such as nausea, abdominal pain, diarrhea, or vomiting)
- Flatulence (gas)
- Headache, dizziness, tiredness, or inability to sleep

However, these were relatively infrequent (10% of users) and did not lead to product discontinuation; furthermore, gastrointestinal intolerance and flatulence typically resolved after the first or second month of oral PrEP use.<sup>14</sup>

Rare, but serious side effects include:

- Rash
- Worsening or new kidney damage
- Bone pain and bone changes such as thinning and softening
- Allergic reaction
- Lactic acidosis (buildup of too much acid in the body). Lactic acidosis can cause shortness of breath, nausea and liver failure
- Individuals with HBV who suddenly stop taking Truvada may get a “flare” or worsening of hepatitis symptoms

Little prospective data is available for Truvada tablet use during pregnancy by HIV-negative women, and therefore there may be some risk to pregnant women from using a product whose full safety profile is unknown. However, the benefits of using this HIV prevention method are anticipated to outweigh the risks for the pregnant women targeted for this study, who live in regions with high HIV incidence. Furthermore, the study was designed to minimize risk from product exposure by taking a carefully monitored, step-wise approach to dosing starting at later gestational ages, then progressing to earlier gestational ages only once safety is confirmed via interim safety review.

Site staff will make every effort to protect participant privacy while in the study. 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-positive or “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.

### **13.4.2 Benefits**

Given that the DPV VR received a positive scientific opinion to reduce the risk of HIV infection in adult women from the EMA under Article 58 and has been included in the WHO recommendations for HIV prevention, participants in MTN-042 will experience the direct benefit of using an HIV-1 prevention product currently being considered for potential regulatory approval. Furthermore, Truvada is an FDA licensed product that is used to treat HIV infection as well as reduce the risk of HIV infection.

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to understand issues important for broader implementation of the DPV VR and PrEP and/or for the development of other

interventions to prevent HIV acquisition in pregnant women. Participants may also appreciate the opportunity to contribute to the field of HIV prevention research.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, pelvic examination, obstetric abdominal examination, and routine laboratory testing. Participants will be provided with an obstetric ultrasound if not already performed as part of their routine antenatal care. Participants will be provided STI treatment in accordance with WHO guidelines free of charge. In addition, STI testing, counseling and treatment, as well as HIV testing and counseling will be available for participants' 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 as a result may have decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals. Antenatal care and delivery services will not be provided by the study and must be accessed in local care facilities as would have occurred in the absence of study participation.

### **13.5 Informed Consent Process**

Written informed consent will be obtained from all participants as per US regulations and local authorities. Informed consent is required prior to initiation of MTN-042 procedures. Written informed consent will also be obtained for long-term specimen storage and possible future testing, although consent for specimen storage and future testing 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 the DAIDS SCORE Manual (<https://www.niaid.nih.gov/research/daids-score-manual>). Participants will be provided with copies of the ICFs if they are willing to receive them.

In addition to ICFs, the Protocol Team will work with study staff and community representatives to develop 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 MTN-042 SSP manual.

The informed consent process will cover all elements of informed consent as required by the OHRP and applicable local research regulations. In addition, the process will specifically address the following topics of importance to this study:

- The importance of adherence to the study visit and procedures schedule
- The importance of study product adherence to its effectiveness
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real benefit of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time
- New information on either study product or about other effective HIV-prevention products will be provided to MTN-042 participants

## **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. For example, participants will be counseled about keeping all study materials (e.g., study products, handouts) and communications (e.g., text messages, phone calls, health records) confidential. 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. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and ICFs, will be stored securely. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' identification numbers to identifying information will be stored in a locked file in an area with limited access. All digital audio files will be stored on password-protected computers. Audio files will be translated and transcribed in English and securely stored. Please see MTN-042 SSP Manual for guidance.

Participants' study information will not be released without their written permission, except as necessary for review, monitoring, and/or auditing by the following:

- Representatives of the US Federal Government, including the US FDA, the US OHRP, NIH and/or contractors of the NIH, and other local, US, and international regulatory entities
- Representatives of IPM
- Representatives of Gilead Sciences, Inc.
- PPD
- Study staff
- Site IRBs/ECs

## **13.7 Special Populations**

### **13.7.1 Pregnant Women**

Based on an assessment of potential risks and benefits associated with the MTN-042 study products and procedures, the MTN-042 study team provides the following rationale to support the assertion that this study may be conducted. Final determination rests with each site's local IRB/EC.

As specified in US 45 CFR 46.204, pregnant women or fetuses may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.

- To date, studies of the DPV VR and Truvada oral tablet have not identified significant safety risks to pregnant women and fetuses. Product safety data is included in [Section 2](#) of this protocol.
2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
    - Due to projected low exposure to either DPV, FTC or TDF for the fetus, associated risks are expected to be minimal. In addition, evidence pointing to the protective effect of both the DPV VR and the Truvada oral tablet against HIV in women holds out the prospect of direct benefit to both the woman and the fetus, as primary maternal infection with HIV poses significant risk to the fetus. Product efficacy data is included in [Section 2](#).
  3. Any risk is the least possible for achieving the objectives of the research.
    - The MTN-042 study team has minimized participant risk for this study by taking a carefully monitored, step-wise approach to dosing, starting at later gestational ages, then progressing earlier in pregnancy once safety is confirmed. The rationale for the study design is detailed in [Section 2.9](#).
  4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part.
    - The MTN-042 study includes an informed consent process consistent with all applicable requirements in the CFR.
  5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
    - This section is not applicable, as there is the prospect of direct benefit to the pregnant woman from participation in the MTN-042 study.
  6. Each individual providing consent under paragraph (d) I(e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
    - This information has been included in the MTN-042 Sample Informed Consent documents, will be included in site-specific informed consent documents, and will be covered thoroughly during the informed consent process, including throughout the pregnant woman's study participation. In addition, the pregnant woman will be informed of any applicable new information learned throughout this or other studies.
  7. For children as defined in 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part.

- This section is not applicable to MTN-042, as children under 18 years old who are pregnant will not be enrolled.
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
    - Inducements to terminate a pregnancy will not be offered by MTN-042 study site staff.
  9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
    - Individuals engaged in MTN-042 will have no part in decisions as to the timing, method, or procedures used to terminate a pregnancy by participants.
  10. Individuals engaged in the research will have no part in determining the viability of a neonate.
    - Individuals engaged in MTN-042 will have no part in determining the viability of a neonate.

### 13.7.2 Children

The NIH has mandated that children be included in research studies when appropriate. Based on an assessment of potential risks and benefits associated with the MTN-042 study products and procedures, the MTN-042 study team provides the following rationale to support the assertion that this study may be conducted. Final determination rests with each site's local IRB/EC.

As specified in US 45 CFR 46.205, viable neonates and neonates of uncertain viability may be involved in research if all of the following conditions are met:

1. Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.
  - To date, studies of DPV VR and Truvada oral tablet exposure in pregnancy have not identified significant safety risks to neonates. Product safety data is included in [Section 2](#) of this protocol.
2. Each individual providing consent for the neonate is fully informed regarding the reasonably foreseeable impact of the research on the neonate.
  - Individuals providing consent for participation in MTN-042 will be fully informed regarding the reasonably foreseeable impact of the research on the neonate, using IRB-approved consent materials.
3. Individuals engaged in the research will have no part in determining the viability of a neonate.
  - Individuals engaged in MTN-042 will have no part in determining the viability of a neonate.
4. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or the purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research.

- MTN-042 will enroll pregnant female participants who are age 18-40 years old at the time of enrollment for this study, as verified per site SOPs, as well as their infants once they are born. MTN-042 will provide critical safety data related to study drug exposure for the fetuses of those female participants. The research holds out the prospect of preventing HIV infection in the mother of the neonate, which may decrease the risk of neonatal HIV infection, a condition known to have a negative impact on neonatal survival. Neonates may experience benefit from increased medical screening during study participation, beyond the standard of care, which may have a positive impact on survival.
5. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.
    - The legally effective informed consent of either parent's legally authorized representative would be obtained in accordance with the referenced regulation.

As specified in US 45 CFR 46.405, children may be involved in research of greater than minimal risk but presenting the prospect of direct benefit to the individual subjects if all of the following conditions are met:

1. The risk is justified by the anticipated benefit to the subjects.
  - The risk involved in this research is considered greater than minimal risk but presents the prospect of direct benefit to both female and infant participants. Both products being used in this study have been shown to be well-tolerated and to provide a statistically significant reduction in the risk of HIV-1 infection for adult women when used as instructed, but DPV is still under consideration for potential regulatory approval as an HIV-1 prevention product, and Truvada for oral PrEP has not yet been made widely accessible in the countries where the implementation of this study is planned. Therefore, this research holds out the prospect of direct benefit to the health and well-being of both adult and infant MTN-042 participants.
2. The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches.
  - The anticipated benefit to risk ratio of MTN-042 participation is acceptable for a safety study of HIV chemoprevention products, which are not currently available to pregnant women as local standard of care in study site communities.
3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in § 46.408.
  - MTN-042 will follow an IRB-approved informed consent process as part of enrollment procedures for pregnant female participants who are aged 18-40 years at the time of enrollment for this study, as verified per site SOPs, as well as their infants once they are born.

## **13.8 Compensation**

Pending IRB/EC approval, participants will be compensated for time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study informed consent forms.

If a participant becomes ill or injured as a result of participation in this trial, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer the participant for ongoing treatment for the injury, if needed. The study sponsor will be responsible for ensuring that insurance to cover appropriate medical expenses for treatment of any such illness or injury is provided if required by law or regulation. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation.

## **13.9 Communicable Disease Reporting**

Study staff will comply with local requirements to report communicable diseases identified among study participants to health authorities, including HIV-1. 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-1 screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV-1 testing time point. Testing will be performed in accordance with the algorithms in [Appendices III](#) and [IV](#). Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will provide information regarding the known efficacy of the study products in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1 test results to take part in this study. Condoms will be offered to participants throughout the duration of their participation.

### **13.10.2 Care for Participants Identified as HIV-Infected**

Care for participants identified as HIV-infected is described in [Section 9.6](#).

## **13.11 Study Discontinuation**

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

## **14 PUBLICATION POLICY**

DAIDS/NIAID and MTN policies and a CTA between IPM, 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/NIAID, NICHD, National Institute of Mental Health (NIMH), IPM, and Gilead for review prior to submission.

## **15 APPENDICES**

## APPENDIX I: Table of Visits and Study Procedures – Mothers

	Visit 1 SCR	Visit 2 ENR	Phone Contacts Prior to Pregnancy Outcome	Cohorts 2-3 only		Bi- weekly Visits After 36 <sup>th</sup> Week	PPO Visit	1-week PPO Phone Contact	6-week PPO Visit/SEV/ Early SEV
				2- week Visit	4- week Visit(s)				
<b>ADMINISTRATIVE AND REGULATORY</b>									
Obtain/confirm informed consent	X	X							
Obtain/review/update signed medical records release and antenatal/delivery care provider information (if required per local laws/regulations)	X						X		
Schedule ultrasound (if records not available at Screening)	X								
Assign a unique Participant Identification (PTID) number	X								
Assess and/or confirm eligibility	X	X							
Collect demographic information	X								
Collect/review/update locator information	X	X	X	X	X	X	X	X	X
Obtain/review/update planned/actual location of delivery	X		X			X	X		
Randomization		X							
Provide reimbursement (sites to reference SOPs)	X	X	X	X	X	X	X	X	X
Schedule next visit/contact	*	*	X	X	X	X	*	X	*
<b>BEHAVIORAL</b>									
HIV pre- and post-test counseling	X	X		*	X	▲	*		X
HIV/STI risk reduction counseling	X	X	*	*	X	▲	*	*	X
Contraceptive counseling						▲	*		X
Protocol adherence counseling		X	*	X	X	X	X	*	X
Behavioral assessment		X			φ		X (Cohorts 2-3 only)		X
Product acceptability assessment (Cohorts 2-3 only)		X			φ				
Social harms assessment					φ				X
Social benefits assessment									X
In-depth interview (IDI) (subset)					◆	◆			
<b>CLINICAL</b>									
Review/update medical history and obstetric symptoms	X	X	X	X	X	X	X	X	X
Review/update available ultrasound results and antenatal/delivery/postpartum care records	X	X			X	X	X		X
Review/update concomitant medications and vaginal products	X	X	X	X	X	X	X	X	X
Physical exam (Targeted after Screening Visit)	X	*		*	X	*	X		*
Pelvic exam	*	X		*	*	*			*
Obstetric abdominal exam	X	X		X	X	X			
Calculate/confirm gestational age	X	X							
Treat RTI/UTI/STIs	*	*	*	*	*	*	*	*	*

	Visit 1 SCR	Visit 2 ENR	Phone Contacts Prior to Pregnancy Outcome	Cohorts 2-3 only		Bi-weekly Visits After 36 <sup>th</sup> Week	PPO Visit	1-week PPO Phone Contact	6-week PPO Visit/SEV/ Early SEV
				2-week Visit	4-week Visit(s)				
Disclose available test results	X	X	X	X	X	X	X	X	X
Collect AEs			X	X	X	X	X	X	X
<b>LABORATORY</b>									
<b>URINE</b>	Dipstick UA (and/or culture)**	X	X		*	∇	*	*	X
	Offer pregnancy testing								X
<b>BLOOD</b>	HIV-1 testing	X	X		*	X	▲	*	X
	HBsAG	X							
	AST/ALT	X	X		*	∇	*	*	X
	Creatinine (Cohort 1 only)	X	X				▲	*	X
	Creatinine (Cohorts 2-3)	X	X		*	π	*	*	X
	CBC with platelets	X	X		*	∇	*	*	X
	Syphilis serology	X	*		*	*	*	*	X
	DBS for TFV-DP and FTC-TP drug levels (after Visit 2, for Truvada group only)		X		X	X	X	X	
	Plasma for DPV drug levels (for DPV group)				X	X	X	X	
	Plasma archive		X						
<b>PELVIC</b>	NAAT for GC/CT/Trich	X	*		*	*	*	*	X
	Wet prep/KOH wet mount for candidiasis and/or BV	*	*		*	*	*	*	*
	Vaginal pH	*	X		*	*	*		X
	Vaginal swab(s) for microbiota		X		X	X	X		X
	Vaginal Gram stain		X		X	X	X		X
	Vaginal swab(s) for biomarkers		X		X	X	X		X
<b>STUDY PRODUCT</b>	Adherence assessment(s): Returned Study VR(s)								
<b>STUDY PRODUCT / SUPPLIES</b>									
Provide study VR or study tablets		X			X	*			
Provide product use instructions		X			X	*			
Insertion of study VR at the clinic (clinician check of VR placement done with initial insertion by participant; check done as needed for subsequent VRs) (for DPV group) or DOD of first study tablet (for Truvada group)		X			X	v			
Remove and/or collect study VR or study tablets					X	*	X (if final VR or tablets not already collected)		
Offer condoms	X	X		X	X	X	X		X



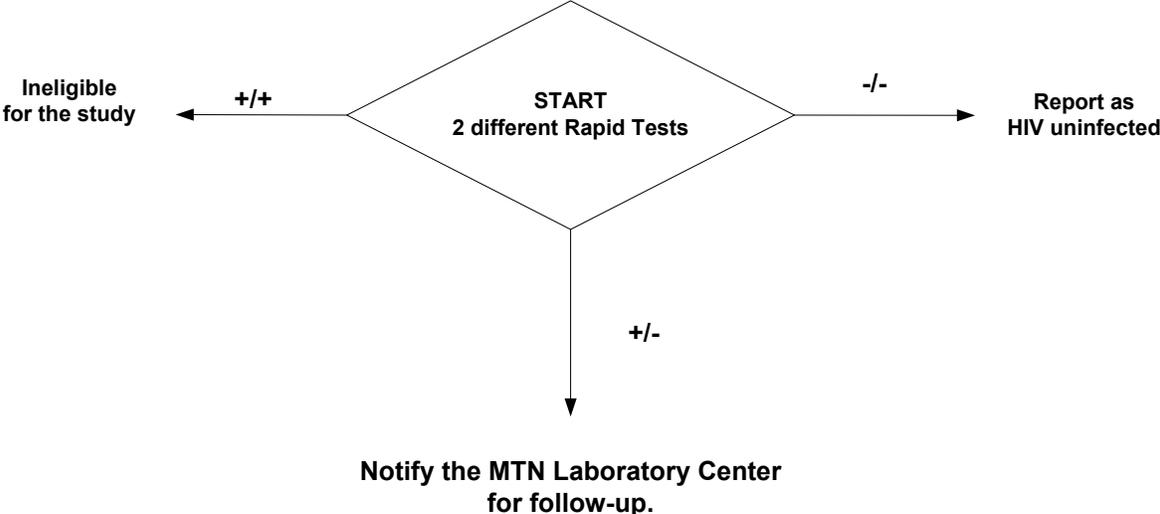
## APPENDIX II: Table of Visits and Study Procedures – Infants

	PPO Visit	1-week PPO Phone Contact	6-week PPO Visit	6-month PPO Visit	12-month PPO Visit/Early SEV
<b>ADMINISTRATIVE AND REGULATORY</b>					
Obtain consent for infant if not already obtained	X				
Collect/review/update locator information	X	X	X	X	X
Provide reimbursement (sites to reference SOPs)	X	X	X	X	X
Schedule next visit/contact	*	X	X	X	*
<b>CLINICAL</b>					
Review infant health, anthropometry, feeding history	X	X	X	X	X
Review/update delivery records	X				
Review/update infant health records	X		X	X	X
Review/update concomitant medications	X	X	X	X	X
Physical exam (Targeted after PPO Visit)	X		X	X	X
Collect AEs	X	X	X	X	X
Disclose available test results	X	X	X	X	X
<b>LABORATORY – BLOOD</b>					
HIV-1 testing	*		*	*	*
AST/ALT	*		*	*	*
Creatinine	X		X	*	*
CBC with platelets	*		*	*	*
DBS for TFV-DP and FTC-TP drug levels (for infants born to mothers in the Truvada group)	X				
Plasma for DPV drug levels (for infants born to mothers in the DPV group)	X				
<b>STUDY SUPPLIES</b>					
Offer condoms to mother				X	X

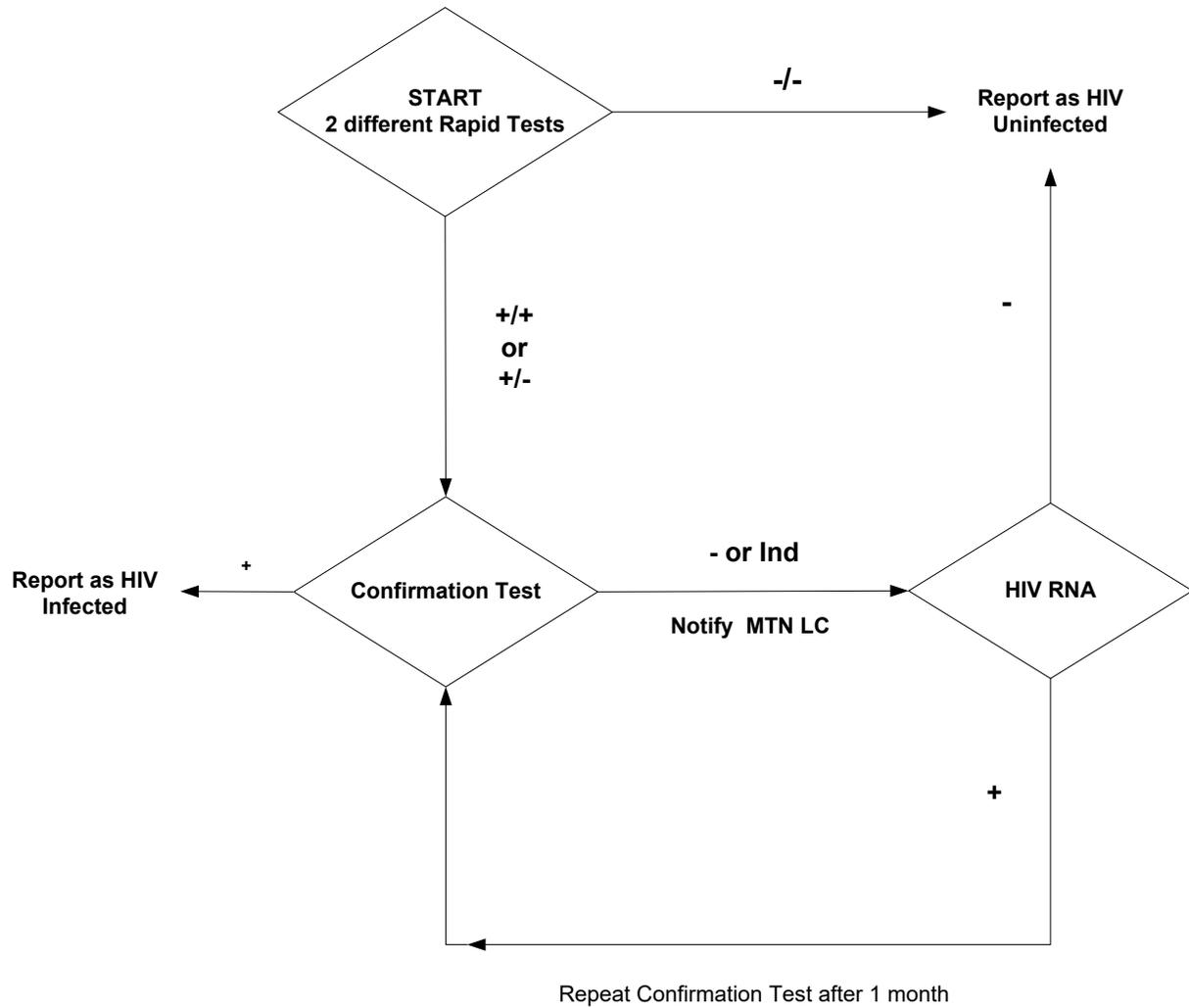
X = required

\* = if indicated and/or per local standard of care

**APPENDIX III: Algorithm For HIV Testing – SCREENING/ENROLLMENT**



## APPENDIX IV: Algorithm For HIV Testing – FOLLOW-UP



Ind: Indeterminate test results  
LC: Laboratory Center

**APPENDIX V: Sample Informed Consent Form  
(Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER –  
COHORT 1**

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

**MTN-042**

**Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and  
Oral TRUVADA® Use in Pregnancy**

**Version 2.0**

**May 20, 2021**

**PRINCIPAL INVESTIGATOR:** *[Site to insert]*

**PHONE:** *[Site to insert]*

**Short Title for the Study:** DELIVER: A Phase 3b Safety Study of the Dapivirine Ring and PrEP in Pregnant Women

**INFORMED CONSENT**

You are being invited to join a research study funded by the US government [US National Institutes of Health (NIH)] and conducted by the Microbicide Trials Network (MTN). There is a separate consent document for your baby. There are two products being used in this study: a ring inserted in the vagina and a tablet taken by mouth. The ring is supplied by International Partnership for Microbicides (IPM) and the tablet is supplied by Gilead Sciences, Inc. The person in charge of this study at this site is *[INSERT NAME OF PRINCIPAL INVESTIGATOR]*.

**STUDY SUMMARY**

Important things you should know:

- The study products in this research study each contain a different anti-HIV medication:
  - The vaginal ring (VR) contains 25 mg of dapivirine (DPV). It is inserted in the vagina and worn continuously for approximately one month, to be replaced every month. We will refer to it in this document as the ring.
  - The oral tablet, Truvada, contains two drugs- 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF). It is taken once a day by mouth. We will refer to it in this document as the tablet.
- The purpose of this study is to find out if using the ring or the tablet during pregnancy is safe and well-tolerated by women and their babies.
- If you qualify and choose to participate, you will be randomly assigned to use one of the two study products for the remainder of your pregnancy (you will not use study product after the end of your pregnancy).
- You will be asked to complete up to eleven (11) study visits (not including unscheduled visits), including the visit today and including up to four (4) phone contacts. Study visits will take place either at this study clinic, at the hospital where you intend to deliver your baby, or at other locations with your permission. You must intend to deliver at a hospital or similar health facility to be eligible for this study, such as *[SITES TO INSERT NAMES OF LOCATIONS AFFILIATED WITH THE SITE]*. The approximate length of your participation in

this study will be about 10 weeks. This includes the time remaining in your pregnancy and six additional weeks of follow-up for you. You will only take the study product while you are pregnant.

- At some of the clinic visits, you will be asked to complete the following: a physical exam (including abdominal exam and ultrasound) , blood draw, urine and vaginal fluid collection, several short interviews (and possibly a longer interview at one or more visits, if you are selected), and you will be asked permission to access your medical records and contact your health care provider.
- Some common risks or discomforts from the ring include: vaginal irritation, discharge, and/or discomfort. One serious but rare side effect is toxic shock syndrome caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacteria.
- Some common risks or discomforts from the tablet include: nausea, abdominal pain, diarrhea, vomiting, passing gas, headache, dizziness, tiredness, and inability to sleep. More serious but rare side effects include: rash, liver problems, kidney problems, allergic reaction, and lactic acidosis.
- You will be using a study product that may prevent you from getting HIV if you use it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may also help in the development of ways to prevent the spread of HIV in the future. You will receive testing for HIV and other sexually transmitted infections (STI), medical examinations, HIV and contraceptive counseling, and routine laboratory testing to check your overall health.
- Taking part in this research study is voluntary. You do not have to participate and you can stop at any time.
- If you decide not to join this study, there are currently available methods to prevent sexually transmitted HIV: condom use during sex and/or the use of daily oral Truvada for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Study staff can provide you with additional information about PrEP and PEP if you are interested.

Please take time to read this entire form and ask questions before deciding to join this study. If you are willing to take part in the study, you will sign your name on this form. A copy of this form will be offered to you. Signing this consent form does not mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible. It is important to know that your and your infant's participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

## **STUDY DETAILS**

### ***Study Products***

The ring was tested and found to be well-tolerated for use by adolescent (15-17 years old) and adult (18 years and older) women. DPV works by stopping HIV from making copies of itself. It was found to reduce HIV infection in women when used consistently. Researchers believe that younger women were not protected from getting HIV because they did not use the ring consistently. The ring received a positive opinion from the European Medicines Agency to reduce the risk of HIV infection in adult women and is now recommended by the World Health Organization as an HIV prevention option. It remains under review by the US Food and Drug Administration (FDA) and has yet to be approved for HIV prevention in any country.

The tablet, called Truvada, is an HIV prevention method approved for adults called oral pre-exposure prophylaxis (PrEP). The tablet works by stopping HIV from making copies of itself and

reduces risk of HIV infection when used consistently. The tablet is also approved to treat HIV infection in people older than 12 years when combined with other drugs.

Neither study product is effective against common sexually transmitted diseases other than HIV. Neither study product can guarantee protection from HIV.

***Who will be in this research study?***

Five hundred fifty (550) healthy, pregnant women who are 18 to 40 years old will be enrolled in the study across various sites in Malawi, South Africa, Uganda and Zimbabwe. Of these, 150 women who are between 36 and 38 weeks in their pregnancy will be enrolled at this time.

***What will I be asked to do if I join this research study?***

For the remainder of your pregnancy, you will either insert a ring and leave it in place for a month, replacing it every month, or take an oral tablet every day. Which of the two products you will use will be decided by chance [*SITES TO INSERT PREFERRED DESCRIPTION OF 'RANDOMIZATION'*] – for every 2 women who will receive the ring, there will be 1 woman who will receive the tablet. Neither you nor the study staff can decide which of the two products you will use.

You will come to the clinic every two weeks for the remainder of your pregnancy. You will also have a phone contact with study staff a week from today and every two weeks after that until delivery, and then one call up to two weeks after delivery. You will allow study staff to access your medical records, and to conduct a study visit as soon as possible after you deliver your baby, no later than two weeks after you deliver. This visit may occur at the study clinic, at the hospital where you deliver, or other location (with your permission). Your final visit will occur 6 weeks after you deliver, for a total maximum of eleven (11) study visits including the visit today and the phone contacts (but not including any unscheduled visits). You will be in the study for approximately 10 weeks. Your baby will also have study visits, which are outlined in a separate consent form. Each visit will take about [*SITES TO INSERT THE APPROXIMATE LENGTH OF TIME*]. During your visit after delivery and the 6 week visit, your baby will also have study procedures completed.

***Do I have to be in this study?***

You do *not* have to be in this study. You can still get the care you need even if you do not join the study. If you join today but change your mind later, you can inform the study staff that you no longer wish to participate. If you do not join the study, your baby cannot join the study.

***What procedures will be done for this study?***

Your first visit will happen today after you read, discuss, understand and sign/mark this form. The procedures done at this visit will let us know if you can join this study, and will take about [*SITES TO INSERT THE APPROXIMATE LENGTH OF TIME*].

If it seems like you can join, you will be asked to come back for an Enrollment visit no later than 35 days from today. During the Enrollment Visit, you will begin using the ring or begin taking the tablet, depending on which study group you have been assigned to.

The following things will happen during your study visits:

- We will ask questions about your health, any medications you may be taking, and any vaginal products you may be using. We will ask questions about your thoughts and feelings and your mood. We will also ask questions about your living situation to see if it affects your use of the study products, and about your reasons for wanting to join this study and how

worried you are about getting HIV.

- We will ask your permission to access your medical records, including your delivery records to gather information about your baby at the time of birth. We will also ask your permission to contact your care provider and to conduct a study visit as soon as possible after you have your baby.
- We will talk with you about what you need to do to be in the study, how to use the study products, and how to protect yourself from getting an infection, including HIV. We may audio-record these conversations to assess how our study staff counsel you and work with them to improve the quality of the counseling you receive, and to learn about experiences and concerns participants may have. The recordings will be kept confidential. If you do not want to have your counseling session recorded, let study staff know.
  - **It is important that you know if you do not intend to deliver your baby at a hospital or similar health facility [SITES TO INSERT NAMES OF LOCATIONS AFFILIATED WITH THE SITE], you will not be eligible to participate in this study.**
- After the birth of your infant, we will also talk with you about how to keep from getting pregnant.
- We will schedule you for an ultrasound if you have not had one or do not have your ultrasound results with you today.
  - **It is important that you know if you do not have an ultrasound, you will not be eligible to participate in this study.**
- At each study visit, we will draw up to 30 mL (about 2 tablespoons) of blood per visit [*Sites to insert local amount*] to make sure you are healthy and to test you for HIV and other STIs. We will also test your blood to see if you are using the study products. More blood may be collected if you become ill.
- At some visits, we will collect a urine sample to test you for STIs.
- At some visits, we will give you a physical exam to make sure you are healthy.
- At all visits before the birth of your infant, we will give you an abdominal exam to make sure your pregnancy is going well.
- At the Enrollment Visit, we will give you a pelvic exam to check for infections and to make sure you are healthy. We may give you a pelvic exam at other visits, if needed. The study doctor or nurse will use a speculum to do the pelvic exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine your vagina and cervix and take some fluids.
- At some visits, we will take fluids from your vagina using a swab (e.g., Q-Tip or earbud). Vaginal fluids will be collected to look for any changes that may occur during your participation in the study and to test for STIs.
- At some visits, you will answer questions about using the study products and other behaviors, including sexual activity. Some of the questions may be sensitive. If you ever feel uncomfortable, you can choose not to answer questions at any time. Your answers will be kept confidential and no one other than the study team will have access to your responses.
- We may also ask you to do one or more longer interviews with study staff. You may choose not to do these interviews. During the interview(s), we may ask you to discuss your use of the study products, your feelings about the study products and about being in the study, and other questions that can help researchers to better understand participants' experiences while in the study. We may audio-record the interview(s). We will keep the audio recording and related materials confidential and no one other than the study team will have access to your responses.
- For every month you are in the study until the end of your pregnancy, we will give you either another ring to use, or another month of tablets to take.

- We will give you the results of any blood or urine tests when available.
- We will give you treatment for sexually transmitted and other kinds of infections, if you need them.
- In the event a problem with a pregnancy is suspected, an ultrasound can be ordered at the site or a referral will be provided.
- We will give you referrals for other services, if you need them.
- These visits will take about *[SITES TO INSERT AVERAGE VISIT DURATION]* to complete.

If you enroll in the study, only for 24 hours prior to your clinic visits you will be asked to abstain from sex, tampon use and other non-study products.

<i>Activity:</i>	<i>Not Permitted For How Long?</i>
Receptive sexual practices, including: <ul style="list-style-type: none"> <li>• Penile-vaginal intercourse</li> <li>• Penile-anal intercourse</li> <li>• Receptive oral intercourse</li> <li>• Finger stimulation</li> </ul>	For 24 hours before each clinic visit
Tampon use	For 24 hours before each clinic visit
Inserting any non-study objects into your vagina, including: <ul style="list-style-type: none"> <li>• Pessaries</li> <li>• Sex toys</li> <li>• Female condoms</li> <li>• Diaphragms</li> <li>• Menstrual cups</li> <li>• Cervical caps or any other vaginal barrier method</li> </ul>	For 24 hours before each clinic visit

Using vaginal products like spermicides, lubricants, contraceptive vaginal rings, douches, vaginal medications, etc., is not allowed at any time during this study.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

You may be asked to make additional visits so we can do more laboratory tests or have study procedures repeated. We will do this if there are abnormal test results or a mistake during the collection or the processing of your samples. We will also do this if you experience any changes in your physical condition, including symptoms of infection (urinary or sexually transmitted).

***What if I become infected with HIV?***

Being in this study will not cause HIV infection for you or your infant. But, there is always a chance that you can get HIV through condomless sex or other activities. If you become HIV-positive, you will stop using the study product. But, we will ask you to continue to come for your study visits and to complete some of the study procedures for a minimum of twelve months. This study does not provide medication for treatment of HIV. If you become infected with HIV, the study staff will refer you for medical care and other available services to prevent your infant from getting HIV. If you get HIV, it is possible that the virus is resistant to some drugs. This means that some drugs may not work well to treat your HIV. This is also possible if your infant becomes infected. We will do a blood test to find out if you have drug resistance. These results can help us know which drugs would be best to treat your HIV.

Depending on local and national health requirements, the study staff may need to report certain diseases, including HIV. The reportable diseases at this site are *[SITES TO INSERT]*. We must inform the following *[SITES TO INSERT MORE DETAILED INFORMATION REGARDING WHO*

*WILL BE INFORMED OF THE REPORTABLE DISEASES*]. *[SITES TO INCLUDE/AMEND THE FOLLOWING]*: Outreach workers from the *[LOCAL HEALTH AUTHORITY]* may then contact you about informing your partner/s, since they also should be tested. If you do not want to inform your partner/s yourself, the outreach workers will contact them, according to the confidentiality guidelines of the *[LOCAL HEALTH AUTHORITY]*.

## **RISKS AND/OR DISCOMFORTS**

### ***Risks of Blood Draws***

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, or small clot where the needle is inserted. Rarely, drawing blood can cause an infection where the needle goes into your hand or arm.

### ***Risks of Pelvic Exams***

You may feel discomfort or pressure during the pelvic exam. You may have a small amount of vaginal bleeding or spotting which should stop shortly after the exam.

### ***Risks of the DPV VR***

We do not yet know all the side effects of the ring. Most people who have used the ring did not have any side effects. Some women who used the ring in other studies have had: discharge from the vagina; pelvic pain; burning or itchiness in the vagina; and urinary tract infections. Less common side effects included: irritation, bruising, swelling, inflammation, wearing, and discharge from the cervix; bladder pain and inflammation; vaginal odor, itching, inflammation, tearing, and discomfort; pelvic discomfort; abdominal pain and discomfort; and problems urinating.

Although rare, the ring may cause an allergic reaction. Signs of an allergic reaction include, but are not limited to: rash or other skin irritation, itching, joint pain, or difficulty in breathing.

There is the possibility of getting toxic shock syndrome, although this is very rare. Toxic shock syndrome is a serious but rare infection caused by bacteria. Any product placed inside the vagina can cause it. Getting toxic shock syndrome from using the ring is unlikely. But, it is important that you tell the study staff as soon as possible if you have any of the following symptoms: sudden high fever, a faint feeling, diarrhea, headache, rash, and muscle aches.

It is possible that the side effects from ring use may be different in women who are pregnant, or that the side effects may resemble normal symptoms of pregnancy. Studies with pregnant animals showed that DPV did not cause side effects to the animals or their fetuses. Women who became pregnant while using the ring in clinical studies did not experience more side effects than non-pregnant women, and neither did their infants. However, there is not enough information to know for sure. One small study found that DPV can be detected in breastmilk from women who used the ring while lactating, but it is unknown whether the small amounts of drug detected could produce side effects in babies.

### ***Risks of the Truvada tablet***

Most people who take the tablet do not have any side effects. The side effects that some people taking the tablet may have are well known because the drugs have been used by many people. People with hepatitis B who suddenly stop taking the tablet may get a flare-up or worsening of their hepatitis symptoms.

One in ten people who take the tablet may have mild side effects that usually go away after

stopping the drug. These occasional side effects include: mild kidney problems that are only detected by laboratory tests, inability to sleep, lack of energy or tiredness, headache, upset stomach, passing gas, vomiting, soft or liquid stools, and dizziness. Upset stomach, passing gas, vomiting and soft or liquid stools typically go away after the first or second month of use.

Other side effects are more serious, but less than one in a hundred people who take the tablet may have them. These rare side effects include: rash, liver problems, serious kidney damage, and allergic reaction. People taking the tablet may also have bone pain and/or small changes in the thickness of their bones, but these changes have not caused problems for the people who had them.

In rare cases, some people with HIV who take the tablet in combination with other drugs may get lactic acidosis. This is a serious side effect of some drugs used to treat HIV that can cause shortness of breath, nausea, and liver failure. This serious side effect has been seen more often in women taking the tablet in combination with other drugs. You should call or come to the clinic if you have unexplained changes in urination, weight loss, cramps, muscle pain, dizziness, tiredness, nausea, vomiting, or shortness of breath.

The use of antiretroviral drug combinations may lead to changes in body fat, some of which 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; and breast enlargement. If you have these symptoms, or any other symptoms that concern you, the study staff will check you and see if you should stop taking the tablet.

It is possible that the side effects from using the tablet may be different in women who are pregnant, or that the side effects may resemble normal symptoms of pregnancy. Studies with pregnant animals showed that FTC and TDF, the drugs in the tablet, did not cause any effects on the animals' fertility or their fetuses, although TDF led to changes in the menstrual cycles of rats. HIV-infected pregnant women and women who became pregnant while taking the tablet in clinical studies did not experience more side effects than non-pregnant women, and their infants did not have more birth defects than the general infant population. However, there is not enough information to know for sure.

A small number of people in this study may have these side effects or other side effects that we do not know about yet. But, we will screen your kidneys and overall health before you join the study and during the study. This will reduce your chances of having any side effects.

### ***Risks of HIV and Sexually Transmitted Infection (STI) Testing***

HIV and STI testing may make you feel anxious regardless of the test results. Finding out your HIV status may cause sadness, depression, and thoughts of suicide, and may also cause problems with your family, friends, or partner.

### ***Other Possible Risks***

You may feel embarrassed and/or worried when talking about sexual activities, your living situation, ways to protect against HIV and STIs, and your test results. You can choose not to answer questions at any time. Trained study counselors will help you with any feelings or questions.

It is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. If you have any problems, study counselors will talk with you and try to help you.

The ring and the tablet can protect you from getting HIV, but based on what we know, the level of protection may be different between the two products. This difference may have an effect on your and your infant's risk of getting HIV. Trained study counselors will help you with any feelings or questions.

## **BENEFITS**

You will be using one of two study products that may prevent you from getting HIV if you use it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may help us learn how to prevent pregnant women from getting HIV. You will receive medical exams, and you will receive counseling and testing for HIV and STIs. You will also have tests to check your overall health.

This study cannot give you antenatal care or delivery services, and cannot give you general medical care. Study staff will refer you to another medical provider for care, if needed. You will get free condoms, if you need them. You will be offered a family planning method after delivery, if you need it. If you have an STI diagnosed, you will receive medicine or a referral, if you need it.

## **NEW INFORMATION**

You will be told any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the study products may be causing bad side effects. We will tell you any new information about preventing HIV, regardless of the product, if we learn that it works during pregnancy. We will also tell you when study results may be available, and how to learn about them.

A description of this research study will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## **WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE ASKED TO LEAVE THE STUDY**

You may need to leave the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, IPM, Gilead Sciences, Inc., the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants.
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. The SMC reviews the progress of the study.
- The Interim Review Panel (IRP) recommends that the study be stopped early. The IRP reviews results after each group of participants finishes the study and decides if the next group should begin the study.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the study products if you:

- Acquire an HIV infection.
- Acquire a hepatitis B infection (Truvada users only).
- Use drugs for HIV prevention beyond what the study gives you.
- Use drugs to prevent infection after being exposed to HIV.

- Use injectable drugs for reasons other than treating disease.
- Go into labor.
- Experience the death or serious health issue with your unborn child.
- Have a bad reaction to study product, or a study doctor decides that using study product would be bad for you.
- Are unable or unwilling to follow the study rules.

If a study doctor asks you to stop using study product, we will ask that you and your infant come in for all remaining study visits to have some of the procedures we talked about earlier.

If you are removed from the study or choose to leave, we will ask you to return the study product and to come back for one final clinic visit. If you do not have the study product with you when you come to the clinic, staff members will make every effort to assist you in returning it as soon as possible. *[SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES.]* If you leave the study, we will ask you to check in with study staff until the end of your pregnancy and for one year after giving birth so we can follow your health and the health of your infant. If you choose to leave the study and later wish to rejoin, you may resume using study product (if applicable) and come in for all study visits remaining in your original visit schedule after consultation with the Protocol Safety Review Team.

#### **ALTERNATIVES TO BEING IN THE STUDY**

*[SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE: You may be able to join other studies here or in the community. There may be other places where you can go for HIV counseling and testing and family planning. We will tell you about those studies and those places if you wish.]*

#### **COSTS TO YOU**

*[SITE TO COMPLETE ACCORDING TO SITE CAPACITY]* There is no cost to you for study visits, study products, medical exams, laboratory tests or other procedures. We can give you treatments for STIs other than HIV free of charge while you are in the study, or we can refer you for available treatment.

#### **REIMBURSEMENT**

*[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT]: You will receive [SITES TO INSERT AMOUNT \$xx] for your time, effort, and travel to and from the clinic for each study visit. You may receive [SITES TO INSERT AMOUNT \$xx] for any extra study visits. If you are chosen to take part in the longer interview(s) with staff, you will receive [SITES TO INSERT AMOUNT \$xx].*

#### **CONFIDENTIALITY**

We will make every effort to keep your and your infant's information private and confidential. But, we cannot guarantee it.

Study visits will take place in private. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you. We will only record your study ID number. If you are selected to do the longer interview(s), you can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. *[Sites to modify with their site-specific source documentation storage*

*duration requirements if required by their IRBs/IECs:* All original study documents that provide information about you for this study will be kept for at least two years after either the dapivirine vaginal ring is approved for use or the clinical research development program for the dapivirine vaginal ring is stopped.]

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us you may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

The study staff may use your personal information to verify that you are not in any other research studies. *[SITES TO INSERT INFORMATION ABOUT SYSTEMS CURRENTLY IN PLACE TO ENSURE PARTICIPANTS ARE NOT PART OF OTHER CONFLICTING STUDIES, INCLUDING BIOMETRIC IDENTIFICATION SYSTEMS.]* This study will not use your name or identify you personally in any publication.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US OHRP, NIH and/or NIH contractors, and other US, local, and international regulatory entities
- *[SITES TO INSERT APPLICABLE LOCAL AUTHORITIES]*
- IPM, the organization that supplies the ring
- Gilead Sciences, Inc., the company that supplies the tablets
- Study monitors
- Site IRB/EC
- Study staff

The study staff will do everything they can to protect your privacy.

### **RESEARCH-RELATED INJURY**

It is unlikely that you or your infant will be injured by being in this study. The U.S. NIH does not have a mechanism to pay money or give other forms of financial compensation for research related injuries. You are not giving up any legal rights by signing this form. *[Sites to replace with their site-specific research-related injury institutional policy if they already provide clinical trials insurance:]* If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. The study sponsor will be responsible for ensuring that insurance is provided to cover appropriate medical expenses for treatment of any such illness or injury if required by law or regulation. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.

**YOUR RIGHTS AS A RESEARCH PARTICIPANT**

*[SITES TO SPECIFY INSTITUTIONAL POLICY]:* Being in this study is completely voluntary. You may choose not to join this study or leave this study at any time. If you choose not to join or to leave the study, you can still join other studies and access non-study services you would normally get at this clinic. If you want the results of the study after it is over, let the study staff members know.

**PROBLEMS OR QUESTIONS**

If you ever have any questions about the study, or if you have a research-related injury, you should contact *[INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]* at *[INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS]*.

If you have questions about your rights as a research participant, you should contact *[INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]* at *[INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER]*.

*[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS IS REQUIRED]*

**CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION**

There may be a small amount of urine, blood, and vaginal fluids left over after we have done all of the study related testing. We would like to store your leftover body fluids for future work that could include testing for study products, testing for HIV risk and testing related to COVID-19 infection (if such testing is available and needed to better understand the impact of COVID-19 infection on the study data). If you agree, your samples and related health information will be stored safely and securely.

Only approved researchers will be able to use these samples and health information. Some employees will need to have access to these samples to store them and keep track of where they are, but these people will not have information that directly identifies you. The de-identified data and specimens could then be used for future research by our research team or other researchers without notifying you or asking your permission for this use.

There is no time limit on how long your samples will be stored. Your samples may be shipped and/or stored outside of the country. We do not yet know the specific type of testing that will be done with these samples. But, they may be used to check that certain laboratory tests perform correctly. Any other testing beyond that will have to be approved by an IRB/EC. We do not plan to do genetic testing or sequencing (for example, the mapping of all of your genes, which is also known as whole genome sequencing) of any kind. Your specimens will never be used for commercial profit.

You can still be in this study if you decide we cannot store your urine, blood, and vaginal fluids. You can change your mind about storing and using these samples for future tests at any time by writing to the person in charge of this study. We will then destroy the leftover samples. But, researchers will not be able to destroy samples or information from research that is already started.

PARTICIPANT INITIALS OR MARK	
_____	I DO agree to allow my biological specimens and health data to be stored and used in future research studies.
Initials/Mark                      Date	
_____	I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies.
Initials/Mark                      Date	

## CONSENT FOR OFF-SITE VISITS

*[Sites to modify as needed]*

Members of the research team at this clinic may be able to schedule off site visits with you at your home or at another location as part of the study. With your permission, some of the scheduled study visits and some of the study procedures may take place at your home or other location outside of the research clinic, if you are unable to come into the clinic. For example, if you need to receive a new ring or to have a urine or blood sample collected, study staff could come to you your home or meet you at another location, if you give your permission and if the study staff determine that it is appropriate. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in-place to maintain your information in a confidential manner. However, it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

In order to conduct visits outside of the clinic, we will need you to give us permission to do so. Please read carefully the following statement and initial/mark and date one option. Choosing not to have study visit procedures outside of the study clinic will not affect your participation in this study. Even if you agree today, you can withdraw your consent for off-site visits at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

### PARTICIPANT INITIALS OR MARK

\_\_\_\_\_  
Initials/Mark

\_\_\_\_\_  
Date

I DO agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary.

\_\_\_\_\_  
Initials/Mark

\_\_\_\_\_  
Date

I DO NOT agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary.

**SIGNATURE PAGE**

*[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC:]*

All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights or my infant's rights as research participants will be answered by *[INSERT LOCAL IRB/EC INFORMATION]*.

I voluntarily agree to be in this research study. A copy of this permission form will be given to me.

\_\_\_\_\_  
Participant's Name (Print)

\_\_\_\_\_  
Participant's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Study Staff's Name Conducting  
Consent Discussion (Print)

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (Signature)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness Name (Print)

\_\_\_\_\_  
Witness Signature

\_\_\_\_\_  
Date

**APPENDIX VI: Sample Informed Consent Form  
(Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER –  
COHORT 2**

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

**MTN-042**

**Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and  
Oral TRUVADA® Use in Pregnancy**

**Version 2.0**

**May 20, 2021**

**PRINCIPAL INVESTIGATOR:** *[Site to insert]*

**PHONE:** *[Site to insert]*

**Short Title for the Study:** DELIVER: A Phase 3b Safety Study of the Dapivirine Ring and PrEP in Pregnant Women

**INFORMED CONSENT**

You are being invited to join a research study funded by the US government [US National Institutes of Health (NIH)] and conducted by the Microbicide Trials Network (MTN). There is a separate consent document for your baby. There are two products being used in this study: a ring inserted in the vagina and a tablet taken by mouth. The ring is supplied by International Partnership for Microbicides (IPM) and the tablet is supplied by Gilead Sciences, Inc. The person in charge of this study at this site is *[INSERT NAME OF PRINCIPAL INVESTIGATOR]*.

**STUDY SUMMARY**

Important things you should know:

- The study products in this research study each contain a different anti-HIV medication:
  - The vaginal ring (VR) contains 25 mg of dapivirine (DPV). It is inserted in the vagina and worn continuously for approximately one month, to be replaced every month. We will refer to it in this document as the ring.
  - The oral tablet, Truvada, contains two drugs- 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF). It is taken once a day by mouth. We will refer to it in this document as the tablet.
- The purpose of this study is to find out if using the ring or the tablet during pregnancy is safe and well-tolerated by women and their babies.
- If you qualify and choose to participate, you will be randomly assigned to use one of the two study products for the remainder of your pregnancy (you will not use study product after the end of your pregnancy)
- You will be asked to complete up to sixteen (16) study visits (not including unscheduled visits), including the visit today and including up to six (6) phone contacts. Study visits will take place either at this study clinic, at the hospital where you intend to deliver your baby, or at other locations with your permission. You must intend to deliver at a hospital or similar health facility to be eligible for this study, such as *[SITES TO INSERT NAMES OF LOCATIONS AFFILIATED WITH THE SITE]*. The maximum length of your participation in

this study will be about 18 weeks. This includes the time remaining in your pregnancy and six additional weeks of follow-up for you. You will only take the study product while you are pregnant.

- At some of the clinic visits, you will be asked to complete the following: a physical exam (including abdominal exam and ultrasound), blood draw, urine and vaginal fluid collection, several short interviews (and possibly a longer interview at one or more visits, if you are selected), and you will be asked permission to access your medical records and contact your health care provider.
- Some common risks or discomforts from the ring include: vaginal irritation, discharge, and/or discomfort. One serious but rare side effect is toxic shock syndrome caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacteria.
- Some common risks or discomforts from the tablet include: nausea, abdominal pain, diarrhea, vomiting, passing gas, headache, dizziness, tiredness, and inability to sleep. More serious but rare side effects include: rash, liver problems, kidney problems, allergic reaction, and lactic acidosis.
- You will be using a study product that may prevent you from getting HIV if you use it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may also help in the development of ways to prevent the spread of HIV in the future. You will receive testing for HIV and other sexually transmitted infections (STI), medical examinations, HIV and contraceptive counseling, and routine laboratory testing to check your overall health.
- Taking part in this research study is voluntary. You do not have to participate and you can stop at any time.
- If you decide not to join this study, there are currently available methods to prevent sexually transmitted HIV: condom use during sex and/or the use of daily oral Truvada for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Study staff can provide you with additional information about PrEP and PEP if you are interested.

Please take time to read this entire form and ask questions before deciding to join this study. If you are willing to take part in the study, you will sign your name on this form. A copy of this form will be offered to you. Signing this consent form does not mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible. It is important to know that your and your infant's participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

## **STUDY DETAILS**

### ***Study Products***

The ring was tested and found to be well-tolerated for use by adolescent (15-17 years old) and adult (18 years and older) women. DPV works by stopping HIV from making copies of itself. It was found to reduce HIV infection in women when used consistently. Researchers believe that younger women were not protected from getting HIV because they did not use the ring consistently. The ring received a positive opinion from the European Medicines Agency to reduce the risk of HIV infection in adult women and is now recommended by the World Health Organization as an HIV prevention option. It remains under review by the US Food and Drug Administration (FDA) and has yet to be approved for HIV prevention in any country.

The tablet, called Truvada, is an HIV prevention method approved for adults called oral pre-exposure prophylaxis (PrEP). The tablet works by stopping HIV from making copies of itself and

reduces risk of HIV infection when used consistently. The tablet is also approved to treat HIV infection in people older than 12 years when combined with other drugs.

Neither study product is effective against common sexually transmitted diseases other than HIV. Neither study product can guarantee protection from HIV.

***Who will be in this research study?***

Five hundred fifty (550) healthy, pregnant women who are 18 to 40 years old will be enrolled in the study across various sites in Malawi, South Africa, Uganda and Zimbabwe. Of these, 150 women who are between 30 and 36 weeks in their pregnancy will be enrolled at this time.

***What will I be asked to do if I join this research study?***

For the remainder of your pregnancy, you will either insert a ring and leave it in place for a month, replacing it every month, or take an oral tablet every day. Which of the two products you will use will be decided by chance [SITES TO INSERT PREFERRED DESCRIPTION OF 'RANDOMIZATION'] – for every 2 women who will receive the ring, there will be 1 woman who will receive the tablet. Neither you nor the study staff can decide which of the two products you will use.

You will come to the clinic every two weeks for the first month you are in the study, and then after you are 36 weeks pregnant, every two weeks for the remainder of your pregnancy. You will also have a phone contact with study staff one and three weeks from today, and after you are 35 weeks pregnant, every two weeks until delivery, and then one call up to two weeks after delivery. You will allow study staff to access your medical records, and to conduct a study visit as soon as possible after you deliver your baby, no later than two weeks after you deliver. This visit may occur at the study clinic, at the hospital where you deliver, or other location (with your permission). Your final visit will occur 6 weeks after you deliver, for a total maximum of sixteen (16) study visits including the visit today and the phone contacts (but not including any unscheduled visits). You will be in the study for up to 18 weeks. Your baby will also have study visits, which are outlined in a separate consent form. Each visit will take about [SITES TO INSERT THE APPROXIMATE LENGTH OF TIME]. During your visit after delivery and the 6 week visit, your baby will also have study procedures completed.

***Do I have to be in this study?***

You do *not* have to be in this study. You can still get the care you need even if you do not join the study. If you join today but change your mind later, you can inform the study staff that you no longer wish to participate. If you do not join the study, your baby cannot join the study.

***What procedures will be done for this study?***

Your first visit will happen today after you read, discuss, understand and sign/mark this form. The procedures done at this visit will let us know if you can join this study, and will take about [SITES TO INSERT THE APPROXIMATE LENGTH OF TIME].

If it seems like you can join, you will be asked to come back for an Enrollment visit no later than 35 days from today. During the Enrollment Visit, you will begin using the ring or begin taking the tablet, depending on which study group you have been assigned to.

The following things will happen during your study visits:

- We will ask questions about your health, any medications you may be taking, and any vaginal products you may be using. We will ask questions about your thoughts and feelings and your mood. We will also ask questions about your living situation to see if it affects your

use of the study products, and about your reasons for wanting to join this study and how worried you are about getting HIV.

- We will ask your permission to access your medical records, including your delivery records to gather information about your baby at the time of birth. We will also ask your permission to contact your care provider, and to conduct a study visit as soon as possible after you have your baby.
- We will talk with you about what you need to do to be in the study, how to use the study products, and how to protect yourself from getting an infection, including HIV. We may audio-record these conversations to assess how our study staff counsel you and work with them to improve the quality of the counseling you receive, and to learn about experiences and concerns participants may have. The recordings will be kept confidential. If you do not want to have your counseling session recorded, let study staff know.
  - **It is important that you know if you do not intend to deliver your baby at a hospital or similar health facility [SITES TO INSERT NAMES OF LOCATIONS AFFILIATED WITH THE SITE], you will not be eligible to participate in this study.**
- After the birth of your infant, we will also talk with you about how to keep from getting pregnant.
- We will schedule you for an ultrasound if you have not had one or do not have your ultrasound results with you today.
  - **It is important that you know if you do not have an ultrasound, you will not be eligible to participate in this study.**
- At each study visit, we will draw up to 30 mL (about 2 tablespoons) of blood per visit [*Sites to insert local amount*] to make sure you are healthy and to test you for HIV and other STIs. We will also test your blood to see if you are using the study products. More blood may be collected if you become ill.
- At some visits, we will collect a urine sample to test you for STIs.
- At some visits, we will give you a physical exam to make sure you are healthy.
- At all visits before the birth of your infant, we will give you an abdominal exam to make sure your pregnancy is going well.
- At the Enrollment Visit, we will give you a pelvic exam to check for infections and to make sure you are healthy. We may give you a pelvic exam at other visits, if needed. The study doctor or nurse will use a speculum to do the pelvic exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine your vagina and cervix and take some fluids.
- At some visits, we will take fluids from your vagina using a swab (e.g., Q-Tip or earbud). Vaginal fluids will be collected to look for any changes that may occur during your participation in the study and to test for STIs.
- At some visits, you will answer questions about using the study products and other behaviors, including sexual activity. Some of the questions may be sensitive. If you ever feel uncomfortable, you can choose not to answer questions at any time. You will also answer questions about what you liked and did not like about this study and about the study products. Your answers will be kept confidential and no one other than the study team will have access to your responses.
- We may also ask you to do one or more longer interviews with study staff. You may choose not to do these interviews. During the interview(s), we may ask you to discuss your use of the study products, your feelings about the study products and about being in the study, and other questions that can help researchers to better understand participants' experiences while in the study. We may audio-record the interview(s). We will keep the audio recording and related materials confidential and no one other than the study team will have access to

your responses.

- For every month you are in the study until the end of your pregnancy, we will give you either another ring to use, or another month of tablets to take.
- We will give you the results of any blood or urine tests when available.
- We will give you treatment for sexually transmitted and other kinds of infections, if you need them.
- In the event a problem with a pregnancy is suspected, an ultrasound can be ordered at the site or a referral will be provided.
- We will give you referrals for other services, if you need them.
- These visits will take about [*SITES TO INSERT AVERAGE VISIT DURATION*] to complete.

If you enroll in the study, only for 24 hours prior to your clinic visits you will be asked to abstain from sex, tampon use and other non-study products.

<i>Activity:</i>	<i>Not Permitted For How Long?</i>
Receptive sexual practices, including: <ul style="list-style-type: none"> <li>• Penile-vaginal intercourse</li> <li>• Penile-anal intercourse</li> <li>• Receptive oral intercourse</li> <li>• Finger stimulation</li> </ul>	For 24 hours before each clinic visit
Tampon use	For 24 hours before each clinic visit
Inserting any non-study objects into your vagina, including: <ul style="list-style-type: none"> <li>• Pessaries</li> <li>• Sex toys</li> <li>• Female condoms</li> <li>• Diaphragms</li> <li>• Menstrual cups</li> <li>• Cervical caps or any other vaginal barrier method</li> </ul>	For 24 hours before each clinic visit

Using vaginal products like spermicides, lubricants, contraceptive vaginal rings, douches, vaginal medications, etc., is not allowed at any time during this study.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

You may be asked to make additional visits so we can do more laboratory tests or have study procedures repeated. We will do this if there are abnormal test results or a mistake during the collection or the processing of your samples. We will also do this if you experience any changes in your physical condition, including symptoms of infection (urinary or sexually transmitted).

***What if I become infected with HIV?***

Being in this study will not cause HIV infection for you or your infant. But, there is always a chance that you can get HIV through condomless sex or other activities. If you become HIV-positive, you will stop using the study product. But, we will ask you to continue to come for your study visits and to complete some of the study procedures for a minimum of twelve months. This study does not provide medication for treatment of HIV. If you become infected with HIV, the study staff will refer you for medical care and other available services to prevent your infant from getting HIV. If you get HIV, it is possible that the virus is resistant to some drugs. This means that some drugs may not work well to treat your HIV. This is also possible if your infant becomes infected. We will do a blood test to find out if you have drug resistance. These results can help us know which drugs would be best to treat your HIV.

Depending on local and national health requirements, the study staff may need to report certain diseases, including HIV. The reportable diseases at this site are [SITES TO INSERT]. We must inform the following [SITES TO INSERT MORE DETAILED INFORMATION REGARDING WHO WILL BE INFORMED OF THE REPORTABLE DISEASES]. [SITES TO INCLUDE/AMEND THE FOLLOWING]: Outreach workers from the [LOCAL HEALTH AUTHORITY] may then contact you about informing your partner/s, since they also should be tested. If you do not want to inform your partner/s yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [LOCAL HEALTH AUTHORITY].

## **RISKS AND/OR DISCOMFORTS**

### ***Risks of Blood Draws***

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, or small clot where the needle is inserted. Rarely, drawing blood can cause an infection where the needle goes into your hand or arm.

### ***Risks of Pelvic Exams***

You may feel discomfort or pressure during the pelvic exam. You may have a small amount of vaginal bleeding or spotting which should stop shortly after the exam.

### ***Risks of the DPV VR***

We do not yet know all the side effects of the ring. Most people who have used the ring did not have any side effects. Some women who used the ring in other studies have had: discharge from the vagina; pelvic pain; burning or itchiness in the vagina; and urinary tract infections. Less common side effects included: irritation, bruising, swelling, inflammation, wearing, and discharge from the cervix; bladder pain and inflammation; vaginal odor, itching, inflammation, tearing, and discomfort; pelvic discomfort; abdominal pain and discomfort; and problems urinating.

Although rare, the ring may cause an allergic reaction. Signs of an allergic reaction include, but are not limited to: rash or other skin irritation, itching, joint pain, or difficulty in breathing.

There is the possibility of getting toxic shock syndrome, although this is very rare. Toxic shock syndrome is a serious but rare infection caused by bacteria. Any product placed inside the vagina can cause it. Getting toxic shock syndrome from using the ring is unlikely. But, it is important that you tell the study staff as soon as possible if you have any of the following symptoms: sudden high fever, a faint feeling, diarrhea, headache, rash, and muscle aches.

It is possible that the side effects from ring use may be different in women who are pregnant, or that the side effects may resemble normal symptoms of pregnancy. Studies with pregnant animals showed that DPV did not cause side effects to the animals or their fetuses. Women who became pregnant while using the ring in clinical studies did not experience more side effects than non-pregnant women, and neither did their infants. However, there is not enough information to know for sure. One small study found that DPV can be detected in breastmilk from women who used the ring while lactating, but it is unknown whether the small amounts of drug detected could produce side effects in babies.

### ***Risks of the Truvada tablet***

Most people who take the tablet do not have any side effects. The side effects that some people taking the tablet may have are well known because the drugs have been used by many people. People with hepatitis B who suddenly stop taking the tablet may get a flare-up or worsening of

their hepatitis symptoms.

One in ten people who take the tablet may have mild side effects that usually go away after stopping the drug. These occasional side effects include: mild kidney problems that are only detected by laboratory tests, inability to sleep, lack of energy or tiredness, headache, upset stomach, passing gas, vomiting, soft or liquid stools, and dizziness. Upset stomach, passing gas, vomiting and soft or liquid stools typically go away after the first or second month of use.

Other side effects are more serious, but less than one in a hundred people who take the tablet may have them. These rare side effects include: rash, liver problems, serious kidney damage, and allergic reaction. People taking the tablet may also have bone pain and/or small changes in the thickness of their bones, but these changes have not caused problems for the people who had them.

In rare cases, some people with HIV who take the tablet in combination with other drugs may get lactic acidosis. This is a serious side effect of some drugs used to treat HIV that can cause shortness of breath, nausea, and liver failure. This serious side effect has been seen more often in women taking the tablet in combination with other drugs. You should call or come to the clinic if you have unexplained changes in urination, weight loss, cramps, muscle pain, dizziness, tiredness, nausea, vomiting, or shortness of breath.

The use of antiretroviral drug combinations may lead to changes in body fat, some of which 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; and breast enlargement. If you have these symptoms, or any other symptoms that concern you, the study staff will check you and see if you should stop taking the tablet.

It is possible that the side effects from using the tablet may be different in women who are pregnant, or that the side effects may resemble normal symptoms of pregnancy. Studies with pregnant animals showed that FTC and TDF, the drugs in the tablet, did not cause any effects on the animals' fertility or their fetuses, although TDF led to changes in the menstrual cycles of rats. HIV-infected pregnant women and women who became pregnant while taking the tablet in clinical studies did not experience more side effects than non-pregnant women, and their infants did not have more birth defects than the general infant population. However, there is not enough information to know for sure.

A small number of people in this study may have these side effects or other side effects that we do not know about yet. But, we will screen your kidneys and overall health before you join the study and during the study. This will reduce your chances of having any side effects.

### ***Risks of HIV and Sexually Transmitted Infection (STI) Testing***

HIV and STI testing may make you feel anxious regardless of the test results. Finding out your HIV status may cause sadness, depression, and thoughts of suicide, and may also cause problems with your family, friends, or partner.

### ***Other Possible Risks***

You may feel embarrassed and/or worried when talking about sexual activities, your living situation, ways to protect against HIV and STIs, and your test results. You can choose not to answer questions at any time. Trained study counselors will help you with any feelings or questions.

It is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. If you have any problems, study counselors will talk with you and try to help you.

The ring and the tablet can protect you from getting HIV, but based on what we know, the level of protection may be different between the two products. This difference may have an effect on your and your infant's risk of getting HIV. Trained study counselors will help you with any feelings or questions.

## **BENEFITS**

You will be using one of two study products that may prevent you from getting HIV if you use it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may help us learn how to prevent pregnant women from getting HIV. You will receive medical exams, and you will receive counseling and testing for HIV and STIs. You will also have tests to check your overall health.

This study cannot give you antenatal care or delivery services, and cannot give you general medical care. Study staff will refer you to another medical provider for care, if needed. You will get free condoms, if you need them. You will be offered a family planning method after delivery, if you need it. If you have an STI diagnosed, you will receive medicine or a referral, if you need it.

## **NEW INFORMATION**

You will be told any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the study products may be causing bad side effects. We will tell you any new information about preventing HIV, regardless of the product, if we learn that it works during pregnancy. We will also tell you when study results may be available, and how to learn about them.

A description of this research study will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## **WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE ASKED TO LEAVE THE STUDY**

You may need to leave the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, IPM, Gilead Sciences, Inc., the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants.
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. The SMC reviews the progress of the study.
- The Interim Review Panel (IRP) recommends that the study be stopped early. The IRP reviews results after each group of participants finishes the study and decides if the next group should begin the study.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the study products if you:

- Acquire an HIV infection.

- Acquire a hepatitis B infection (Truvada users only).
- Use drugs for HIV prevention beyond what the study gives you.
- Use drugs to prevent infection after being exposed to HIV.
- Use injectable drugs for reasons other than treating disease.
- Go into labor.
- Experience the death or serious health issue with your unborn child.
- Have a bad reaction to study product, or a study doctor decides that using study product would be bad for you.
- Are unable or unwilling to follow the study rules.

If a study doctor asks you to stop using study product, we will ask that you and your infant come in for all remaining study visits to have some of the procedures we talked about earlier.

If you are removed from the study or choose to leave, we will ask you to return the study product and to come back for one final clinic visit. If you do not have the study product with you when you come to the clinic, staff members will make every effort to assist you in returning it as soon as possible. *[SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES.]* If you leave the study, we will ask you to check in with study staff until the end of your pregnancy and for one year after giving birth so we can follow your health and the health of your infant. If you choose to leave the study and later wish to rejoin, you may resume using study product (if applicable) and come in for all study visits remaining in your original visit schedule after consultation with the Protocol Safety Review Team.

#### **ALTERNATIVES TO BEING IN THE STUDY**

*[SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE: You may be able to join other studies here or in the community. There may be other places where you can go for HIV counseling and testing and family planning. We will tell you about those studies and those places if you wish.]*

#### **COSTS TO YOU**

*[SITE TO COMPLETE ACCORDING TO SITE CAPACITY]* There is no cost to you for study visits, study products, medical exams, laboratory tests or other procedures. We can give you treatments for STIs other than HIV free of charge while you are in the study, or we can refer you for available treatment.

#### **REIMBURSEMENT**

*[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT]:* You will receive *[SITES TO INSERT AMOUNT \$xx]* for your time, effort, and travel to and from the clinic for each study visit. You may receive *[SITES TO INSERT AMOUNT \$xx]* for any extra study visits. If you are chosen to take part in the longer interview(s) with staff, you will receive *[SITES TO INSERT AMOUNT \$xx]*.

#### **CONFIDENTIALITY**

We will make every effort to keep your and your infant's information private and confidential. But, we cannot guarantee it.

Study visits will take place in private. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you. We will only record your study ID number. If you are selected to do the

longer interview(s), you can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. *[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs: All original study documents that provide information about you for this study will be kept for at least two years after either the dapivirine vaginal ring is approved for use or the clinical research development program for the dapivirine vaginal ring is stopped.]*

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us you may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

The study staff may use your personal information to verify that you are not in any other research studies. *[SITES TO INSERT INFORMATION ABOUT SYSTEMS CURRENTLY IN PLACE TO ENSURE PARTICIPANTS ARE NOT PART OF OTHER CONFLICTING STUDIES, INCLUDING BIOMETRIC IDENTIFICATION SYSTEMS.]* This study will not use your name or identify you personally in any publication.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US OHRP, NIH and/or NIH contractors, and other US, local, and international regulatory entities
- *[SITES TO INSERT APPLICABLE LOCAL AUTHORITIES]*
- IPM, the organization that supplies the ring
- Gilead Sciences, Inc., the company that supplies the tablets
- Study monitors
- Site IRB/EC
- Study staff

The study staff will do everything they can to protect your privacy.

### **RESEARCH-RELATED INJURY**

It is unlikely that you or your infant will be injured by being in this study. The U.S. NIH does not have a mechanism to pay money or give other forms of financial compensation for research related injuries. You are not giving up any legal rights by signing this form. *[Sites to replace with their site-specific research-related injury institutional policy if they already provide clinical trials insurance:]* If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. The study sponsor will be responsible for ensuring that insurance is provided to cover appropriate medical expenses for treatment of any such illness or injury if required by law or regulation. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse.

- Any injury that happens because of negligence on your part.

#### **YOUR RIGHTS AS A RESEARCH PARTICIPANT**

*[SITES TO SPECIFY INSTITUTIONAL POLICY]:* Being in this study is completely voluntary. You may choose not to join this study or leave this study at any time. If you choose not to join or to leave the study, you can still join other studies and access non-study services you would normally get at this clinic. If you want the results of the study after it is over, let the study staff members know.

#### **PROBLEMS OR QUESTIONS**

If you ever have any questions about the study, or if you have a research-related injury, you should contact *[INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]* at *[INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS]*.

If you have questions about your rights as a research participant, you should contact *[INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]* at *[INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER]*.

*[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS IS REQUIRED]*

**CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION**

There may be a small amount of urine, blood, and vaginal fluids left over after we have done all of the study related testing. We would like to store your leftover body fluids for future work that could include testing for study products, testing for HIV risk and testing related to COVID-19 infection (if such testing is available and needed to better understand the impact of COVID-19 infection on the study data). If you agree, your samples and related health information will be stored safely and securely.

Only approved researchers will be able to use these samples and health information. Some employees will need to have access to these samples to store them and keep track of where they are, but these people will not have information that directly identifies you. The de-identified data and specimens could then be used for future research by our research team or other researchers without notifying you or asking your permission for this use.

There is no time limit on how long your samples will be stored. Your samples may be shipped and/or stored outside of the country. We do not yet know the specific type of testing that will be done with these samples. But, they may be used to check that certain laboratory tests perform correctly. Any other testing beyond that will have to be approved by an IRB/EC. We do not plan to do genetic testing or sequencing (for example, the mapping of all of your genes, which is also known as whole genome sequencing) of any kind. Your specimens will never be used for commercial profit.

You can still be in this study if you decide we cannot store your urine, blood, and vaginal fluids. You can change your mind about storing and using these samples for future tests at any time by writing to the person in charge of this study. We will then destroy the leftover samples. But, researchers will not be able to destroy samples or information from research that is already started.

PARTICIPANT INITIALS OR MARK	
_____	I DO agree to allow my biological specimens and health data to be stored and used in future research studies.
Initials/Mark                      Date	
_____	I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies.
Initials/Mark                      Date	

## CONSENT FOR OFF-SITE VISITS

*[Sites to modify as needed]*

Members of the research team at this clinic may be able to schedule off site visits with you at your home or at another location as part of the study. With your permission, some of the scheduled study visits and some of the study procedures may take place at your home or other location outside of the research clinic, if you are unable to come into the clinic. For example, if you need to receive a new ring or to have a urine or blood sample collected, study staff could come to you your home or meet you at another location, if you give your permission and if the study staff determine that it is appropriate. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in-place to maintain your information in a confidential manner. However, it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

In order to conduct visits outside of the clinic, we will need you to give us permission to do so. Please read carefully the following statement and initial/mark and date one option. Choosing not to have study visit procedures outside of the study clinic will not affect your participation in this study. Even if you agree today, you can withdraw your consent for off-site visits at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

### PARTICIPANT INITIALS OR MARK

\_\_\_\_\_  
Initials/Mark

\_\_\_\_\_  
Date

I DO agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary.

\_\_\_\_\_  
Initials/Mark

\_\_\_\_\_  
Date

I DO NOT agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary.

**SIGNATURE PAGE**

*[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC:]*

All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights or my infant's rights as research participants will be answered by *[INSERT LOCAL IRB/EC INFORMATION]*.

I voluntarily agree to be in this research study. A copy of this permission form will be given to me.

\_\_\_\_\_  
Participant's Name (Print)

\_\_\_\_\_  
Participant's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Study Staff's Name Conducting  
Consent Discussion (Print)

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (Signature)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness Name (Print)

\_\_\_\_\_  
Witness Signature

\_\_\_\_\_  
Date

**APPENDIX VII: Sample Informed Consent Form  
(Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER –  
COHORT 3**

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

**MTN-042**

**Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and  
Oral TRUVADA® Use in Pregnancy**

**Version 2.0**

**May 20, 2021**

**PRINCIPAL INVESTIGATOR:** *[Site to insert]*

**PHONE:** *[Site to insert]*

**Short Title for the Study:** DELIVER: A Phase 3b Safety Study of the Dapivirine Ring and PrEP in Pregnant Women

**INFORMED CONSENT**

You are being invited to join a research study funded by the US government [US National Institutes of Health (NIH)] and conducted by the Microbicide Trials Network (MTN). There is a separate consent document for your baby. There are two products being used in this study: a ring inserted in the vagina and a tablet taken by mouth. The ring is supplied by International Partnership for Microbicides (IPM) and the tablet is supplied by Gilead Sciences, Inc. The person in charge of this study at this site is *[INSERT NAME OF PRINCIPAL INVESTIGATOR]*.

**STUDY SUMMARY**

Important things you should know:

- The study products in this research study each contain a different anti-HIV medication:
  - The vaginal ring (VR) contains 25 mg of dapivirine (DPV). It is inserted in the vagina and worn continuously for approximately one month, to be replaced every month. We will refer to it in this document as the ring.
  - The oral tablet, Truvada, contains two drugs- 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF). It is taken once a day by mouth. We will refer to it in this document as the tablet.
- The purpose of this study is to find out if using the ring or the tablet during pregnancy is safe and well-tolerated by women and their babies.
- If you qualify and choose to participate, you will be randomly assigned to use one of the two study products for the remainder of your pregnancy (you will not use study product after the end of your pregnancy)
- You will be asked to complete up to twenty (20) study visits (not including unscheduled visits), including the visit today and including up to six (6) phone contacts. Study visits will take place either at this study clinic, at the hospital where you intend to deliver your baby, or at other locations with your permission. You must intend to deliver at a hospital or similar health facility to be eligible for this study, such as *[SITES TO INSERT NAMES OF LOCATIONS AFFILIATED WITH THE SITE]*. The maximum length of your participation in

this study will be about 36 weeks. This includes the time remaining in your pregnancy and six additional weeks of follow-up for you. You will only take the study product while you are pregnant.

- At some of the clinic visits, you will be asked to complete the following: a physical exam (including abdominal exam and ultrasound), blood draw, urine and vaginal fluid collection, several short interviews (and possibly a longer interview at one or more visits, if you are selected), and you will be asked permission to access your medical records and contact your health care provider.
- Some common risks or discomforts from the ring include: vaginal irritation, discharge, and/or discomfort. One serious but rare side effect is toxic shock syndrome caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacteria.
- Some common risks or discomforts from the tablet include: nausea, abdominal pain, diarrhea, vomiting, passing gas, headache, dizziness, tiredness, and inability to sleep. More serious but rare side effects include: rash, liver problems, kidney problems, allergic reaction, and lactic acidosis.
- You will be using a study product that may prevent you from getting HIV if you use it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may also help in the development of ways to prevent the spread of HIV in the future. You will receive testing for HIV and other sexually transmitted infections (STI), medical examinations, HIV and contraceptive counseling, and routine laboratory testing to check your overall health.
- Taking part in this research study is voluntary. You do not have to participate and you can stop at any time.
- If you decide not to join this study, there are currently available methods to prevent sexually transmitted HIV: condom use during sex and/or the use of daily oral Truvada for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Study staff can provide you with additional information about PrEP and PEP if you are interested.

Please take time to read this entire form and ask questions before deciding to join this study. If you are willing to take part in the study, you will sign your name on this form. A copy of this form will be offered to you. Signing this consent form does not mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible. It is important to know that your and your infant's participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

## **STUDY DETAILS**

### ***Study Products***

The ring was tested and found to be well-tolerated for use by adolescent (15-17 years old) and adult (18 years and older) women. DPV works by stopping HIV from making copies of itself. It was found to reduce HIV infection in women when used consistently. Researchers believe that younger women were not protected from getting HIV because they did not use the ring consistently. The ring received a positive opinion from the European Medicines Agency to reduce the risk of HIV infection in adult women and is now recommended by the World Health Organization as an HIV prevention option. It remains under review by the US Food and Drug Administration (FDA) and has yet to be approved for HIV prevention in any country.

The tablet, called Truvada, is an HIV prevention method approved for adults called oral pre-exposure prophylaxis (PrEP). The tablet works by stopping HIV from making copies of itself and

reduces risk of HIV infection when used consistently. The tablet is also approved to treat HIV infection in people older than 12 years when combined with other drugs.

Neither study product is effective against common sexually transmitted diseases other than HIV. Neither study product can guarantee protection from HIV.

***Who will be in this research study?***

Five hundred fifty (550) healthy, pregnant women who are 18 to 40 years old will be enrolled in the study across various sites in Malawi, South Africa, Uganda and Zimbabwe. Of these, 250 women who are between 12 and 30 weeks in their pregnancy will be enrolled at this time.

***What will I be asked to do if I join this research study?***

For the remainder of your pregnancy, you will either insert a ring and leave it in place for a month, replacing it every month, or take an oral tablet every day. Which of the two products you will use will be decided by chance [*SITES TO INSERT PREFERRED DESCRIPTION OF 'RANDOMIZATION'*] – for every 4 women who will receive the ring, there will be 1 woman who will receive the tablet. Neither you nor the study staff can decide which of the two products you will use.

You will come to the clinic every two weeks for the first month you are in the study, then every four weeks until you are about 36 weeks pregnant, and then every two weeks for the remainder of your pregnancy. You will also have a phone contact with study staff one and three weeks from today, and after you are 35 weeks pregnant, every two weeks until delivery, and then one call up to two weeks after delivery. You will allow study staff to access your medical records, and to conduct a study visit as soon as possible after you deliver your baby, no later than two weeks after you deliver. This visit may occur at the study clinic, at the hospital where you deliver, or other location (with your permission). Your final visit will occur 6 weeks after you deliver, for a total maximum of twenty (20) study visits including the visit today and the phone contacts (but not including any unscheduled visits). You will be in the study for up to 36 weeks. Your baby will also have study visits, which are outlined in a separate consent form. Each visit will take about [*SITES TO INSERT THE APPROXIMATE LENGTH OF TIME*]. During your visit after delivery and the 6 week visit, your baby will also have study procedures completed.

***Do I have to be in this study?***

You do *not* have to be in this study. You can still get the care you need even if you do not join the study. If you join today but change your mind later, you can inform the study staff that you no longer wish to participate. If you do not join the study, your baby cannot join the study.

***What procedures will be done for this study?***

Your first visit will happen today after you read, discuss, understand and sign/mark this form. The procedures done at this visit will let us know if you can join this study, and will take about [*SITES TO INSERT THE APPROXIMATE LENGTH OF TIME*].

If it seems like you can join, you will be asked to come back for an Enrollment visit no later than 35 days from today. During the Enrollment Visit, you will begin using the ring or begin taking the tablet, depending on which study group you have been assigned to.

The following things will happen during your study visits:

- We will ask questions about your health, any medications you may be taking, and any vaginal products you may be using. We will ask questions about your thoughts and feelings and your mood. We will also ask questions about your living situation to see if it affects your

use of the study products, and about your reasons for wanting to join this study and how worried you are about getting HIV.

- We will ask your permission to access your medical records, including your delivery records to gather information about your baby at the time of birth. We will also ask your permission to contact your care provider, and to conduct a study visit as soon as possible after you have your baby.
- We will talk with you about what you need to do to be in the study, how to use the study products, and how to protect yourself from getting an infection, including HIV. We may audio-record these conversations to assess how our study staff counsel you and work with them to improve the quality of the counseling you receive, and to learn about experiences and concerns participants may have. The recordings will be kept confidential. If you do not want to have your counseling session recorded, let study staff know.
  - **It is important that you know if you do not intend to deliver your baby at a hospital or similar health facility [SITES TO INSERT NAMES OF LOCATIONS AFFILIATED WITH THE SITE], you will not be eligible to participate in this study.**
- After the birth of your infant, we will also talk with you about how to keep from getting pregnant.
- We will schedule you for an ultrasound if you have not had one or do not have your ultrasound results with you today.
  - **It is important that you know if you do not have an ultrasound, you will not be eligible to participate in this study.**
- At each study visit, we will draw up to 30 mL (about 2 tablespoons) of blood per visit [*Sites to insert local amount*] to make sure you are healthy and to test you for HIV and other STIs. We will also test your blood to see if you are using the study products. More blood may be collected if you become ill.
- At some visits, we will collect a urine sample to test you for STIs.
- At some visits, we will give you a physical exam to make sure you are healthy.
- At all visits before the birth of your infant, we will give you an abdominal exam to make sure your pregnancy is going well.
- At the Enrollment Visit, we will give you a pelvic exam to check for infections and to make sure you are healthy. We may give you a pelvic exam at other visits, if needed. The study doctor or nurse will use a speculum to do the pelvic exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine your vagina and cervix and take some fluids.
- At some visits, we will take fluids from your vagina using a swab (e.g., Q-Tip or earbud). Vaginal fluids will be collected to look for any changes that may occur during your participation in the study and to test for STIs.
- At some visits, you will answer questions about using the study products and other behaviors, including sexual activity. Some of the questions may be sensitive. If you ever feel uncomfortable, you can choose not to answer questions at any time. You will also answer questions about what you liked and did not like about this study and about the study products. Your answers will be kept confidential and no one other than the study team will have access to your responses.
- We may also ask you to do one or more longer interviews with study staff. You may choose not to do these interviews. During the interview(s), we may ask you to discuss your use of the study products, your feelings about the study products and about being in the study, and other questions that can help researchers to better understand participants' experiences while in the study. We may audio-record the interview(s). We will keep the audio recording and related materials confidential and no one other than the study team will have access to

your responses.

- For every month you are in the study until the end of your pregnancy, we will give you either another ring to use, or another month of tablets to take.
- We will give you the results of any blood or urine tests when available.
- We will give you treatment for sexually transmitted and other kinds of infections, if you need them.
- In the event a problem with a pregnancy is suspected, an ultrasound can be ordered at the site or a referral will be provided.
- We will give you referrals for other services, if you need them.
- These visits will take about [*SITES TO INSERT AVERAGE VISIT DURATION*] to complete.

If you enroll in the study, only for 24 hours prior to your clinic visits you will be asked to abstain from sex, tampon use and other non-study products.

<i>Activity:</i>	<i>Not Permitted For How Long?</i>
Receptive sexual practices, including: <ul style="list-style-type: none"> <li>• Penile-vaginal intercourse</li> <li>• Penile-anal intercourse</li> <li>• Receptive oral intercourse</li> <li>• Finger stimulation</li> </ul>	For 24 hours before each clinic visit
Tampon use	For 24 hours before each clinic visit
Inserting any non-study objects into your vagina, including: <ul style="list-style-type: none"> <li>• Pessaries</li> <li>• Sex toys</li> <li>• Female condoms</li> <li>• Diaphragms</li> <li>• Menstrual cups</li> <li>• Cervical caps or any other vaginal barrier method</li> </ul>	For 24 hours before each clinic visit

Using vaginal products like spermicides, lubricants, contraceptive vaginal rings, douches, vaginal medications, etc., is not allowed at any time during this study.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

You may be asked to make additional visits so we can do more laboratory tests or have study procedures repeated. We will do this if there are abnormal test results or a mistake during the collection or the processing of your samples. We will also do this if you experience any changes in your physical condition, including symptoms of infection (urinary or sexually transmitted).

***What if I become infected with HIV?***

Being in this study will not cause HIV infection for you or your infant. But, there is always a chance that you can get HIV through condomless sex or other activities. If you become HIV-positive, you will stop using the study product. But, we will ask you to continue to come for your study visits and to complete some of the study procedures for a minimum of twelve months. This study does not provide medication for treatment of HIV. If you become infected with HIV, the study staff will refer you for medical care and other available services to prevent your infant from getting HIV. If you get HIV, it is possible that the virus is resistant to some drugs. This means that some drugs may not work well to treat your HIV. This is also possible if your infant becomes infected. We will do a blood test to find out if you have drug resistance. These results can help us know which drugs would be best to treat your HIV.

Depending on local and national health requirements, the study staff may need to report certain diseases, including HIV. The reportable diseases at this site are *[SITES TO INSERT]*. We must inform the following *[SITES TO INSERT MORE DETAILED INFORMATION REGARDING WHO WILL BE INFORMED OF THE REPORTABLE DISEASES]*. *[SITES TO INCLUDE/AMEND THE FOLLOWING]*: Outreach workers from the *[LOCAL HEALTH AUTHORITY]* may then contact you about informing your partner/s, since they also should be tested. If you do not want to inform your partner/s yourself, the outreach workers will contact them, according to the confidentiality guidelines of the *[LOCAL HEALTH AUTHORITY]*.

## **RISKS AND/OR DISCOMFORTS**

### ***Risks of Blood Draws***

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise, swelling, or small clot where the needle is inserted. Rarely, drawing blood can cause an infection where the needle goes into your hand or arm.

### ***Risks of Pelvic Exams***

You may feel discomfort or pressure during the pelvic exam. You may have a small amount of vaginal bleeding or spotting which should stop shortly after the exam.

### ***Risks of the DPV VR***

We do not yet know all the side effects of the ring. Most people who have used the ring did not have any side effects. Some women who used the ring in other studies have had: discharge from the vagina; pelvic pain; burning or itchiness in the vagina; and urinary tract infections. Less common side effects included: irritation, bruising, swelling, inflammation, wearing, and discharge from the cervix; bladder pain and inflammation; vaginal odor, itching, inflammation, tearing, and discomfort; pelvic discomfort; abdominal pain and discomfort; and problems urinating.

Although rare, the ring may cause an allergic reaction. Signs of an allergic reaction include, but are not limited to: rash or other skin irritation, itching, joint pain, or difficulty in breathing.

There is the possibility of getting toxic shock syndrome, although this is very rare. Toxic shock syndrome is a serious but rare infection caused by bacteria. Any product placed inside the vagina can cause it. Getting toxic shock syndrome from using the ring is unlikely. But, it is important that you tell the study staff as soon as possible if you have any of the following symptoms: sudden high fever, a faint feeling, diarrhea, headache, rash, and muscle aches.

It is possible that the side effects from ring use may be different in women who are pregnant, or that the side effects may resemble normal symptoms of pregnancy. Studies with pregnant animals showed that DPV did not cause side effects to the animals or their fetuses. Women who became pregnant while using the ring in clinical studies did not experience more side effects than non-pregnant women, and neither did their infants. However, there is not enough information to know for sure. One small study found that DPV can be detected in breastmilk from women who used the ring while lactating, but it is unknown whether the small amounts of drug detected could produce side effects in babies.

### ***Risks of the Truvada tablet***

Most people who take the tablet do not have any side effects. The side effects that some people taking the tablet may have are well known because the drugs have been used by many people.

People with hepatitis B who suddenly stop taking the tablet may get a flare-up or worsening of their hepatitis symptoms.

One in ten people who take the tablet may have mild side effects that usually go away after stopping the drug. These occasional side effects include: mild kidney problems that are only detected by laboratory tests, inability to sleep, lack of energy or tiredness, headache, upset stomach, passing gas, vomiting, soft or liquid stools, and dizziness. Upset stomach, passing gas, vomiting and soft or liquid stools typically go away after the first or second month of use.

Other side effects are more serious, but less than one in a hundred people who take the tablet may have them. These rare side effects include: rash, liver problems, serious kidney damage, and allergic reaction. People taking the tablet may also have bone pain and/or small changes in the thickness of their bones, but these changes have not caused problems for the people who had them.

In rare cases, some people with HIV who take the tablet in combination with other drugs may get lactic acidosis. This is a serious side effect of some drugs used to treat HIV that can cause shortness of breath, nausea, and liver failure. This serious side effect has been seen more often in women taking the tablet in combination with other drugs. You should call or come to the clinic if you have unexplained changes in urination, weight loss, cramps, muscle pain, dizziness, tiredness, nausea, vomiting, or shortness of breath.

The use of antiretroviral drug combinations may lead to changes in body fat, some of which 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; and breast enlargement. If you have these symptoms, or any other symptoms that concern you, the study staff will check you and see if you should stop taking the tablet.

It is possible that the side effects from using the tablet may be different in women who are pregnant, or that the side effects may resemble normal symptoms of pregnancy. Studies with pregnant animals showed that FTC and TDF, the drugs in the tablet, did not cause any effects on the animals' fertility or their fetuses, although TDF led to changes in the menstrual cycles of rats. HIV-infected pregnant women and women who became pregnant while taking the tablet in clinical studies did not experience more side effects than non-pregnant women, and their infants did not have more birth defects than the general infant population. However, there is not enough information to know for sure.

A small number of people in this study may have these side effects or other side effects that we do not know about yet. But, we will screen your kidneys and overall health before you join the study and during the study. This will reduce your chances of having any side effects.

### ***Risks of HIV and Sexually Transmitted Infection (STI) Testing***

HIV and STI testing may make you feel anxious regardless of the test results. Finding out your HIV status may cause sadness, depression, and thoughts of suicide, and may also cause problems with your family, friends, or partner.

### ***Other Possible Risks***

You may feel embarrassed and/or worried when talking about sexual activities, your living situation, ways to protect against HIV and STIs, and your test results. You can choose not to answer questions at any time. Trained study counselors will help you with any feelings or questions.

It is possible that others may learn of your participation in this study, and because of this, may treat you unfairly or discriminate against you. If you have any problems, study counselors will talk with you and try to help you.

The ring and the tablet can protect you from getting HIV, but based on what we know, the level of protection may be different between the two products. This difference may have an effect on your and your infant's risk of getting HIV. Trained study counselors will help you with any feelings or questions.

## **BENEFITS**

You will be using one of two study products that may prevent you from getting HIV if you use it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may help us learn how to prevent pregnant women from getting HIV. You will receive medical exams, and you will receive counseling and testing for HIV and STIs. You will also have tests to check your overall health.

This study cannot give you antenatal care or delivery services, and cannot give you general medical care. Study staff will refer you to another medical provider for care, if needed. You will get free condoms, if you need them. You will be offered a family planning method after delivery, if you need it. If you have an STI diagnosed, you will receive medicine or a referral, if you need it.

## **NEW INFORMATION**

You will be told any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the study products may be causing bad side effects. We will tell you any new information about preventing HIV, regardless of the product, if we learn that it works during pregnancy. We will also tell you when study results may be available, and how to learn about them.

A description of this research study will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

## **WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE ASKED TO LEAVE THE STUDY**

You may need to leave the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, IPM, Gilead Sciences, Inc., the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants.
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. The SMC reviews the progress of the study.
- The Interim Review Panel (IRP) recommends that the study be stopped early. The IRP reviews results after each group of participants finishes the study and decides if the next group should begin the study.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

The study doctor will ask you to stop using the study products if you:

- Acquire an HIV infection.
- Acquire a hepatitis B infection (Truvada users only).
- Use drugs for HIV prevention beyond what the study gives you.
- Use drugs to prevent infection after being exposed to HIV.
- Use injectable drugs for reasons other than treating disease.
- Go into labor.
- Experience the death or serious health issue with your unborn child.
- Have a bad reaction to study product, or a study doctor decides that using study product would be bad for you.
- Are unable or unwilling to follow the study rules.

If a study doctor asks you to stop using study product, we will ask that you and your infant come in for all remaining study visits to have some of the procedures we talked about earlier.

If you are removed from the study or choose to leave, we will ask you to return the study product and to come back for one final clinic visit. If you do not have the study product with you when you come to the clinic, staff members will make every effort to assist you in returning it as soon as possible. *[SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES.]* If you leave the study, we will ask you to check in with study staff until the end of your pregnancy and for one year after giving birth so we can follow your health and the health of your infant. If you choose to leave the study and later wish to rejoin, you may resume using study product (if applicable) and come in for all study visits remaining in your original visit schedule after consultation with the Protocol Safety Review Team.

#### **ALTERNATIVES TO BEING IN THE STUDY**

*[SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE: You may be able to join other studies here or in the community. There may be other places where you can go for HIV counseling and testing and family planning. We will tell you about those studies and those places if you wish.]*

#### **COSTS TO YOU**

*[SITE TO COMPLETE ACCORDING TO SITE CAPACITY]* There is no cost to you for study visits, study products, medical exams, laboratory tests or other procedures. We can give you treatments for STIs other than HIV free of charge while you are in the study, or we can refer you for available treatment.

#### **REIMBURSEMENT**

*[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT]:* You will receive *[SITES TO INSERT AMOUNT \$xx]* for your time, effort, and travel to and from the clinic for each study visit. You may receive *[SITES TO INSERT AMOUNT \$xx]* for any extra study visits. If you are chosen to take part in the longer interview(s) with staff, you will receive *[SITES TO INSERT AMOUNT \$xx]*.

#### **CONFIDENTIALITY**

We will make every effort to keep your and your infant's information private and confidential. But, we cannot guarantee it.

Study visits will take place in private. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only

enter your information into computers protected by passwords and will not include information that could identify you. We will only record your study ID number. If you are selected to do the longer interview(s), you can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. *[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs: All original study documents that provide information about you for this study will be kept for at least two years after either the dapivirine vaginal ring is approved for use or the clinical research development program for the dapivirine vaginal ring is stopped.]*

Your personal information may be disclosed if required by law. For example, if we learn something that would immediately put you or others in danger, the study staff must take steps to keep you and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us you may be in danger. For example, if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you.

The study staff may use your personal information to verify that you are not in any other research studies. *[SITES TO INSERT INFORMATION ABOUT SYSTEMS CURRENTLY IN PLACE TO ENSURE PARTICIPANTS ARE NOT PART OF OTHER CONFLICTING STUDIES, INCLUDING BIOMETRIC IDENTIFICATION SYSTEMS.]* This study will not use your name or identify you personally in any publication.

Your records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US OHRP, NIH and/or NIH contractors, and other US, local, and international regulatory entities
- *[SITES TO INSERT APPLICABLE LOCAL AUTHORITIES]*
- IPM, the organization that supplies the ring
  - Gilead Sciences, Inc., the company that supplies the tablets
- Study monitors
- Site IRB/EC
- Study staff

The study staff will do everything they can to protect your privacy.

### **RESEARCH-RELATED INJURY**

It is unlikely that you or your infant will be injured by being in this study. The U.S. NIH does not have a mechanism to pay money or give other forms of financial compensation for research related injuries. You are not giving up any legal rights by signing this form. *[Sites to replace with their site-specific research-related injury institutional policy if they already provide clinical trials insurance:]* If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. The study sponsor will be responsible for ensuring that insurance is provided to cover appropriate medical expenses for treatment of any such illness or injury if required by law or regulation. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because you used other medicine during the study that you did not tell us about.

- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.

### **YOUR RIGHTS AS A RESEARCH PARTICIPANT**

*[SITES TO SPECIFY INSTITUTIONAL POLICY]:* Being in this study is completely voluntary. You may choose not to join this study or leave this study at any time. If you choose not to join or to leave the study, you can still join other studies and access non-study services you would normally get at this clinic. If you want the results of the study after it is over, let the study staff members know.

### **PROBLEMS OR QUESTIONS**

If you ever have any questions about the study, or if you have a research-related injury, you should contact *[INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]* at *[INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS]*.

If you have questions about your rights as a research participant, you should contact *[INSERT NAME OR TITLE OF PERSON ON THE IRB/EC OR OTHER ORGANIZATION APPROPRIATE FOR THE SITE]* at *[INSERT PHYSICAL ADDRESS AND TELEPHONE NUMBER]*.

*[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS IS REQUIRED]*

**CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION**

There may be a small amount of urine, blood and vaginal fluids left over after we have done all of the study related testing. We would like to store your leftover body fluids for future work that could include testing for study products, testing for HIV risk and testing related to COVID-19 infection (if such testing is available and needed to better understand the impact of COVID-19 infection on the study data). If you agree, your samples and related health information will be stored safely and securely.

Only approved researchers will be able to use these samples and health information. Some employees will need to have access to these samples to store them and keep track of where they are, but these people will not have information that directly identifies you. The de-identified data and specimens could then be used for future research by our research team or other researchers without notifying you or asking your permission for this use.

There is no time limit on how long your samples will be stored. Your samples may be shipped and/or stored outside of the country. We do not yet know the specific type of testing that will be done with these samples. But, they may be used to check that certain laboratory tests perform correctly. Any other testing beyond that will have to be approved by an IRB/EC. We do not plan to do genetic testing or sequencing (for example, the mapping of all of your genes, which is also known as whole genome sequencing) of any kind. Your specimens will never be used for commercial profit.

You can still be in this study if you decide we cannot store your urine, blood, and vaginal fluids. You can change your mind about storing and using these samples for future tests at any time by writing to the person in charge of this study. We will then destroy the leftover samples. But, researchers will not be able to destroy samples or information from research that is already started.

PARTICIPANT INITIALS OR MARK	
_____	I DO agree to allow my biological specimens and health data to be stored and used in future research studies.
Initials/Mark                      Date	
_____	I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies.
Initials/Mark                      Date	

## CONSENT FOR OFF-SITE VISITS

*[Sites to modify as needed]*

Members of the research team at this clinic may be able to schedule off site visits with you at your home or at another location as part of the study. With your permission, some of the scheduled study visits and some of the study procedures may take place at your home or other location outside of the research clinic, if you are unable to come into the clinic. For example, if you need to receive a new ring or to have a urine or blood sample collected, study staff could come to you your home or meet you at another location, if you give your permission and if the study staff determine that it is appropriate. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in-place to maintain your information in a confidential manner. However, it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

In order to conduct visits outside of the clinic, we will need you to give us permission to do so. Please read carefully the following statement and initial/mark and date one option. Choosing not to have study visit procedures outside of the study clinic will not affect your participation in this study. Even if you agree today, you can withdraw your consent for off-site visits at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

### PARTICIPANT INITIALS OR MARK

\_\_\_\_\_  
Initials/Mark

\_\_\_\_\_  
Date

I DO agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary.

\_\_\_\_\_  
Initials/Mark

\_\_\_\_\_  
Date

I DO NOT agree to have study visit procedures at a location other than the study clinic by clinic staff, when necessary.

**SIGNATURE PAGE**

*[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC:]*

All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights or my infant's rights as research participants will be answered by *[INSERT LOCAL IRB/EC INFORMATION]*.

I voluntarily agree to be in this research study. A copy of this permission form will be given to me.

\_\_\_\_\_  
Participant's Name (Print)

\_\_\_\_\_  
Participant's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Study Staff's Name Conducting  
Consent Discussion (Print)

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (Signature)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness Name (Print)

\_\_\_\_\_  
Witness Signature

\_\_\_\_\_  
Date

**APPENDIX VIII: Sample Informed Consent Form  
(Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography) –  
INFANT**

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

**MTN-042**

**Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and  
Oral TRUVADA® Use in Pregnancy**

**Version 2.0**

**May 20, 2021**

**PRINCIPAL INVESTIGATOR:** *[Site to insert]*

**PHONE:** *[Site to insert]*

**Short Title for the Study:** DELIVER: A Phase 3b Safety Study of the Dapivirine Ring and PrEP in Pregnant Women

**INFORMED CONSENT**

You are being invited to allow your baby to join a research study funded by the US government [US National Institutes of Health (NIH)] and conducted by the Microbicide Trials Network (MTN). Your baby can join the study if you consent to your own participation in this study in the separate consent document, in which you will use one of two products: a ring inserted in the vagina and a tablet taken by mouth. The ring is supplied by International Partnership for Microbicides (IPM) and the tablet is supplied by Gilead Sciences, Inc. The person in charge of this study at this site is *[INSERT NAME OF PRINCIPAL INVESTIGATOR]*.

**STUDY SUMMARY**

Important things you should know for your baby's participation in the study:

- The study products to be used by the mother in this research study each contain a different anti-HIV medication:
  - The vaginal ring (VR) contains 25 mg of dapivirine (DPV). It is inserted in the vagina and worn continuously for approximately one month, to be replaced every month. We will refer to it in this document as the ring.
  - The oral tablet, Truvada, contains two drugs - 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF). It is taken once a day by mouth. We will refer to it in this document as the tablet.
- The purpose of this study is to find out if using the ring or the tablet during pregnancy is safe and well-tolerated by women and their babies.
- You will be asked to allow your baby to complete up to four (4) study visits (not including unscheduled visits), and one (1) phone contact. Study visits will take place either at this study clinic, at the hospital where you intend to deliver your baby, or at other locations with your permission. The approximate length of your baby's participation in this study will be about 12 months.
- Most procedures done in this study are routine medical procedures, with little risk to your baby.

- After the birth of your baby, your baby will receive: a physical exam, blood draws, testing for HIV if needed, and routine laboratory testing to check his/her overall health.
- Some common risks or discomforts from the blood collection may include pain, swelling, bruising, or bleeding where the needle is inserted. Rarely, drawing blood can cause infection where the needle enters the skin.
- Taking part in this research study is voluntary. Your baby does not have to participate, and you can stop his/her participation at any time.
- If you decide not to allow your baby to join this study, there are currently available methods you can use to prevent acquiring HIV and passing it on to your baby: condom use during sex and/or the use of daily oral Truvada for pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Study staff can provide you with additional information about PrEP and PEP if you are interested.

Please take time to read this entire form and ask questions before deciding to allow your baby to join this study. If you decide to allow your baby to take part in the study, you will sign your name on this form. A copy of this form will be offered to you. It is important to know that your and your baby's participation in this research study is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

## **STUDY DETAILS**

### ***Study Products***

Your baby will not use these study products but may be exposed to the study drugs from your use of them. One of the study products you may use is the dapivirine ring, which was found to reduce HIV infection in women ages 22-45 when used consistently. The ring received a positive opinion from the European Medicines Agency to reduce the risk of HIV infection in adult women and is now recommended by the World Health Organization as an HIV prevention option. It remains under review by the US Food and Drug Administration (FDA) and has yet to be approved for HIV prevention in any country.

The other study product you may use is the tablet, called Truvada - an HIV prevention method approved for adults called oral pre-exposure prophylaxis (PrEP). The tablet works by stopping HIV from making copies of itself and reduces risk of HIV infection when used consistently. The tablet is also approved to treat HIV infection in people older than 12 years when combined with other drugs.

Neither study product can guarantee protection from HIV.

### ***Who will be in this research study?***

Five hundred fifty (550) healthy, pregnant women who are 18 to 40 years old and their babies will be enrolled in the study across various sites in Malawi, South Africa, Uganda and Zimbabwe.

### ***What will I be asked to do if my baby joins this research study?***

You will have a study visit with your baby as soon as possible after delivery, then have additional study visits six weeks, six months and twelve months after delivery, for a total maximum of four (4) study visits and one (1) phone contact that will occur within two weeks of delivery (but not including any unscheduled visits). Your baby will be in the study for approximately 12 months. Each visit will take about [SITES TO INSERT THE APPROXIMATE

*LENGTH OF TIME*]. During your baby's first visit after delivery and the 6 week visit, you will also be asked to complete study procedures.

***Does my baby have to be in this study?***

Your baby does *not* have to be in this study. You can still get the care you need for your baby even if your baby does not join the study. If your baby joins the study but you change your mind later about his/her participation, you can inform the study staff that you no longer wish for your baby to participate. Your baby cannot join the study if you are not in the study. If you decide you do not want your baby to be in the study, you cannot join the study.

***What procedures will be done for this study?***

The following things will happen for your baby when you bring him/her for study visits:

- We will ask questions about your baby's health and any medications he or she may be taking.
- We will give your baby a physical exam to make sure he or she is healthy.
- At some visits, we will draw up to 8 mL of blood (about half a tablespoon) per visit [*Sites to insert local amount*] from your baby to make sure he or she is healthy. We will also test your baby's blood to see if there is study drug in his or her system. More blood may be collected if your baby becomes ill; HIV testing may be done if needed.
- If it looks like something might be wrong with your baby, the study doctor might take pictures of your baby and share the pictures with experts who may be able to see what the problem might be. If you agree to have pictures taken of your baby, you will be asked to mark your permission at the end of this consent. We can give you a copy of any of the photographs. If you do not wish to have photographs taken of your baby, you will be able to mark at the end of this consent that no photographs may be taken of your baby.
- These visits will take about [*SITES TO INSERT AVERAGE VISIT DURATION*] to complete.

It is important for you to come to every study visit. If you cannot come to the visit, please tell the study staff as soon as possible so that the visit can be rescheduled.

You may be asked to bring your baby for additional visits so we can do more laboratory tests or have study procedures repeated. We will do this if there are abnormal test results or a mistake during the collection or the processing of your samples. We will also do this if your baby experiences any changes in his or her physical condition.

***What if I become infected with HIV and my baby becomes infected?***

Being in this study will not cause HIV infection for you or your baby. But, there is always a chance that you can get HIV through condomless sex or other activities and if you become infected, your baby could be exposed to HIV. If you become HIV positive, there is a possibility that your baby could become HIV-infected - we will refer you to medical care to prevent HIV transmission between you and your baby.

If you become HIV-positive and agree to the procedures, your baby will be tested for HIV as soon as possible after delivery. If your baby becomes HIV-positive and you agree to the procedures, your baby will have additional tests during their regularly scheduled study visits.

Depending on local and national health requirements, the study staff may need to report certain diseases, including HIV. The reportable diseases at this site are [*SITES TO INSERT*]. We must inform the following [*SITES TO INSERT MORE DETAILED INFORMATION REGARDING WHO WILL BE INFORMED OF THE REPORTABLE DISEASES*]. [*SITES TO INCLUDE/AMEND THE FOLLOWING*]: Outreach workers from the [*LOCAL HEALTH AUTHORITY*] may then contact

you about informing your partner/s, since they also should be tested. If you do not want to inform your partner/s yourself, the outreach workers will contact them, according to the confidentiality guidelines of the [LOCAL HEALTH AUTHORITY].

## **RISKS AND/OR DISCOMFORTS**

### ***Risks of Blood Draws***

Your baby may feel discomfort or pain when your blood is drawn. Your baby may have a bruise, swelling, or small clot where the needle is inserted. Rarely, drawing blood can cause infection where the needle enters the skin.

### ***Risks of the DPV VR***

Studies with pregnant animals showed that DPV did not cause side effects to the animals' fetuses. Babies of women who became pregnant while using the DPV ring in clinical studies did not seem to experience more side effects than babies of women who used a ring without medication in it, but there's not enough information to know for sure. One small study found that DPV can be detected in breastmilk from women who used the ring while lactating, but it is unknown whether the small amounts detected could produce side effects in babies. We anticipate very little exposure of the study drug DPV to your baby.

### ***Risks of the Truvada tablet***

Studies with pregnant animals showed that FTC and TDF, the drugs in the tablet, did not cause any effects on the animals' fetuses. Babies of HIV-infected pregnant women and women who became pregnant while taking the tablet in clinical studies did not have more birth defects than the general infant population. However, there is not enough information to know for sure.

### ***Other Possible Risks***

It is possible that others may learn of your baby's participation in this study, and because of this, may treat you and your baby unfairly or discriminate against you and your baby. If you have any problems, study counselors will talk with you and try to help you.

The ring and the tablet can protect you and therefore your baby from getting HIV, but based on what we know, the level of protection may be different between the two products. Trained study counselors will help you with any feelings or questions.

## **BENEFITS**

You will be using one of two study products that may prevent you, and therefore your baby, from getting HIV if you use it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may help us learn how to prevent pregnant women from getting HIV and passing it on to their babies. Your baby will receive medical exams. Your baby will also have tests to check his/her overall health.

As appropriate, study staff will refer you to other medical providers for care.

## **NEW INFORMATION**

You will be told any new information learned during this study that may affect your willingness for you and your baby to stay in the study. For example, we will let you know if we learn that the study products may be causing bad side effects. We will tell you any new information about preventing HIV, regardless of the product, if we learn that it works during pregnancy. We will also tell you when study results may be available, and how to learn about them.

A description of this research study will be available on <http://www.ClinicalTrials.gov>, as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

### **WHY YOUR BABY MAY BE ASKED TO LEAVE THE STUDY**

Your baby may need to leave the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, IPM, Gilead Sciences, Inc., the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants.
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. The SMC reviews the progress of the study.
- The Interim Review Panel (IRP) recommends that the study be stopped early. The IRP reviews results after each group of participants finishes the study and decides if the next group should begin the study.
- You leave the study.
- You are not able to keep appointments.
- Other reasons that may prevent your baby from completing the study successfully.

If your baby is asked to leave the study or you choose to stop his/her participation, we will ask you to come back for one final clinic visit. *[SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES.]*

### **ALTERNATIVES TO BEING IN THE STUDY**

*[SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE: Your baby may be able to join other studies here or in the community. We will tell you about those studies if you wish.]*

### **COSTS TO YOU**

*[SITE TO COMPLETE ACCORDING TO SITE CAPACITY]* There is no cost to you for your baby's study visits, medical exams, laboratory tests or other procedures. We can refer your baby for available treatment if needed.

### **REIMBURSEMENT**

*[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT]:* You will receive *[SITES TO INSERT AMOUNT \$xx]* for you and your baby's time, effort, and travel to and from the clinic for each study visit.

### **CONFIDENTIALITY**

We will make every effort to keep your and your baby's information private and confidential. We cannot guarantee it.

Study visits will take place in private. We will keep the information about your baby's study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your baby's information into computers protected by passwords and will not include information that could identify your baby. We will only record your baby's study ID number. *[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs: All original study documents that provide information about your baby for this study will be kept for at least two years after either the dapivirine vaginal ring is approved for use or the clinical research development program for the dapivirine vaginal ring is stopped.]*

Your baby's personal information may be disclosed if required by law. For example, if we learn something that would immediately put your baby or others in danger, the study staff must take steps to keep your baby and others safe. This means that we have to share any information with the authorities (hospital, police, or social services) that tells us your baby may be in danger. For example, if you tell us that you plan to hurt or kill yourself or your baby, or if you tell us that someone is abusing or neglecting your baby.

The study staff may use your baby's personal information to verify that your baby is not in any other research studies. *[SITES TO INSERT INFORMATION ABOUT SYSTEMS CURRENTLY IN PLACE TO ENSURE PARTICIPANTS ARE NOT PART OF OTHER CONFLICTING STUDIES, INCLUDING BIOMETRIC IDENTIFICATION SYSTEMS.]* This study will not use your baby's name or identify your baby personally in any publication.

Your baby's records may be reviewed by:

- Representatives of the US Federal Government, including the US FDA, US OHRP, NIH and/or NIH contractors, and other US, local, and international regulatory entities
- *[SITES TO INSERT APPLICABLE LOCAL AUTHORITIES]*
- IPM, the organization that supplies the DPV VR
- Gilead Sciences, Inc., the company that supplies the Truvada tablets
- Study monitors
- Site IRB/EC
- Study staff

The study staff will do everything they can to protect your baby's privacy.

### **RESEARCH-RELATED INJURY**

It is unlikely that you or your baby will be injured by being in this study. The U.S. NIH does not have a mechanism to pay money or give other forms of financial compensation for research related injuries. You are not giving up any legal rights by signing this form. *[Sites to replace with their site-specific research-related injury institutional policy if they already provide clinical trials insurance:]* If your baby becomes ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer your baby for ongoing treatment for the injury, if needed. The study sponsor will be responsible for ensuring that insurance is provided to cover appropriate medical expenses for treatment of any such illness or injury if required by law or regulation. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:

- Any injury that happens because your baby used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse regarding your baby's participation in the study.
- Any injury that happens because of negligence on your part.

### **YOUR BABY'S RIGHTS AS A RESEARCH PARTICIPANT**

*[SITES TO SPECIFY INSTITUTIONAL POLICY]:* Being in this study is completely voluntary. You may choose not to allow your baby to join this study or stop your baby's participation in this study at any time. If you choose not to allow your baby to join or to stop your baby's participation in the study, your baby can still join other studies and access non-study services you would

normally get at this clinic. If you want the results of the study after it is over, let the study staff members know.

**PROBLEMS OR QUESTIONS**

If you ever have any questions about the study, or if your baby has a research-related injury, you should contact *[INSERT NAME OF THE INVESTIGATOR OR OTHER STUDY STAFF]* at *[INSERT TELEPHONE NUMBER AND/OR PHYSICAL ADDRESS]*.

If you have questions about your 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]*.

*[SITES TO OMIT THE FOLLOWING IF A SEPARATE CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS IS REQUIRED]*

**CONSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION**

There may be a small amount of blood left over after we have done all of the study related testing on your baby. We would like to store your baby’s leftover blood for future work that could include testing for study products, testing for HIV risk and testing related to COVID-19 infection (if such testing is available and needed to better understand the impact of COVID-19 infection on the study data). If you agree, your baby’s samples and related health information will be stored safely and securely.

Only approved researchers will be able to use these samples and health information. Some employees will need to have access to these samples to store them and keep track of where they are, but these people will not have information that directly identifies your baby. The de-identified data and specimens could then be used for future research by our research team or other researchers without notifying you or asking your permission for this use.

There is no time limit on how long your baby’s samples will be stored. Your baby’s samples may be shipped and/or stored outside of the country. We do not yet know the specific type of testing that will be done with these samples. But, they may be used to check that certain laboratory tests perform correctly. Any other testing beyond that will have to be approved by an IRB/EC. We do not plan to do genetic testing or sequencing (for example, the mapping of all of your baby’s genes, which is also known as whole genome sequencing) of any kind. Your baby’s specimens will never be used for commercial profit.

Your baby can still be in this study if you decide that we cannot store your baby’s blood. You can change your mind about storing and using these samples for future tests at any time by writing to the person in charge of this study. We will then destroy the leftover samples. But, researchers will not be able to destroy samples or information from research that is already started.

PARTICIPANT INITIALS OR MARK	
_____	I DO agree to allow my baby’s biological specimens and health data to be stored and used in future research studies.
Initials                      Date	
_____	I DO NOT agree to allow my baby’s biological specimens and health data to be stored and used in future research studies.
Initials                      Date	

## CONSENT FOR OFF-SITE VISITS

*[Sites to modify as needed]*

Members of the research team at this clinic may be able to schedule off site visits with you at your home or at another location as part of the study. With your permission, some of the scheduled study visits and some of the study procedures may take place at your home or other location outside of the research clinic, if you are unable to come into the clinic. For example, if your baby needs blood sample collected, study staff could come to your home or meet you at another location, if you give your permission and if the study staff determine that it is appropriate. The study personnel will explain in greater detail the requirements of these visits (like the conditions of the place, the type of visit and the time it will take) and the procedures in place to maintain your information in a confidential manner. However it is important that you know that off-site visits may eventually affect your confidentiality even if the study staff take precautions not to disclose the purpose of the visits.

In order to conduct visits outside of the clinic, we will need you to give us permission to do so. Please read carefully the following statement and initial/mark and date one option. Choosing not to have study visit procedures outside of the study clinic will not affect your baby's participation in this study. Even if you agree today, you can withdraw your consent for off-site visits for your baby at any time by providing your request in writing to the person in charge of this study. In addition, before each off-site visit, we will confirm with you that you still agree and remember today's discussion.

### PARTICIPANT INITIALS OR MARK

\_\_\_\_\_  
Initials/Mark

\_\_\_\_\_  
Date

I DO agree to have study visit procedures for my baby at a location other than the study clinic by clinic staff, when necessary.

\_\_\_\_\_  
Initials/Mark

\_\_\_\_\_  
Date

I DO NOT agree to have study visit procedures for my baby at a location other than the study clinic by clinic staff, when necessary.

## CONSENT FOR TAKING PHOTOGRAPHS OF BABY

Please initial/mark one of the following to show whether you agree/do not agree to have photograph(s) of your baby taken as may be requested by study staff:

PARTICIPANT INITIALS OR MARK

\_\_\_\_\_  
Initials/Mark      Date

I DO agree to allow study staff to take photograph(s) of my baby

\_\_\_\_\_  
Initials/Mark      Date

I DO NOT agree to allow study staff to take photograph(s) of my baby

**SIGNATURE PAGE**

*[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC:]*

All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my baby's rights as a research participant will be answered by *[INSERT LOCAL IRB/EC INFORMATION]*.

I voluntarily agree to allow my baby to be in this research study. I understand that my baby is not allowed to participate in this research study without my permission. I voluntarily agree to allow my baby to be in this research study when he/she is born. A copy of this permission form will be given to me.

\_\_\_\_\_  
Participant's Name (Print)

\_\_\_\_\_  
Participant's Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Study Staff's Name Conducting  
Consent Discussion (Print)

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (Signature)

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness Name (Print)

\_\_\_\_\_  
Witness Signature

\_\_\_\_\_  
Date

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