MTN-043

Phase 3B, Randomized, Open-Label, Safety, and Drug Detection Study of Dapivirine Vaginal Ring and Oral TRUVADA® in Breastfeeding Mother-Infant Pairs

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

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DAIDS

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Pharmaceutical Company Collaborator:
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July 24, 2019

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LIST OF ABBREVIATIONS AND ACRONYMS

AAP	American Academy of Pediatrics
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
ASCP	American Society of Clinical Pathology
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
AUC	area under the curve
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
CI	confidence interval
C_{max}	maximum concentrations
C_{min}	minimum concentrations
CMRB	Clinical Microbicide Research Branch
CRF	case report form
CRMS	Clinical Research Management System
CROI	Conference on Retroviruses and Opportunistic Infections
CRS	clinical research site
CT	*Chlamydia trachomatis*
CTI	clinical trial insurance
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
DOT	direct observed therapy
DPV	dapivirine
DREAM	Dapivirine Ring Extended Access and Monitoring
DSMB	Data and Safety Monitoring Board

EAE	expedited adverse event
EMA	European Medicines Agency
EC	ethics committee
EC_{50}	50% effective concentration
EFV	efavirenz
FDA	Food & Drug Administration (U.S.)
FHCRC	Fred Hutchinson Cancer Research Center
FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
FTP	File Transfer Protocol
g	grams
GC	*Neisseria gonorrhoeae*
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 (US)
HIV	Human immunodeficiency virus
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
HOPE	HIV Open-label Prevention Extension
HPTN	HIV Prevention Trials Network
HSV-2	herpes simplex virus 2
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
IQR	interquartile range
IRB	institutional review board
KOH	potassium hydroxide
3TC	lamivudine
LC	Laboratory Center
LDMS	Laboratory Data Management System
LOC	Leadership and Operations Center
LPVr	Lopinavir/Ritonavir
µg	microgram
µM	micromolar (10^{-3} mol/m^3)
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
NDA	New Drug Application
ng	nanogram
NGOs	non-governmental organizations
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	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^3)
NNRTI	non-nucleoside reverse transcriptase inhibitor
NOEL	No observed effect level
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
PEPFAR	President's Emergency Plan for AIDS Relief (US)
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.
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PTID	participant identification
PUEV	Product Use End 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
SDMC	Statistical Data Management Center
SEV	Study Exit Visit
SOP	standard operating procedure
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
UNICEF	United Nations Children's Fund
UPMC	University of Pittsburgh Medical Center
US	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-043

Phase 3B, Randomized, Open-Label, Safety, and Drug Detection Study of Dapivirine Vaginal Ring and Oral TRUVADA® in Breastfeeding Mother-Infant Pairs

INVESTIGATOR SIGNATURE FORM

Version 1.0; July 24, 2019
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: 38591)

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, European Medicines Agency and other global regulatory authority 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-043

Phase 3B, Randomized, Open-Label, Safety, and Drug Detection Study of Dapivirine Vaginal Ring and Oral TRUVADA® in Breastfeeding Mother-Infant Pairs

PROTOCOL SUMMARY

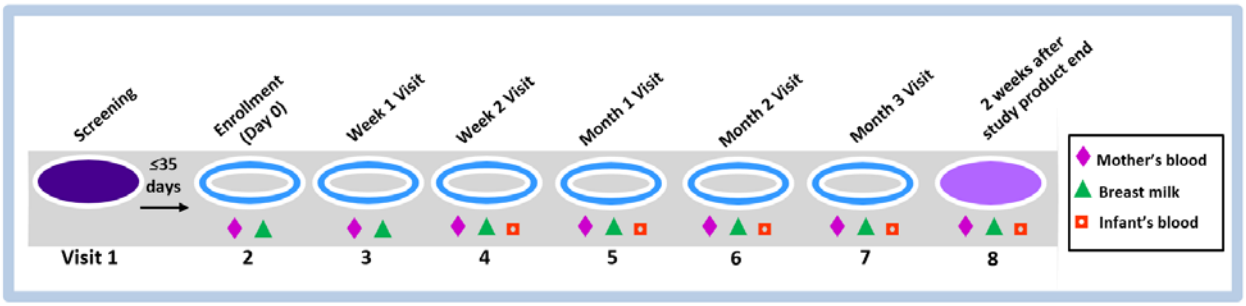
Short Title:	B-PROTECTED: Mother-Infant Pair Study of Dapivirine Ring and PrEP in Breastfeeding
IND Sponsor:	DAIDS
Funders:	Division of AIDS, NIAID, NIMH, NICHD, US NIH
Protocol Chair:	Maxensia Owor, MBChB, MMed, MPH
Protocol Co-Chairs:	Lisa Noguchi, PhD, CNM Jennifer Balkus, PhD, MPH
Sample Size:	Approximately 200 mother-infant pairs
Study Population:	Healthy, HIV-uninfected breastfeeding women and their healthy infants between 6 and 12 weeks old (inclusive) at the time of enrollment
Study Sites:	MTN-043 site(s) selected by the MTN Executive Committee
Study Hypotheses:	• Maternal exposure to study products will be safe for mothers and their breastfeeding infants. • Dapivirine (DPV) will be detectable at low levels in breast milk of participant mothers using the vaginal ring (VR). • Emtricitabine (FTC) and tenofovir (TFV) will be detectable at low levels in breast milk of participant mothers taking Truvada. • DPV will be detectable in the blood of some breastfeeding infants. • Emtricitabine triphosphate (FTC-TP) and/or tenofovir diphosphate (TFV-DP) will be detectable in the blood of some breastfeeding infants.
Study Design:	Phase 3B, randomized, open-label, multi-site, mother-infant pair safety and drug detection study, with 12 weeks of planned study product exposure to either DPV VR (25 mg) or oral Truvada tablet (200 mg emtricitabine [FTC]/300 mg tenofovir disoproxil fumarate [TDF]).
Study Duration:	Each enrolled mother-infant pair will be followed for approximately three and a half months (14 weeks). Note: If a mother seroconverts on study, her infant will have an additional visit, 12 weeks after seroconversion is diagnosed, for additional HIV testing.

Study Products:

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

Study Regimen: Mother-infant pairs will be randomized to the above study products in a 3:1 ratio (VR: tablet). For mothers randomized to the DPV VR, the VR will be worn continuously for approximately one month (4 weeks), to be replaced monthly (4 weeks) for approximately three months (12 weeks). Mothers using Truvada tablet will take one tablet by mouth daily for approximately three months (12 weeks).

Figure 1: **Study Visit Schedule**



Primary Objectives:

Maternal Safety Outcomes: To describe the maternal safety profile associated with study product exposure during breastfeeding in both study arms.

Infant Safety Outcomes: To describe the infant safety profile associated with study product exposure during breastfeeding in both study arms.

Drug Detection: To summarize the frequency of study drug detection and concentration of study drug(s) in mothers and their breastfeeding infants.

Primary Endpoints:

Maternal safety (composite)

- All serious adverse events (SAEs) including maternal deaths in both study arms
- All Grade 3 or higher adverse events (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])* in both study arms

Infant safety (composite)

- All SAEs including infant deaths in both study arms
- 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* in both study arms

Drug Detection

- Maternal plasma DPV concentrations
- Maternal blood FTC-TP and TFV-DP concentrations
- Maternal breast milk DPV concentrations
- Maternal breast milk FTC and TFV concentrations
- Infant plasma DPV concentrations
- Infant blood FTC-TP and TFV-DP concentrations

Secondary Objectives:

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

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

Secondary Endpoints:

Adherence

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

Acceptability

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

Exploratory Objectives:

Expanded Acceptability: To explore attitudes about, preferences for, and experiences with open-label use of the DPV VR (25 mg) and oral Truvada in breastfeeding women.

Genital Microenvironment: To describe the genital microenvironment in participant mothers exposed to study product.

Breastfeeding: To describe infant feeding patterns during study participation.

Exploratory Endpoints:

Expanded Acceptability

- Self-reported experiences with study products and preferences for product attributes
- Self-reported attitudes about study products and perceived attitudes of key influencers (e.g., male partners, family members, providers)

Genital Microenvironment

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

Breastfeeding

- Duration of breastfeeding and reasons for weaning (if weaning occurs during participation)
- Timing and type of infant supplementation

1 KEY ROLES

1.1 Protocol Identification

Protocol Title: Phase 3B, Randomized, Open-Label, Safety, and Drug Detection Study of Dapivirine Vaginal Ring and Oral Truvada® in Breastfeeding Mother-Infant Pairs

Protocol Number: MTN-043

Date: July 24, 2019

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2 INTRODUCTION

2.1 HIV Prevention among Breastfeeding Women

Guidance from the World Health Organization (WHO) supports the promotion of exclusive breastfeeding up to six months of age, with continued breastfeeding along with appropriate complementary foods up to two years of age or beyond.[1] Global Targets 2025 specifically addresses breastfeeding in its goal to increase the rate of exclusive breastfeeding in the first six months up to at least 50%, and countries that have already surpassed this target are encouraged to continue progressing towards higher rates.[2] In many countries within the global south, it is common for breastfeeding to continue for several years. Significant overlap exists between high-parity countries where extended breastfeeding is the norm and those most impacted by the HIV/AIDS epidemic. The average woman in a high HIV-prevalence area of the epidemic spends many years of her life breastfeeding. Thus, breastfeeding women do not represent a separate, special population at risk for HIV, but a very significant proportion of the general population of women at any given time. In addition, the postpartum period may be a time of increased HIV acquisition risk for women, and primary HIV infection during breastfeeding puts infants at higher risk for HIV infection.[3,4] In some parts of the world, cultural norms related to extra primary relationships and postpartum abstinence may contribute to the increased risk of HIV/AIDS faced by many women.[5] However, without adequate safety and drug detection data among breastfeeding infants, regulatory approval and public-sector roll-out of effective HIV chemoprevention strategies may exclude breastfeeding women as has been seen in some settings with oral pre-exposure prophylaxis (PrEP).[6]

2.2 Guidance from US Food and Drug Administration (FDA)

The US FDA has drafted guidance for the conduct of clinical studies of lactation.[7] It is common for a woman to need and take medications while she is breastfeeding, potentially exposing her child to the effects of these medications. Surveys in various countries indicate that 90-99 percent of nursing mothers receive a medication during the first week postpartum, 17-25 percent of nursing mothers will take medication by four months postpartum and five percent of nursing mothers receive long-term drug therapy.[8]

The presence of a drug in breast milk does not necessarily indicate a health risk for the breastfed child. Detecting the presence or absence of the drug in milk is only the first step in determining risk. For most drugs, little scientific information is available about the extent of their passage into breast milk, their effects on milk production, their effects on the breastfed infant, or whether a dose adjustment is needed to treat a lactating woman. Therefore, breastfeeding women and their health care providers must make decisions regarding treatment of maternal medical conditions in the absence of data. In some cases, this can result in a decision to stop breastfeeding to take needed drug therapy, thereby eliminating the benefits of breastfeeding for mothers and their infants. The American Academy of Pediatrics (AAP) has tried to fill the information void regarding infant safety by issuing consensus documents on the use of drugs in lactation or breastfeeding women[9], but data upon which to make these assessments are sparse. Clinical lactation studies provide much needed additional data on which to base treatment decisions.

Since data on dosing lactating women are rarely available, most clinicians treat lactating women with the dose studied in and recommended for non-pregnant adults. This practice disregards the impact of the physiologic changes that occur during lactation and the effects of additional breast and milk compartments. A variety of potential differences in pharmacokinetics might be important

in the postpartum and lactating periods, including differences caused by endogenous hormonal changes, altered body fat proportion, and changes in weight or muscle mass.[10]

Circumstances for which the U.S. FDA recommends clinical studies in lactating women be done include the following:[8]

- A drug under review for approval is expected to be used by women of reproductive age
- After approval, use of a drug in lactating women becomes evident (e.g., via reports in the medical literature or lay press)
- A new indication is being sought for an approved drug and there is evidence of use or anticipated use of the drug by lactating women
- Marketed medications that are commonly used by women of reproductive age (e.g., antidepressants, antihypertensives, anti-infectives, diabetic and pain medications)

Breastfeeding women and women of reproductive age are an important population for antiretroviral-based prevention of HIV, and therefore HIV prevention products should be subject to studies among breastfeeding women.

2.3 Guidance from World Health Organization on Infant Feeding

Over the past decades, evidence for the health advantages of breastfeeding and recommendations for practice have continued to increase. The WHO now states "with full confidence" that breastfeeding reduces child mortality and has health benefits that extend into adulthood.[9] On a population basis, exclusive breastfeeding for the first six months of life is the recommended way of feeding infants, followed by continued breastfeeding with appropriate complementary foods for up to two years or beyond.

To enable mothers to establish and sustain exclusive breastfeeding for six months, WHO and United Nations Children's Fund (UNICEF) recommend the following:

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

Breast milk is the natural first food for babies, it provides nearly all the energy and nutrients that the infant needs for the first months of life, and it continues to provide up to half or more of a child's nutritional needs during the second half of the first year, and up to one-third during the second year of life. Breast milk promotes sensory and cognitive development and protects the infant against infectious and chronic diseases. Exclusive breastfeeding reduces infant mortality due to common childhood illnesses such as diarrhea or pneumonia and helps for a quicker recovery during illness. Breastfeeding contributes to the health and well-being of mothers, helps to space children, reduces the risk of ovarian cancer and breast cancer, increases family and national resources, is a secure way of feeding, and is safe for the environment.[11]

2.4 Description of DPV VR and Truvada Tablet

2.4.1 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, who 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] benzonitrile. 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 (STI), 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 *Dapivirine Vaginal Ring Investigator Brochure (IB)*.[12]

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. 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.[12]

2.4.2 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).[13]

Truvada was originally approved by the US Food and Drug Administration (FDA) in 2004 in combination with other ARV agents as a treatment of HIV-1 infection in adults. Currently, Truvada has been approved to treat HIV infection in both adult and pediatric patients (12 years of age and older and weighing greater than or equal to 35kg) when combined with other drugs. 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 is the first agent to be approved for HIV prevention in uninfected adults; known as PrEP.[14] Truvada for oral PrEP has also been approved for use by adults at high risk of sexually acquiring HIV-1 infection by the European Medicines Agency (EMA) and in a number of countries, including South Africa, Malawi, Kenya, and Zimbabwe.[15] A Technical Working Group was 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, the Technical Group 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 WHO recommends use of Truvada in pregnant and lactating women at significant risk of HIV; guidelines regarding use in pregnancy and lactation differ by country. In 2017, the WHO included

oral TDF, FTC/TDF, and lamivudine/TDF tablets in the *20th WHO Model List of Essential Medicines*, with the new indication for use as oral PrEP of HIV infection https://apps.who.int/iris/bitstream/handle/10665/273826/EML-20-eng.pdf.

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.[16] However, a secondary analysis[17] 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. Detailed information on Truvada is available in the *Truvada Package Insert.*[13]

2.4.3 Mechanism of Action

DPV VR
DPV is an NNRTI; NNRTIs bind to the HIV reverse transcriptase (RT) enzyme thereby preventing viral replication and the production of an infectious virus.[12]

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.[13]

2.4.4 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.[12]

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-043 are the same as licensed doses, and the safety profile has been assessed as part of FDA licensure.[13]

2.5 Nonclinical Studies – 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_{50}) values ranged from 0.3 ng/mL (0.9 nM) against laboratory isolates to <33 ng/mL (<100 nM) against 80% of HIV-1 isolates encoding one or more known NNRTI resistance mutations.[18,19] The anti-HIV activity of DPV was also confirmed in an *ex vivo* model of human cervical explant cultures.[18,19] 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_{50} = 0.1 nM [0.03 ng/mL]) (IB). More information regarding anti-HIV-1 activity can be found in the *Dapivirine Vaginal Ring Investigator Brochure*.[12]

Resistance to DPV

In vitro studies showed that selection of DPV-resistant strains typically required more than one substitution in the reverse transcriptase gene, including V90I/V, A98S, L100I, K101E, K103N, V106I/V, V108I, E138E/G/K/Q/R, T165I, V179E/F/I/M/V, Y181C, Y188H, G190A/E, L214F, F227Y, and M230I.

In the Phase 3 trials, a low and similar proportion of women in both DPV VR and placebo ring groups had NNRTI mutations identified in samples taken soon after HIV-1 infection. The proportion of participants with mutations associated with resistance to efavirenz and nevirapine was similar in both treatment groups.

Imbalances were noted for the E138A substitution, (higher in the DPV group), a known polymorphic mutation reported to have been observed in up to 8% of antiretroviral-naïve subtype C HIV-1 infected patients, and the V90I substitution (higher in the placebo ring group). In one Phase III trial (IPM 027) E138A occurred more frequently in virus of participants who seroconverted and had a NNRTI resistance assessment in the DPV group (11.7% [9/77]) compared to the placebo group (3.6% [2/56]), while no difference between treatment groups was observed in the other Phase III trial (MTN-020, 4.3% [3/69] vs 5.2% [5/96]). Additionally, there was an imbalance of participants with more than one resistance-associated mutation in the DPV group observed in the MTN-020 trial (10.1% [7/69] of participants in the DPV group and 1% [1/96] of participants in the placebo ring group).

It is not clear whether these imbalances represent the transmission of HIV-1 variants with these mutations already encoded or if they appeared due to selective pressure by dapivirine as a result of continued use following HIV-1 infection.[12]

Cross-resistance of DPV

In comparison with NVP, DLV, EFV and emivirine, 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_{50} was below 32.9 ng/mL (100 nM) for 80% of the strains compared with only 56% of the strains for EFV.[12] 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.[12]

DPV cross-resistance was also evaluated using plasma samples derived from HIV-1 subtype C-infected individuals failing first-line neviripine- 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.[20] More information regarding cross-resistance activity can be found in the *Dapivirine Vaginal Ring Investigator Brochure (IB)*.[12]

Preclinical Safety of DPV

Dapivirine has been investigated in a comprehensive nonclinical safety assessment program that included single and repeat dose toxicity studies, in a range of reproductive toxicity and mutagenicity studies, and in a carcinogenicity study. In vaginal studies in rabbits, there were no significant local or systemic findings following repeat administration at up to 20 mg/mL for 14 days, up to 5 mg/mL for 13 weeks, or up to 2 mg/mL for 39 weeks, which is 185, 46 and 19 times higher than the maximum concentration measured in the vaginal fluid of women using the DPV VR,

respectively. There were also no effects in reproductive toxicity studies in rats and rabbits performed vaginally at concentrations up to 2 mg/mL. In studies conducted via the oral route of administration, a no observed effect level (NOEL) was not established in the rat. However, the main findings (effects on liver, thyroid, and pituitary) were considered adaptive rather than adverse responses, and therefore the no observed adverse effect level (NOAEL) was considered to be 20 mg/kg/day. This dosage was also the NOAEL in the dog. At higher dose levels, hepatotoxicity and adrenal cortical fatty changes were observed in dogs, and slight hematological and clinical chemistry changes were observed in rats. The NOAEL in oral reproductive toxicity studies in the rat was also 20 mg/kg/day, whereas in the rabbit no effects were seen at dosages up to 90 mg/kg/day. Dapivirine was considered to be non-genotoxic. In the guinea pig, dapivirine (2 mg/mL) did not demonstrate any potential to cause contact sensitization. No treatment-related neoplastic or non-neoplastic findings were seen in a vaginal carcinogenicity study in rats at concentrations up to 5 mg/mL.[12]

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: 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).[12]

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.[12]

2.6 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*.[13]

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*.[13]

Cross-Resistance

Emtricitabine and Tenofovir Disoproxil Fumarate: Cross-resistance among certain NRTIs has been recognized. The M184V/I and/or K65R substitutions selected in cell culture by the combination of FTC and tenofovir are also observed in some HIV-1 isolates from subjects failing treatment with tenofovir in combination with either FTC or lamivudine, and either abacavir or

didanosine. Therefore, cross-resistance among these drugs may occur in patients whose virus harbors either or both of these amino acid substitutions.[13]

Preclinical Safety of FTC and TDF

Both FTC and TDF were evaluated in nonclinical safety assessment programs inclusive of toxicity, pharmacology, reproductive toxicity, mutagenicity and long-term carcinogenicity studies. FTC was not found to be genotoxic in mutagenicity studies. 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). 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.[13]

For TDF, long-term oral carcinogenicity study of TDF in mice showed that the frequency of liver adenomas was increased in females at the high dose, at which systemic exposure was 16 times that in humans. In a study in rats, there was no evidence of carcinogenicity at exposures up to five 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 in rats, dogs, and monkeys, tenofovir exposure (based on AUCs) greater than or equal to 6-fold those observed in humans caused 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 calcinuria 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.[13] 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.[21]

2.7 Clinical Studies – DPV

To date, a total of 31 Phase 1 and Phase 2 clinical research studies of DPV have been conducted: 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 (71 women received DPV vaginal film).[12]

Two Phase 3 studies, IPM 027 (The Ring Study) and MTN-020 (ASPIRE), 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.[22,23] Two Phase 3B open-label extension trials, IPM 032 (DREAM) and MTN-025 (HOPE),

are ongoing, and offer the extended use of the DPV VR to former participants of The Ring Study and ASPIRE, respectively.

As of April 2018, a total of 3122 adult women between 18 and 65 years of age have been exposed to the DPV VR across the clinical development program.[12]

2.7.1 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 with continuous use of the VR or gel up to 84 days (12 weeks). 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_{max} after oral administration at the maximum tolerated dose (MTD) [300 mg bid for 14 days] was 2286 ng/mL).[24]

The clinical PK profile of the Dapivirine Vaginal Ring-004 formulation evaluated in all trials showed a rapid increase in plasma and vaginal fluid concentrations of DPV after VR insertion.[12] 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 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.[12] 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).[12]

2.7.2 Phase 1 and 2 Studies of DPV

Across all clinical trials conducted in healthy participants evaluating multiple VR configurations, the DPV VR was generally safe and well-tolerated.[12]

The Dapivirine Vaginal Ring-004 has been evaluated in ten completed clinical research studies, each demonstrating the relative safety of this VR.[12] Among them, one study has been conducted of Ring-004 use in lactating, but not breastfeeding, women, with no infant exposure to study drug.

DPV Use and Breastfeeding

MTN-029/IPM 039 was a Phase I, 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.[5] 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 six 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 (milk: plasma ratio ~2.0), and 36.25ng/mg in CVF. Six participants experienced ten total AEs, none of which required VR discontinuation. Estimated potential daily infant exposure (if breastfeeding had occurred in this study) was 74.3 ng/kg/day (45.5, 103.1). 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.[5]

2.7.3 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.

The median age at enrollment was 25 years, and 91% were unmarried. At the data cut-off point, there were 2805 person-years of follow-up, and 761 women had completed the two-year follow-up period. A total of 133 post-randomization HIV-1 infections occurred: 77 among women assigned to DPV VR (incidence 4.08 per 100 person-years) and 56 among women assigned to placebo (incidence 6.10 per 100 person-years). The DPV VR reduced the risk of HIV-1 infection by 30.7% (95% CI: 0.90-51.5%; p=0.0401) relative to placebo. A 37.5% (95% CI: 3.5-59.5%) reduction in HIV-1 infection was observed in a subgroup analysis of women older than 21 years.[22,25]

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. The proportion of participants with any NNRTI mutation was low and similar between the DPV and placebo treatment groups. The only exception is the E138A mutation identified in virus from 11.7% (9/77) of the DPV VR group compared to 3.6% (2/56) in the placebo ring group. The significance of this finding is unclear due to the small numbers.[12]

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 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.[23,26]

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 ≥ 25 years [CI: 32%, 77%)] p<0.001, and 10% reduced risk for women < 25 years (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.[23]

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).[12]

IPM 032 (DREAM)

IPM 032, the Dapivirine Ring Extended Access and Monitoring (DREAM) study, a Phase 3B multi-site, open-label follow-up trial to The Ring Study, was implemented in six of the IPM 027 sites. Enrollment was completed in February 2018. Like the HOPE study (described below), DREAM study participants were asked to use the DPV VR for up to 12 months, replacing it monthly, and to attend monthly visits for the first one to three months of study with follow-up visits quarterly thereafter. At the close of accrual, the DREAM study had enrolled a total of 941 former IPM 027 participants who were HIV-negative and otherwise eligible to enroll.

MTN-025 (HOPE)

MTN-025, the HIV Open-label Prevention Extension (HOPE) study, a multi-site, open-label, randomized, Phase 3B trial was implemented at the ASPIRE clinical research sites which are now closed to follow-up. Eligible HIV-uninfected ASPIRE participants received the same DPV 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 three months and quarterly thereafter, reflecting a transition to a more real-world type of follow-up (versus a clinical trial approach). At the close of accrual, the HOPE study had enrolled 1456 former ASPIRE participants who were HIV-negative and otherwise eligible to enroll.

Studies of the DPV VR in Pregnancy

Understanding the effects of a medication used during pregnancy may contribute to better understanding of its potential impact in breastfeeding infants. The use of DPV VR was well-tolerated and helped to reduce the risk of HIV-1 infection in non-pregnant reproductive-aged women. However, 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.[27] However, of the 2629 women enrolled in ASPIRE, 169 did become 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 to 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.[28] 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.[12] In both IPM 027 and MTN-020, the frequency of congenital abnormalities was similar between the DPV VR group and the placebo ring group.[27] As of March 2018, 22 pregnancies were reported in the

DREAM study and 53 in the HOPE study; while less than 50% of the pregnancy outcomes are available, no new safety signals have been found and no congenital anomalies were reported in the available data.[27]

The U.S. NIH-funded MTN is planning a Phase 3B study, MTN-042, entitled Phase 3B, Randomized, Open-Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy. This study will help answer key questions about the safety of oral PrEP and the DPV VR when used during pregnancy. The study will be conducted at four African trial sites in Malawi, Uganda, South Africa, and Zimbabwe, and enroll 750 women at different stages of pregnancy who would be randomly assigned to use either oral PrEP or the DPV VR until the time they deliver.

The MTN-042 trial design involves a stepwise backwards approach involving four cohorts. Only women late in pregnancy (approximately 36 weeks gestation) will be enrolled into the first cohort. Participants will be carefully monitored during product use, and after each cohort has completed study product use, an interim safety review will be conducted. Rates of adverse pregnancy outcomes observed in the clinical trial cohort will be compared to the local background rates. The background pregnancy outcome 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. If no safety concerns are identified in the MTN-042 study, the second cohort (30-35 weeks) will begin enrollment and a similar review be conducted after the second cohort has completed study product. This process will be repeated for the next cohort (20-29 weeks) before the last and largest cohort (12-20 weeks) is enrolled. The MTN-042 study is currently anticipated to begin enrollment prior to the initiation of MTN-043.

2.8 Clinical Studies – Truvada

2.8.1 Clinical Pharmacokinetics of FTC and TDF

Truvada (200 mg FTC/300 mg TDF) may be administered with or without food.[13] *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, co-administration 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.[13]

2.8.2 Phase 3 Studies of FTC with TDF

Clinical Studies of FTC with TDF in HIV Prevention

A review[29] 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 one to two 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).

Resistance in individuals seroconverting while taking Truvada has been assessed from five 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.[30-34] 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 (five 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 (seven cases in 17 participants).[35-40] The risk of resistance with Truvada is low if acute HIV-1 infection is excluded before starting oral PrEP.[41]

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.[34] 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 three 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%.[42] 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 Partners PrEP data with relevance for MTN-043 were the efficacy of TFV-containing PrEP in reducing HSV-2 incidence,[17] safety in early pregnancy,[43] the low incidence of drug resistance in PrEP users detected by sensitive assays,[37] and the low incidence and reversibility of renal glomerular changes.[44]

Studies of Truvada in Breastfeeding

A growing body of evidence supports the use of Truvada in breastfeeding women.[45,46] Mugwanya and colleagues conducted a prospective short-term, open-label study of daily oral FTC/TDF PrEP among 50 HIV-uninfected breastfeeding African mother–infant pairs between 1–24 weeks postpartum. The primary aim was to quantify steady-state concentrations of TFV and FTC in infant plasma ingested via breastfeeding. PrEP was given to women through daily directly observed therapy (DOT) for ten consecutive days and discontinued thereafter. Overall, median (IQR) time-averaged peak concentrations in breast milk were 3.2 ng/mL (2.3 to 4.7) for TFV and 212.5 ng/mL (140.0 to 405.0) for FTC. Similarly, median (IQR) time-averaged trough concentrations in breast milk were 3.3 ng/mL (2.3 to 4.4) for TFV and 183.0 ng/mL (113.0 to 250.0) for FTC, reflecting trough-to-peak breast milk concentration ratios of 1.0 for TFV and 0.8 for FTC, respectively. In infant plasma, TFV was unquantifiable in 46/49 samples (94%), and FTC was detectable in 47/49

(96%) (median [IQR] concentration: 13.2 ng/mL [9.3 to 16.7]). Estimated equivalent doses an infant would ingest daily from breastfeeding were 0.47 µg/kg (IQR 0.35 to 0.71) for TFV and 31.9 µg/kg (IQR 21.0 to 60.8) for FTC, equivalent to a <0.01% and 0.5% relative dose when compared to the 6 mg/kg dose that is proposed for therapeutic treatment of infant HIV infection and for prevention of infant postnatal HIV infection; a dose that has not shown safety concerns. No serious adverse effects were recorded during study follow-up. These data suggest Truvada could be safely used during breastfeeding with minimal infant drug exposure.[45] Results from the International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group (IMPAACT) PROMISE study also showed that both maternal antiretroviral therapy (TDF/FTC/Lopinavir/Ritonavir[LPVr]) and prolonged infant antiretroviral prophylaxis (iNVP) were safe and associated with very low breastfeeding HIV-1 transmission and high infant HIV-1-free survival at 24 months.[47]

Studies of Truvada as PrEP During Pregnancy

Recent data from the Partners Demonstration Project showed women using Truvada throughout pregnancy had no greater frequency of adverse pregnancy outcomes or restricted infant growth as compared to those without any exposure (data from the placebo arm of a prior efficacy trial of Truvada conducted in the same setting. These findings support recommendations permitting Truvada during pregnancy.[48]

Finally, data from the VOICE study, a five-arm, double-blinded, randomized, placebo-controlled trial evaluating the effectiveness of daily oral TDF, oral FTC/TDF and vaginal TFV for HIV prevention, showed that pregnancy incidence and outcomes were similar across all arms. The results suggest that these drugs are safe in the peri-conception period. Of note, the drug adherence and detection in this cohort were low, thereby limiting the interpretation of these data.[49]

IMPAACT 2009

IMPAACT 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 six months following delivery, and to compare pregnancy outcomes among participants who take PrEP and participants who decline PrEP during the antenatal period. The Postpartum PK component of the IMPAACT 2009 study will enroll mothers and their infants when they are between approximately six weeks and 12 weeks following delivery exactly similar to the MTN-043 study period with the follow -up of approximately three months. The study is open to accrual at sites located in Zimbabwe, Malawi, Uganda, and South Africa.[50]

2.9 Outcomes among Women Who Seroconverted While Using DPV VR or Truvada

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.

2.9.1 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 six months of ART, or plasma HIV RNA rebound to ≥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, eight 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 ≥six 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.[51]

2.9.2 Truvada Tablet

Resistance in individuals seroconverting while taking Truvada has been assessed from five 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.[30-34] 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 (five cases in 160 seroconverters assigned to TDF/FTC in five PrEP studies). Resistance to TFV and FTC is much more common (41%) if TDF/FTC PrEP is started during undiagnosed acute HIV-1 infection (seven cases in 17 participants).[35-40] The risk of resistance with Truvada is low if acute HIV-1 infection is excluded before starting oral PrEP.[41]

2.10 Acceptability and Adherence

2.10.1 DPV VR

Multiple clinical trials have also evaluated adherence to the DPV VR among reproductive-aged women in Africa and the US.[52-56] 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. Subgroup analyses of residual VR data suggest that the majority of women inconsistently used the VR throughout their participation in ASPIRE.[54]

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. Other reasons for removing the VR included male partner's wishes, 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. This shift in drug levels was corroborated by participant narratives in the nested qualitative component of the ASPIRE study.[57]

2.10.2 Truvada Tablet

Multiple clinical trials have evaluated the acceptability of and adherence to the Truvada oral tablet among reproductive-aged women in Africa.[32,34,54,58-64] 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, 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.

2.11 Rationale for the MTN-043 Study Design

The purpose of this study is to characterize the safety, drug detection, adherence, and acceptability of the DPV VR (25 mg), inserted every four weeks, and once-daily Truvada (200 mg FTC/300 mg TDF) tablet used by women from sub-Saharan African countries during breastfeeding. This study will provide further understanding of product safety for mothers and their breastfeeding infants by testing the following hypotheses:

- Maternal exposure to study products will be safe for mothers and their breastfeeding infants.
- DPV will be detectable at low levels in breast milk of participant mothers using the VR.

- FTC and TFV will be detectable at low levels in breast milk of participant mothers taking Truvada.
- DPV will be detectable in the blood of some breastfeeding infants.
- FTC-TP and/or TFV-DP will be detectable in the blood of some breastfeeding infants.

The safety and drug detection endpoints were selected based on clinical relevance and importance for future drug labeling to guide product use. Information on the presence of DPV, FTC, and TFV in human milk, the potential effects of DPV and Truvada on the breastfed infant, and the effects of DPV and Truvada on milk production are all relevant for prescribers and regulators.

Mothers and Breastfeeding Infants

Breastfeeding women are an important population for biomedical HIV prevention strategies but are rarely included in HIV chemoprevention trials.[65] Several factors support this evaluation of DPV and Truvada for mothers and their breastfeeding infants: (1) Of note, in countries with high HIV incidence, a high fertility rate and extended periods of breastfeeding are common and significant risk for HIV acquisition postpartum appears to continue during breastfeeding. (2) The WHO recommends exclusive breastfeeding for six months minimum and continued breastfeeding with appropriate complementary foods up to two years of age or beyond. (3) Normal physiologic changes during the postpartum period (e.g. hormonal, body fat, and muscle mass) may impact pharmacokinetics therefore the pharmacokinetic profiles may differ from non-lactating women. (4) Although the US FDA advises clinical lactation studies when drug use is anticipated in women of reproductive age and a recent FDA drug labeling rule includes provisions for a lactation risk summary with actual or estimated infant dose, few studies have included lactating women in evaluations of HIV chemoprevention products.

The first study of dapivirine exposure during lactation, MTN-029/IPM 039 (25 mg DPV VR used for 14 days by lactating women who had completed weaning their infants), found no significant safety concerns in women and extremely low levels of dapivirine in breast milk and maternal blood. Estimated levels of infant dapivirine exposure were also low. Based on these data, it is reasonable to expect that dapivirine will be detectable in both blood and breast milk of breastfeeding mothers at low levels. However, given the low levels of dapivirine anticipated in breast milk, and the poor oral bioavailability of dapivirine, it is not anticipated that infants will have detectable levels of dapivirine in their blood. It is not anticipated that participation in MTN-043 will pose significant safety concerns for either women or their breastfeeding infants.

Truvada, as an approved drug in many settings, already has guidance for prescribers that includes available data on the potential effect of drug exposure on breastfeeding infants. Additionally, drug exposure in breastfeeding infants is low. Based on data from Mugwanya et al[45], FTC and TDF are detected in breast milk at very low concentrations (0.3–2% of the levels required for infant treatment). In recent guidance, WHO stated that existing safety data support the use of PrEP in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection. However, WHO also acknowledged that more data are needed on TDF and FTC/TDF safety during breastfeeding. Not all countries that have approved FTC/TDF for PrEP have approved its use for breastfeeding women, presumably due to the desire for additional safety data.[66]

In summary, the emerging evidence on increased risk of HIV infection during the postnatal period, the ethical imperative to include mothers and breastfeeding infants in drug safety studies, and the limited but favorable safety profiles for DPV and Truvada in these populations supports this evaluation of DPV and Truvada by breastfeeding mother-infant pairs in Sub-Saharan African countries with high incidence of sexually transmitted HIV infection.

Safeguards to Mitigate Risk

Several safeguards are in place to mitigate potential risks for the mother-infant pairs enrolled in MTN-043. Study eligibility criteria will restrict enrollment to healthy, HIV-uninfected females, 18 years or older, at least six weeks postpartum at enrollment, who are willing to be randomized to study product, and their infants. Infants are to be generally healthy, according to judgment of the IoR/designee. Another safeguard for mitigating risk is the continuous ongoing safety monitoring by the Site IoRs/designees and Protocol Safety Review Team (PSRT). The site IoRs/designees are responsible for the close safety monitoring of all study participants and alerting the Protocol Team if unexpected concerns should arise. A sub-group of the Protocol Team serve on the PSRT and in collaboration with the SDMC, review safety data and address any potential safety concerns monthly or as needed. More detailed information on the safety monitoring by the PSRT and other mechanisms is available in Section 8. Finally, a mother may voluntarily withdraw herself or her infant from the study for any reason and/or the Investigator may withdraw the mother and infant to protect their safety and/or if the mother demonstrates an unwillingness to comply with required study procedures.

Data from prior DPV VR and Truvada trials suggest that HIV-1 risk reduction in reproductive age women is correlated with adherence to product use. If women do not adhere to the use of the products, there is no HIV-1 infection risk reduction. Therefore, participants will be counselled throughout the study to adhere strictly to the recommended dosing regimen, either continuous use of the DPV VR with replacement every four weeks or once-daily oral administration of Truvada. Objective measures of study product use, including plasma levels and residual drug levels for the DPV VR, and plasma levels for Truvada will be collected at specified study visits. This study will document all HIV infections that occur in participants and follow all HIV seroconverters, both mothers and infants, as part of the study. However, we anticipate too few HIV infections during this study to have the statistical power necessary to compare HIV incidence between product use groups or to historical controls.

Understanding cultural beliefs, societal norms and roles within the community is critically important for the success of a study involving breastfeeding women. In order to do so, MTN-041, a qualitative study was conducted to identify specific factors, belief systems and attitudes that may affect breastfeeding women's perceptions of the MTN-043 study and potential interest in using a monthly vaginal ring or daily PrEP during breastfeeding. In addition, it assessed who within a woman's sphere of influence is most likely to support or discourage the use of either or both products. The MTN-041 study took place at the planned trial sites for MTN-043 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. Data collection was completed in November 2018 and findings will be utilized to inform recruitment, retention, community activities, data collection instruments, and study tools. The information gained from MTN-041 will help the MTN-043 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 breastfeeding participants and the study team, bringing potential issues of concern to attention sooner than later.

Findings from the MTN-043 study will provide important prospective safety and drug detection data from postpartum women and their breastfeeding infants rarely obtained in prior studies,

particularly for the DPV VR. Data on acceptability will provide further understanding of attitudinal and behavior aspects to the DPV VR and Truvada as well as other HIV prevention methods.

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.

3 OBJECTIVES

3.1 Primary Objectives:

Maternal Safety Outcomes: To describe the maternal safety profile associated with study product exposure during breastfeeding in both study arms.

Infant Safety Outcomes: To describe the infant safety profile associated with study product exposure during breastfeeding in both study arms.

Drug Detection: To summarize the frequency of study drug detection and concentration of study drug(s) in mothers and their breastfeeding infants.

3.2 Secondary Objectives:

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

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

3.3 Exploratory Objectives:

Expanded Acceptability: To explore attitudes about, preferences for, and experiences with open-label use of the DPV VR (25 mg) and oral Truvada in breastfeeding women.

Genital Microenvironment: To describe the genital microenvironment in participant mothers exposed to study product.

Breastfeeding: To describe infant feeding patterns during study participation.

4 STUDY DESIGN

4.1 Identification of Study Design

Phase 3B, randomized, open-label, multi-site, mother-infant pair safety and drug detection study, with 12weeks of planned study drug exposure.

4.2 Summary of Major Endpoints

Primary Endpoints:

Maternal safety (composite)

- All SAEs including maternal deaths in both study arms
- 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])* in both study arms

Infant safety (composite)

- All SAEs including infant deaths in both study arms
- 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* in both study arms

Drug Detection

- Maternal plasma DPV concentrations
- Maternal blood FTC-TP and TFV-DP concentrations
- Maternal breast milk DPV concentrations
- Maternal breast milk FTC and TFV concentrations
- Infant plasma DPV concentrations
- Infant blood FTC-TP and TFV-DP concentrations

Secondary Endpoints:

Adherence

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

Acceptability

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

Exploratory Endpoints:

Expanded Acceptability

- Self-reported experiences with study products and preferences for product attributes
- Self-reported attitudes about study products and perceived attitudes of key influencers (e.g., male partners, family members, providers)

Genital Microenvironment

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

Breastfeeding

- Duration of breastfeeding and reasons for weaning (if weaning occurs during participation)
- Timing and type of infant supplementation

4.3 Description of Study Population

Healthy HIV-uninfected breastfeeding women and their healthy infants between 6 and 12 weeks old (inclusive) at the time of enrollment.

4.4 Time to Complete Accrual

Time to complete accrual will be approximately 4 - 6 months (16 - 26 weeks).

4.5 Expected Duration of Participation

Each enrolled mother-infant pair will be followed for approximately three and a half months (14 weeks). If a mother seroconverts while on study, the infant will have an additional visit, 12 weeks after seroconversion is diagnosed, for additional HIV testing.

4.6 Sites

MTN-043 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 200 women and their infants will be enrolled in this study. Inclusion and exclusion criteria in Sections 5.2 and 5.3 are used to ensure the appropriate selection of study participants for MTN-043.

5.1.1 Recruitment

Participants will be recruited from a variety of sources across sites including, but not limited to, healthcare facilities and community-based outreach. It is anticipated that all participating MTN-043 sites will have established relationships with hospitals and other facilities serving pregnant and postpartum women and infants. 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/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

5.2.1 Inclusion Criteria – Mother

Participant mothers must meet all the following criteria to be eligible for inclusion in the study:

1. Age 18 years or older at Screening, as verified per site Standard Operating Procedures (SOPs).
2. At Enrollment, between 6 to 12 weeks postpartum (verified by birth records and/or similar supportive documentation and defined as between 42 – 84 days after delivery, inclusive).
3. By participant report at Screening and Enrollment, currently exclusively breastfeeding one infant and willing and able to continue exclusively breastfeeding that infant for the duration of their participation in the study.

   Note: Exclusive breastfeeding will be defined as infant nutrition solely from breast milk, as determined by 7-day recall breastfeeding history.[67] For the purposes of MTN-043, "breastfeeding" refers to all human milk feeding situations when an infant is fed with participant's own human milk whether the milk is received directly from the breast or as expressed milk.
4. Consistently using an effective method of contraception per participant report at Enrollment, and intending to continue use of an effective method for the duration of study participation. Effective methods include contraceptive implants, intrauterine device, injectable progestin, oral contraceptive pills, and surgical sterilization.
5. Able and willing to comply with all study requirements and complete all study procedures.
6. Able and willing to provide the following:
   a. Written informed consent to be screened for and to take part in the study.
   b. Written informed consent for the breastfed infant to be screened for and take part in the study.
7. Intention to stay within study catchment area for study duration and willingness to give adequate locator information, as defined in site SOPs.

8. At Screening and Enrollment, HIV-uninfected based on HIV testing performed by study staff (per algorithm in Appendix III).
9. At Screening and Enrollment, willing to be randomized at time of enrollment to either of the study products, and to continue study product use for at least 12 weeks.

5.2.2 Inclusion Criteria – Infant

Each mother eligible for MTN-043 will be asked to provide written informed consent for herself and her infant to participate in the study if the infant meets the following criteria:

1. At Screening and Enrollment, infant is exclusively breastfed.

   Note: Exclusive breastfeeding will be defined as infant nutrition solely from breast milk, as determined by 7-day recall breastfeeding history.[67] For the purposes of MTN-043, "breastfeeding" refers to all human milk feeding situations when an infant is fed with participant's own human milk whether the milk is received directly from the breast or as expressed milk.
2. At Screening and Enrollment, the infant is generally healthy, according to the judgment of the IoR/designee.
3. At Enrollment, the infant is between the ages of 6 and 12 weeks postpartum (verified by birth records and/or similar supportive documentation with age defined as between 42 - 84 days after delivery, inclusive).

5.3 Exclusion Criteria

5.3.1 Exclusion Criteria – Mother

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

1. At Screening or Enrollment, breastfeeding infant ineligible for enrollment in the study.
2. At Screening or Enrollment, participant reports any of the following:
   a. Known adverse reaction to any of the study products (ever).
   b. Known adverse reaction to latex and polyurethane (ever).
   c. Post-exposure prophylaxis (PEP) for HIV exposure within 6 months prior to Enrollment.
   d. Use of vaginal medications(s) or other vaginal products within five days prior to Enrollment.
   e. Non-therapeutic injection drug use in the 12 months prior to Enrollment.
   f. History of exposure to any investigational drug(s) during pregnancy, including participation in MTN-042.
3. At Screening or Enrollment, has a positive HIV test.
4. At Screening or Enrollment, Grade 2 or higher breast or genitourinary findings.
5. At Screening or Enrollment, has a positive urinary pregnancy test.
6. At Screening, has any of the following laboratory abnormalities:
   a. Positive for hepatitis B surface antigen (HBsAg).

b. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≥ Grade 2.

c. Creatinine ≥ Grade 1.

d. Estimated creatinine clearance ≥ Grade 1 (Cockcroft Gault formula).

7. Diagnosed with urinary tract infection (UTI), pelvic inflammatory disease (PID), STI or reproductive tract infection (RTI), requiring treatment per WHO Guidelines.

   Note: Otherwise eligible participants diagnosed during Screening with a UTI, PID or STI/RTI requiring treatment per WHO Guidelines – other than asymptomatic bacterial vaginosis (BV) and asymptomatic vulvovaginal candidiasis – are offered treatment consistent with WHO recommendations and may be enrolled after completing treatment if all symptoms have resolved. If treatment is completed and symptoms have resolved prior to obtaining informed consent for Screening, the participant may be enrolled. Genital warts requiring treatment also must be treated prior to enrollment. Genital warts requiring treatment are defined as those that cause undue burden or discomfort to the participant, including bulky size, unacceptable appearance, or physical discomfort.

8. As determined by the IoR/designee, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease.

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

10. At Enrollment, participant reports any of the following:

    a. Participation in any research study involving drugs, vaccines, or medical devices 30days or less prior to enrollment.

    b. Currently participating in other research studies involving drugs, vaccines, or medical devices.

    c. Expected to participate in other research studies involving drugs, vaccines, or medical devices during study participation.

5.3.2 Exclusion Criteria – Infants

1. Has any condition that, in the opinion of the IoR/designee, would preclude eligibility, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

   Note: Examples of exclusionary infant conditions include clinical evidence of stunting or illness.

2. At Enrollment, according to the report of the mother, any of the following apply for the infant:

    a. Infants with birth weight less than 2000g.

    b. Participation in any research study involving drugs, vaccines, or medical devices since birth.

    c. Currently participating in other research studies involving drugs, vaccines, or medical devices.

    d. Expected to participate in other research studies involving drugs, vaccines, or medical devices for the duration of study participation.

5.4 Co-enrollment Guidelines

As indicated in Sections 5.2 and 5.3, mothers and infants 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 after approval from Protocol Team:

- Participants may take part in ancillary studies approved by the MTN-043 Protocol Team.
- Participants who acquire HIV may take part in observational and/or interventional studies for HIV-positive persons.

6 STUDY PRODUCT

6.1 Regimen

Mothers will be randomized in a 3:1 ratio to one of two study products: a VR containing 25 mg of DPV to be inserted monthly or an oral Truvada tablet containing 200 mg FTC/300 mg TDF taken daily. Participants will use one of the two study products for approximately three months (12 weeks).

Table 1: **Study Regimen**

Group	N	Study Product Description
A	150	Dapivirine Vaginal Ring-004 (25 mg)
B	50	Truvada (200 mg FTC/300 mg TDF) oral tablet

6.2 Administration

6.2.1 Dapivirine Vaginal Ring-004 (25 mg)

The participant will insert the study VR at the clinic, and 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 VR (VR insertion, removal, procedures in the event of expulsion or loss) will be provided in the *MTN-043 SSP Manual*.

6.2.2 Truvada Tablet

Study participants will be instructed to take one oral Truvada tablet daily 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 six hours. If the next dose is estimated to be due within six hours, the missed dose must be skipped. The next dose must be taken as originally scheduled.

6.3 Study Product Formulation

6.3.1 Dapivirine Vaginal Ring-004 (25 mg)

The study VR is an off-white, flexible ring containing 25 mg of dapivirine 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. Dapivirine 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. FTC is a synthetic nucleoside analogue of cytidine. 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 VRs will be supplied by IPM (Silver Spring, MD). Truvada tablets will be 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-043 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 will be dispensed only to 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 will take place on the day of enrollment and at each scheduled monthly visit. If additional study products are needed between visits, participants will be instructed to come to the study site. If the participant is unable to attend her next 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 dispensation.

6.5 Retrieval of Study Product

Study participants will be instructed to return all study products (unused/used VR and unused Truvada tablets) 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.

Study product must be retrieved within 24 hours and returned to the clinic when product use is permanently discontinued for HIV seroconversion or held temporarily due to potential HIV seroconversion (see Table 2 below). Additional study product retrieval specifications in response to product holds, discontinuations for other reasons, or IoR discretion, can be found in the table below. Study product retrieval may occur either by the participant returning the unused Truvada tablets or VR (used and unused) to study staff within the specified timeframe or by study staff conducting outreach to retrieve the product from the participant (e.g., at her home).

If study product is not returned within the time frames outlined below for permanent discontinuations or temporary holds, the MTN-043 PSRT must be notified.

Table 2: 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 business days
Temporary hold for reasons other than pregnancy with expected duration of at least 7 days	Within 7 business 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 tablets remaining in the participant's possession should be retrieved at the PUEV (Month 3 visit). If the participant does not bring her study product to this visit, study staff must arrange to retrieve it within five business days. Attempts to retrieve study product are to be documented.

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 and Practices

The use of PEP and PrEP is prohibited outside the context of study participation. Individuals who need PEP or PrEP due to known or potential HIV exposure will permanently discontinue study product use. See Section 9.3 for additional information.

6.8 Condoms

All mothers will be offered male 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 visits and evaluation 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 are provided in the *MTN-043 SSP Manual* available at https://www.mtnstopshiv.org/research/studies.

Figure 2: **Study Visit Schedule**

7.1 Pre-Screening

As part of participant outreach and recruitment strategies, study staff may sensitize and pre-screen potential study participants at either on-site or at off-site locations including antenatal care clinics and in the postnatal wards before the mother is discharged after delivery. Study staff may consult with their local IRBs/ECs regarding pre-screening pregnant and potentially breastfeeding mothers and their infants. 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.

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.

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. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined. Participants who fail their first screening attempt may be re-screened once.

Table 3: Visit 1 – Screening Visit - Mothers

Visit 1 – Screening Visit - Mothers		
Component		**Procedures**
Administrative and Regulatory		• Obtain informed consent for screening and enrollment^ • Obtain signed medical records release and pediatric care provider information • Assign a unique Participant Identification (PTID) Number • Assess eligibility • Collect demographic information • Collect locator information • Provide reimbursement • Schedule next visit*
Behavioral/Counseling		• HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Contraception counseling
Clinical		• Review medical history • Infant feeding assessment • Review concomitant medications and vaginal products • Physical exam • Pelvic exam • Treat RTI/UTI/STIs* • Disclose available test results
Laboratory	**Urine**	• Urine dipstick and/or culture* • Pregnancy test
	Blood	• HIV-1 testing • HBsAg • AST/ALT • Creatinine clearance • Complete blood count (CBC) with platelets • Syphilis serology
	Pelvic	• Nucleic acid amplification test (NAAT) for *Neisseria gonorrhoeae* (GC)/*Chlamydia trachomatis* (CT)/*Trichomonas vaginalis* (TV) • Wet prep/potassium hydroxide (KOH) wet mount for candidiasis and/or BV* • Vaginal pH*

Visit 1 – Screening Visit - Mothers	
Component	**Procedures**
Study Product/Supplies	• Offer male condoms

^ Informed consent can be separate or combined for Screening & Enrollment; depending upon site criteria
* If indicated and/or per local standard of care

Table 4: Visit 1 – Screening Visit - Infants

Visit 1 – Screening Visit - Infants	
Component	**Procedures**
Administrative and Regulatory	• Obtain informed consent for screening and enrollment^ • Assign a unique Participant Identification (PTID) Number • Assess eligibility • Collect demographic information
Clinical	• Review pediatric care records▲ • Review medical history • Review concomitant medications • Physical exam, including weight

^ Informed consent can be separate or combined for Screening & Enrollment; depending upon site criteria
▲ Review pediatric care records as available once all required permissions have been obtained

7.3 Visit 2: Enrollment Visit (Day 0)

The Enrollment Visit must be completed within 35 days of the Screening Visit. Enrollment for the mother and infant must occur at the same visit.

Table 5: Visit 2 – Enrollment Visit - Mothers

Visit 2 – Enrollment Visit - Mothers	
Component	**Procedures**
Administrative and Regulatory	• Re-assess and confirm eligibility • Review/confirm informed consent • Randomization • Review/update locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling	• Baseline behavioral assessment • Product acceptability assessment • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol adherence counseling • Contraception counseling
Clinical	• Review/update medical history • Infant feeding assessment • Review/update concomitant medications and vaginal products • Targeted physical exam • Pelvic exam • Treat RTI/UTI/STIs▼ • Disclose available test results

Visit 2 – Enrollment Visit - Mothers		
Component		**Procedures**
Laboratory	**Urine**	• Urine dipstick and/or culture* • Pregnancy test
	Blood	• HIV-1 testing • Syphilis serology* • Plasma archive • Dried blood spot (DBS) for baseline FTC-TP & TFV-DP drug levels (DPV & Truvada groups)
	Pelvic	• NAAT for GC/CT/TV* • Wet prep/KOH wet mount for candidiasis and/or BV* • Vaginal pH* • Vaginal swab(s) for microbiota • Vaginal Gram stain • Vaginal swab(s) for biomarkers
Study Product/Supplies		• Provide study VR or study tablets • Insertion of study VR at the clinic (clinician to check VR placement) or DOD of first study tablet • Provide product use instructions • Offer male condoms

* If indicated and/or per local standard of care
▼ Enrollment delayed until symptoms resolved if treatment is indicated

Table 6: Visit 2 – Enrollment Visit - Infants

Visit 2 – Enrollment Visit - Infants	
Component	**Procedures**
Administrative and Regulatory	• Re-assess and confirm eligibility • Review/confirm informed consent
Clinical	• Review/update medical history • Review pediatric care records • Review/update concomitant medications • Targeted physical exam

* If indicated and/or per local standard of care

7.4 Follow-up Visits

7.4.1 Visits 3 and 4 (1- and 2-week Visits)

These visits will occur one week (i.e., approximately 7 days) and two weeks (i.e., approximately 14 days) following Enrollment. These visits can occur no earlier than two days before the target date and no later than two days following the target date.

Table 7: Visits 3 and 4 (1- and 2-week Visits) - Mothers

Visits 3 and 4 (1 and 2-week Visits) - Mothers	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement • Schedule next visit/contact

Visits 3 and 4 (1 and 2-week Visits) - Mothers		
Component		**Procedures**
Behavioral/Counseling		• Behavioral assessment • Product acceptability assessment • HIV pre- and post-test counseling* • HIV/STI risk reduction counseling* • Contraception counseling* • Protocol adherence counseling • Social harms assessment
Clinical		• Review/update medical history • Review/update concomitant medications and vaginal products • Infant feeding assessment • Targeted physical exam* • Pelvic exam* • Collect AEs • Treat RTI/UTI/STIs* • Disclose available test results
Laboratory	**Urine**	• Urine dipstick and/or culture* • Pregnancy test*
	Blood	• HIV-1 testing* • AST/ALT* • Creatinine clearance* • CBC with platelets* • Syphilis serology* • Plasma for DPV drug levels (DPV group) • DBS for FTC-TP and TFV-DP drug levels (Truvada group)
	Breast milk	• Breast milk for DPV drug levels (DPV group) • Breast milk for FTC & TFV drug levels (Truvada group)
	Pelvic	• NAAT for GC/CT/TV* • Wet prep/KOH wet mount for candidiasis and/or BV* • Vaginal pH*
Study Product/Supplies		• Offer male condoms

* If indicated and/or per local standard of care

Table 8: Visits 3 and 4 (1- and 2-week Visits) - Infants

Visits 3 and 4 (1 and 2-week Visits) - Infants	
Component	**Procedures**
Clinical	• Review/update medical history • Review pediatric care records • Review/update concomitant medications • Targeted physical exam* • Collect AEs

Visits 3 and 4 (1 and 2-week Visits) - Infants		
Component		**Procedures**
Laboratory	**Blood**	• Plasma for DPV drug levels (V4) (DPV group) • DBS for FTC-TP & TFV-DP drug levels (V4) (Truvada group)

* If indicated and/or per local standard of care

7.4.2 Visits 5 and 6 (1-month and 2-month Visits)

These visits will occur one month and two months (i.e., approximately 28 and 56 days, respectively) following enrollment. For both Visit 5 and 6, the visit can occur no earlier than 7 days before the target date and no later than 7 days following the target date.

Table 9: Visits 5 and 6 (1-month and 2-month Visits) - Mothers

Visits 5 and 6 (1-month and 2-month Visits) - Mothers		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• Behavioral assessment • Product acceptability assessment • Social harms assessment • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol adherence counseling • Contraception counseling
Clinical		• Review/update medical history • Review/update concomitant medications and vaginal products • Infant feeding assessment • Targeted physical exam* • Pelvic exam* • Collect AEs • Treat RTI/UTI/STIs* • Disclose available test results
Laboratory	**Urine**	• Urine dipstick and/or culture* • Pregnancy test*
	Blood	• HIV-1 testing • AST/ALT* • Creatinine clearance* • CBC with platelets* • Syphilis serology* • Plasma for DPV drug levels (DPV group) • DBS for FTC-TP and TFV-DP drug levels (Truvada group)
	Breast milk	• Breast milk for DPV drug levels (DPV group) • Breast milk for FTC & TFV drug levels (Truvada group)

Visits 5 and 6 (1-month and 2-month Visits) - Mothers		
Component		**Procedures**
	Pelvic	• NAAT for GC/CT/TV* • Wet prep/KOH wet mount for candidiasis and/or BV* • Vaginal pH*
	Study Product	• Adherence assessment: Returned study VR
Study Product/Supplies		• Remove and/or collect study VR or unused study tablets • Provide study VR or study tablets • Provide product use instructions • Insertion/removal of study VR at the clinic (clinician to check VR placement, as needed) • Offer male condoms

* If indicated and/or per local standard of care

Table 10: Visits 5 and 6 (1-month and 2-month Visits) - Infants

Visits 5 and 6 (1-month and 2-month Visits) - Infants		
Component		**Procedures**
Clinical		• Review pediatric care records • Review/update medical history • Review/update concomitant medications • Targeted physical exam* • Collect AEs
Laboratory	**Blood**	• Plasma for DPV drug levels (DPV group) • DBS for FTC-TP & TFV-DP drug levels (Truvada group)

* If indicated and/or per local standard of care

7.4.3 Visit 7 - Product Use End Visit (PUEV) 3-month Visit

The Visit 7, PUEV, will occur three months (i.e., approximately 84 days) following enrollment. This visit can occur no earlier than 7 days before the target date and no later than 7 days following the target date.

Table 11: Visit 7 PUEV Visit (3-Month Visit) - Mothers

Visit 7 PUEV (3-Month Visit) - Mothers	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling	• Behavioral assessment • Product acceptability assessment • Social harms assessment • In-depth interview (IDI) (subset)♦ • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol adherence counseling • Contraception counseling

Visit 7 PUEV (3-Month Visit) - Mothers		
Component		**Procedures**
Clinical		• Review/update medical history • Infant feeding assessment • Review/update concomitant medications and vaginal products • Targeted physical exam • Pelvic exam • Collect AEs • Treat RTI/UTI/STIs* • Disclose available test results
Laboratory	**Urine**	• Urine dipstick and/or culture* • Pregnancy test
	Blood	• HIV-1 testing • AST/ALT • Creatinine clearance • CBC with platelets • Syphilis serology* • Plasma for DPV drug levels (DPV group) • DBS for FTC-TP & TFV-DP drug levels (Truvada group)
	Breast milk	• Breast milk for DPV drug levels (DPV group) • Breast milk for FTC & TFV drug levels (Truvada group)
	Pelvic	• NAAT for GC/CT/TV* • Wet prep/KOH wet mount for candidiasis and/or BV* • Vaginal pH* • Vaginal swab(s) for microbiota • Vaginal Gram stain • Vaginal swab(s) for biomarkers
	Study Product	• Adherence assessment: Returned study VR
Study Product/Supplies		• Removal and collection of study VR or unused study tablets • Offer male condoms

♦ May be scheduled any time between PUEV and SEV
* If indicated and/or per local standard of care

Table 12: Visit 7 PUEV (3-Month Visit) - Infants

Visit 7 PUEV (3-Month Visit) - Infants		
Component		**Procedures**
Clinical		• Review/update medical history • Review pediatric care records • Review/update concomitant medications • Targeted physical exam • Collect AEs
Laboratory	**Blood**	• Plasma for DPV drug levels (DPV group) • DBS for FTC-TP & TFV-DP drug levels (Truvada group)

7.4.4 Visit 8 – Study Exit Visit (SEV) - Two weeks after PUEV

The Visit 8, Study Exit Visit (SEV) will occur two weeks (i.e., approximately 14 days) after the PUEV. This visit can occur no earlier than 7 days before the target data and no later than 14 days after the PUEV.

Table 13: Visit 8 – SEV (2 weeks after PUEV) - Mothers

Visit 8 – SEV (2 weeks after PUEV) - Mothers		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling		• Social harms assessment • HIV pre- and post-test counseling • HIV/STI risk reduction counseling* • Contraception counseling • PrEP counseling
Clinical		• Review/update medical history • Review/update concomitant medications and vaginal products • Targeted physical exam* • Pelvic exam* • Collect AEs • Treat RTI/UTI/STIs* • Disclose available test results
Laboratory	**Urine**	• Urine dipstick and/or culture* • Pregnancy test*
	Blood	• HIV-1 testing* • AST/ALT* • Creatinine clearance* • CBC with platelets* • Syphilis serology* • Plasma for DPV drug levels (DPV group) • DBS for FTC-TP & TFV-DP drug levels (Truvada group)
	Breast milk	• Breast milk for DPV drug levels (DPV group) • Breast milk for FTC & TFV drug levels (Truvada group)
	Pelvic	• NAAT for GC/CT/TV* • Wet prep/KOH wet mount for candidiasis and/or BV* • Vaginal pH*
Study Product/Supplies		• Offer male condoms

* If indicated and/or per local standard of care

Table 14: Visit 8 – SEV (2 weeks after PUEV) - Infants

Visit 8 – SEV (2 weeks after PUEV) - Infants		
Component		**Procedures**
Clinical		• Review/update medical history • Review pediatric care records • Review/update concomitant medications • Targeted physical exam* • Collect AEs
Laboratory	**Blood**	• Plasma for DPV drug levels (DPV group) • DBS for FTC-TP & TFV-DP drug levels (Truvada group)

If a participant mother and/or infant should leave the study prior to completion of the required study visits, the following study procedures will be conducted if the participant is willing for herself and/or for her infant at the Early Termination Visit:

Table 15: Early Termination Visit - Mothers

Early Termination Visit - Mothers		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling		• Behavioral assessment • Product acceptability assessment • Social harms assessment • In-depth interview (IDI) (subset) • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Contraception counseling • PrEP counseling
Clinical		• Review/update medical history • Infant feeding assessment • Review/update concomitant medications and vaginal products • Targeted physical exam • Pelvic exam • Collect AEs • Treat RTI/UTI/STIs* • Disclose available test results
Laboratory	**Urine**	• Urine dipstick and/or culture* • Pregnancy test
	Blood	• HIV-1 testing • AST/ALT • Creatinine clearance • CBC with platelets • Syphilis serology* • Plasma for DPV drug levels (DPV group) • DBS for FTC-TP & TFV-DP drug levels (Truvada group)

Early Termination Visit - Mothers		
Component		**Procedures**
	Breast milk	• Breast milk for DPV drug levels (DPV group) • Breast milk for FTC & TFV drug levels (Truvada group)
	Pelvic	• NAAT for GC/CT/TV* • Wet prep/KOH wet mount for candidiasis and/or BV* • Vaginal pH* • Vaginal swab(s) for microbiota • Vaginal Gram stain • Vaginal swab(s) for biomarkers
	Study Product	• Adherence assessment: Returned study VR
Study Product/Supplies		• Removal and collection of study VR or unused study tablets • Offer male condoms

* If indicated and/or per local standard of care

Table 16: Early Termination Visit - Infants

Early Termination Visit - Infants		
Component		**Procedures**
Clinical		• Review/update medical history • Review pediatric care records • Review/update concomitant medications • Targeted physical exam • Collect AEs
Laboratory	**Blood**	• Plasma for DPV drug levels (DPV group) • DBS for FTC-TP & TFV-DP drug levels (Truvada group)

7.5 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 temporary and permanent discontinuation of study product, including additional information regarding consultation with the PSRT, is included in Section 9.3.

7.5.1 Participants Who Become Infected with HIV

If a mother or an infant acquires HIV-1 after the Enrollment Visit, they will be referred to local services that have capacity to provide comprehensive HIV care and treatment. If a mother seroconverts on study, her infant will have an additional visit 12 weeks after seroconversion is diagnosed, as stated below. Protocol-specified procedures for the monthly study visits for the mother or the infant will continue except the following:

- HIV-1 testing
- Provision of study product VR or tablets, provision of product use instructions, and retrieval and collection of study VR or 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 on the mother regardless of whether 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

Per the algorithm in Appendix IV, upon confirmation of HIV infection of the mother, 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.
- HIV-1 genotyping will be performed on the stored plasma closest to the time of confirmed HIV-1 infection. It may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center (LC).

Upon confirmation of maternal HIV infection, the following procedures are performed on the infant at the following timepoints:

- Either HIV-1 RNA PCR or DNA PCR (Standard of Care) will be performed at the clinic visit immediately following confirmation of the maternal HIV infection and 12 weeks later.
- Upon confirmation of infant HIV infection:
    - Repeat HIV-1 RNA PCR test and do HIV-1 genotyping. HIV-1 genotyping may be performed at additional/alternate time points as requested by site IOR or at the discretion of the LC.
    - Facilitate rapid referral of the infant for appropriate further management including necessary blood tests (CD4+ T cell count, FBC), urgent ART initiation, and adherence counselling and follow -up for the mother/guardian.

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

Infants whose mothers become infected with HIV while breastfeeding are at high risk for HIV acquisition. All women diagnosed with HIV during study participation will be counseled per national guidelines regarding immediate initiation of maternal ART with or without cessation of breastfeeding. The potential of infant prophylaxis will also be discussed if applicable. The women will be immediately referred for HIV treatment and long-term care as indicated above. Infant HIV testing and referral for care will also be performed as detailed above.

7.5.2 Participants Who Become Pregnant

Participant mothers will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

A participant who becomes pregnant during study participation will have study product discontinued and will be terminated from the study. Upon documentation of the pregnancy, the following procedures must be performed regardless of whether they are scheduled to be completed:

- CBC with platelets
- AST/ALT
- Collection of drug level and biomarker specimens
- Behavioral and product acceptability assessments

A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained).The study site will make every reasonable effort to contact participants and collect infant outcome data at approximately one year after delivery for those pregnancies that result in a live birth. Pregnancy and infant outcomes will be reported on relevant CRFs; outcomes meeting criteria for EAE reporting also will be reported on EAE forms. For additional details regarding obtaining pregnancy and infant outcomes, please reference the *MTN-043 SSP Manual*.

7.5.3 Participants Who Permanently Discontinue Study Product Use for Reasons other than Seroconversion or Pregnancy

Participants who permanently discontinue study product use for any reason (clinician-initiated or self-initiated) other than seroconversion or pregnancy will continue follow-up visits with a modified study visit/procedure schedule until their originally scheduled study exit date. Infants of participants who are permanently discontinued from study product use will also continue follow-up visits with a modified study visit/procedure schedule until their originally scheduled study exit date. Additional details of the modified visits can be found in the *MTN-043 SSP Manual*.

Upon documentation of the product discontinuation, the following procedures must be performed regardless of whether 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
- Behavioral and product acceptability assessments

7.5.4 Participants Who Temporarily Hold Study Product Use

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

- Provision of study VR or study tablets, 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 they were scheduled; however, they are to be discontinued at subsequent visits.

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

7.6 Participants who Discontinue Breastfeeding

Mothers who discontinue breastfeeding (e.g., due to decision to wean) will continue to receive study product and will continue with all regularly scheduled visits for the duration of their originally

scheduled participation in MTN-043. Reasons for discontinuation of breastfeeding will be captured on CRFs.

Infants of mothers who report complete discontinuation of breastfeeding will discontinue drug detection procedures and remain in follow-up for the duration of their originally scheduled participation in MTN-043.

7.7 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 visits 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 Section 8 and Section 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.
- 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. Information regarding the study visit windows are provided in the *MTN-043 SSP Manual* available at https://www.mtnstopshiv.org/research/studies.

7.8 Final Contact

Since participant mothers' final study visit (two weeks after end of study product exposure) includes laboratory testing for HIV (as indicated) and other conditions, and PrEP counseling based on the current country policies and availability of PrEP, 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 Counseling

HIV testing and risk reduction counseling will be provided to all participant mothers upon study screening and any time HIV testing is conducted during follow-up. When applicable, PrEP counseling based on current country policies and availability of PrEP at the time of counseling will be provided. Contraception counseling will be provided to all participant mothers starting at

Screening Visit and throughout the study. Protocol adherence counseling, including product use adherence counseling during the product use period, will be provided to all participant mothers upon enrollment into the study. 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 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.

7.10 Drug Detection and Biomarker Collection

The mother-infant pairs will provide specimens for drug detection and biomarkers throughout this study. At Visit 2, all mothers will provide DBS for FTC-TP and TFV-DP. Following enrollment, mother and infant drug detection will be stratified by study product assignment as specified in Table 17 and Table 18 below. Vaginal swabs for microbiota and biomarkers will be collected from mothers at Visit 2, Visit 7 and the Early Termination Visit. Details on blood sampling procedures for mothers and infants, inclusive of capillary/venous blood usage for DBS procedures, as per site procedures, will be included in the *MTN-043 SSP Manual*.

Table 17: Drug Detection and Biomarkers Specimen Collection Schedule – Mothers

Visit	Specimens Collected for Drug Detection	Specimens Collected for Microbiota & Biomarkers
Visit 2 – Enrollment	• DBS for FTC-TP & TFV-DP (DPV & Truvada groups)	• Vaginal swab for microbiota • Vaginal swab for biomarkers • Vaginal swab for Gram stain
Visit 3 – Week 1 Visit 4 – Week 2	• Plasma for DPV (DPV group) • Breast milk for DPV (DPV group) • DBS for FTC-TP and TFV-DP (Truvada group) • Breast milk for FTC and TFV (Truvada group)	
Visit 5 – Month 1 Visit 6 – Month 2 Visit 7 – Month 3 (PUEV) Visit 8 – 2 weeks after PUEV (SEV) Early Termination	• Plasma for DPV (DPV group) • Breast milk for DPV (DPV group) • DBS for FTC-TP and TFV-DP (Truvada group) • Breast milk for FTC and TFV (Truvada group)	• Vaginal swab for microbiota* • Vaginal swab for biomarkers* • Vaginal swab for Gram stain*

* Visit 7 and Early Termination Visit only

Table 18: Drug Detection and Biomarkers Specimen Collection Schedule – Infants

Visit	Specimens Collected for Drug Detection	Specimens Collected for Microbiota & Biomarkers
Visit 4 – Week 2 Visit 5 – Month 1 Visit 6 – Month 2 Visit 7 – Month 3 (PUEV) Visit 8 – 2 weeks after PUEV (SEV) Early Termination	• Plasma for DPV (DPV group) • DBS for FTC-TP and TFV-DP (Truvada group)	_____

7.11 Behavioral Evaluations

Behavioral endpoints will be assessed via CRFs with all participants. A short Baseline Behavioral Questionnaire will be administered in the clinic at the Enrollment Visit to all participants. All mothers will be asked questions about sexual behavior, 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 breastfeeding, and other preliminary acceptability measures of the study product. At Week 1 and Week 2 visits, mothers will be asked to complete a brief assessment about their experiences using the study product, including reasons for non-use, if applicable, willingness to use in the future, and any perceived effect on the infant. Mothers will also complete the Follow-up Behavioral Questionnaire at the monthly visits afterwards.

In-depth interviews (IDIs) will also be conducted with a subset of participants at the PUEV. All IDIs will be conducted by trained and experienced interviewers 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.

7.12 Clinical Evaluations and Procedures

Physical exams of the mothers will include the following assessments:

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

- Lungs*
- Extremities*
- Skin*
- Neurological*

**May be omitted after the Screening Visit.*

Physical exams of infants will include the following assessments (including assessment for and documentation of any anomalies):

- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- General appearance
- Weight
- Length
- Head circumference
- Heart
- Lungs
- Abdomen*
- Head, eye, ear, nose and throat (HEENT)*
- Lymph nodes*
- Neck*
- Extremities*
- Skin*
- Neurological*
- Ages and Stages® assessment

**May be omitted after the Screening 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*, at http://www.who.int/iris/handle/10665/69748.

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 examination.

The required sequence of procedures and specimen collection performed during pelvic exams will be specified in the *MTN-043 SSP Manual*.

7.13 Laboratory Evaluations

Local Laboratory

- Urine
  - Dipstick and/or culture, if indicated or per local standard of care
  - Pregnancy test

- 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
  - HBsAg

- Pelvic
  - NAAT for GC/CT/TV
  - Vaginal pH
  - Wet prep/KOH wet mount for candidiasis and/or BV

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
  - HIV-1 drug resistance

- Breast Milk
  - FTC and TFV concentrations
  - DPV concentrations

- Pelvic
  - Vaginal Gram stain
  - Vaginal swabs for microbiota
  - Vaginal swabs for biomarkers

Designated Laboratory:

- VR for residual DPV levels

Once all required study analyses of collected specimens are complete, any remaining sample 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.

7.14 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-043 SSP Manual,* https://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* at
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.

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 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 product” 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.

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 vulvovaginal candidiasis.
- 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.
- Weight loss that is judged by the clinician to be within the range normally anticipated in the postnatal period.
- Vaginal bleeding that is judged by the clinician to be within the range normally anticipated in the postnatal period.

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 identified 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 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. 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).

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 are available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

8.4.4 Expedited Adverse Event 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. If 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-043 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 ≥ Grade 2 creatinine clearance (for Truvada group only).
- Confirmation of ≥ Grade 2 glycosuria or proteinuria (for Truvada group only).
- Allergic reaction to the study product.

- Reported use of PrEP for HIV prevention outside of the study.
- Reported use of PEP for potential HIV exposure.
- Non-therapeutic injection drug use.
- Pregnancy.

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.
- 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

Study product may be held per IoR/designee discretion for any reason. In these instances, the IoR/designee should notify the PSRT.

The following outlines product use considerations for observed adverse events. Except for deep epithelial disruption, study product use will depend on the adverse event grade and relations to study product.

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.

Grade 1 or 2

In general, a mother or infant who develops a Grade 1 or 2 AE, regardless of relatedness to study product, may continue product use.

Grade 3

Mothers who develop a Grade 3 AE that is judged by the IoR/designee to be not related to study product may continue product use.

In general, for mothers who develop a Grade 3 AE 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 two weeks.
- Resume study product if improvement to ≤ Grade 2 is documented within two weeks.
- Consult PSRT regarding further study product management if improvement to severity ≤ Grade 2 cannot be documented within two 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.

Mothers whose infant develop a Grade 3 AE (regardless of relationship to study product) should have their study product held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT.

Grade 4

Mothers who develop a Grade 4 AE (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.

Mothers whose infant develop a Grade 4 AE (regardless of relationship to study product) should have their study product held. The IoR/designees must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT.

9.5 HIV Infection

A participant mother 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 (See Section 7.5.1). Participants identified as infected with HIV and their infants, if also infected with HIV, are managed or referred for management according to the standard of care of test and treat guidelines.

The care provided at the referral sites should be 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 through breastfeeding. Written SOPs for referral for HIV care and treatment will be in place at each study site at study start and site investigators will be encouraged to identify 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 breastfeeding mothers and their infants 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.

9.6 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 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., US, local, and international 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. Study staff members will record the reason(s) for all withdrawals in participants' study records. If participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date, pending consultation with the PSRT.

10 ANALYTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

The MTN-043 study is a Phase 3b, randomized, open-label, multi-site, mother-infant pair study, with 12 weeks of planned exposure to the DPV VR (25 mg) or oral Truvada tablet (200 mg FTC/300 mg TDF). Two hundred mother-infant pairs will be randomized to the above study products in a 3:1 ratio (VR: tablet). Mothers randomized to the DPV VR will use VR to be replaced each month for approximately 12 weeks. Mothers using Truvada tablet will take one tablet orally daily for approximately 12 weeks.

10.2 Study Endpoints

10.2.1 Primary Endpoints

Maternal safety (composite)

- All SAEs including maternal deaths in both study arms
- 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, Correct Version 2.1, July 2017* and/or *Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])* in both study arms

Infant safety (composite)

- All SAEs including infant deaths in both study arms
- 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* in both study arms

Drug detection

- Maternal plasma DPV concentrations
- Maternal blood FTC-TP and TFV-DP concentrations
- Maternal breast milk DPV concentrations
- Maternal breast milk FTC and TFV concentrations
- Infant plasma DPV concentrations
- Infant blood FTC-TP and TFV-DP concentrations

10.2.2 Secondary Endpoints

Adherence

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

Acceptability

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

10.2.3 Exploratory Endpoints

Expanded Acceptability

- Self-reported experiences with study products and preferences for product attributes
- Self-reported attitudes about study products and perceived attitudes of key influencers (e.g., male partners, family members, providers)

Genital Microenvironment

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

Breastfeeding

- Duration of breastfeeding and reasons for weaning (if weaning occurs during participation)
- Timing and type of infant supplementation

10.3 Primary Study Hypotheses

It is hypothesized that:

- Maternal exposure to study products will be safe for mothers and their breastfeeding infants.
- DPV will be detectable at low levels in breast milk of participant mothers using the VR.
- FTC and TFV will be detectable at low levels in breast milk of participant mothers taking Truvada.

- DPV will be detectable in the blood of some breastfeeding infants.
- FTC-TP and/or TFV-DP will be detectable in the blood of some breastfeeding infants.

10.4 Sample Size and Power Calculations

The proposed sample size is 200 mother-infant pairs randomized 3:1 to vaginal ring vs oral Truvada.

10.5 Primary Endpoints

Maternal safety and Infant safety

To characterize the statistical properties of this study, Table 19 below presents the probability of observing zero, at least one, ten or more and fifty or more safety endpoints in each arm for various "true" event rates, ranging from low to high:

Table 19: 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=150	n=50	n=150	n=50	n=150	n=50	n=150	n=50
1%	22.15	60.50	77.85	39.50	8.94	0.00	0.00	0.00
5%	0.05	7.69	99.95	92.31	72.06	0.00	0.00	0.00
10%	0.00	0.52	100.00	99.48	96.62	0.94	0.00	0.00
15%	0.00	0.03	100.00	99.97	99.71	11.99	0.00	0.00
25%	0.00	0.00	100.00	100.00	99.99	73.78	0.85	0.00

[a] Sample sizes in the table based on the proposed cohort sizes and study design. With 3:1 randomization, there will be 150 participants in the VR arm and 50 participants in the FTC-TDF 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 20 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 150 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 2.43%.

Table 20: 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	
	n=50	n=150
0	0.00, 7.11	0.00, 2.43
1	0.05, 10.65	0.02, 3.66
2	0.49, 13.71	0.16, 4.73
3	1.25, 16.55	0.41, 5.73
4	2.22, 19.23	0.73, 6.69
5	3.33, 21.81	1.09, 7.61
6	4.53, 24.31	1.48, 8.5
8	7.17, 29.11	2.33, 10.24
10	10.03, 33.72	3.24, 11.92
12	13.06, 38.17	4.2, 13.56
15	17.86, 44.61	5.71, 15.96
20	26.41, 54.82	8.34, 19.84
30	45.18, 73.59	13.92, 27.3

[a] Sample sizes in the table based on the proposed cohort sizes and study design.

Maternal safety (composite)

- All SAEs including maternal deaths in both study arms
- 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, Correct Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])* in both study arms

Infant safety (composite)

- All SAEs including the infant deaths and in both study arms
- 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* in both study arms

Drug detection

The tables above can also inform the hypotheses around drug detection where number of events is the number of participants with detectable drug levels.

10.6 Participant Accrual, Follow-up and Retention

Time to complete accrual will be approximately 4 - 6 months (16 - 26 weeks). Each enrolled mother-infant pair will be followed for approximately three and a half months (14 weeks). If a mother seroconverts while on study, the infant will have an additional visit, 12 weeks after seroconversion is diagnosed, for additional HIV testing.

10.7 Randomization

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

10.8 Data and Safety Monitoring Procedures

No DSMB oversight is planned for this study. The MTN-043 Management Team will review study progress, including rates of participant accrual, retention, completion of primary and secondary endpoint assessments, and study or laboratory issues on monthly calls and make recommendations to resolve any issues identified during those reviews. Safety monitoring will be done by the PSRT.

10.8.1 Statistical 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). To assess the adequacy of the randomization, participants in each of the two arms will be compared for baseline characteristics including demographics and laboratory measurements using descriptive statistics. No formal statistical comparisons will be performed.

10.8.2 Primary Analyses

An intent to treat analysis will be performed to summarize the frequency of primary endpoints (maternal safety, infant safety and drug detection) by study arm. A secondary analysis will be conducted including only visits in which a participant has been exposed to the study product. Consistent with the primary objectives to describe the safety profile and drug detection in each arm, 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. A secondary analysis will be performed to summarize the total number of primary and secondary safety endpoints reported per participant by study arm.

10.8.3 Analysis of Secondary Endpoints

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

Acceptability: To assess acceptability of the study products, information about acceptability 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 product 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.

10.8.4 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. Sensitivity analyses will be conducted comparing the regimens using only the first study product use period data for all the outcomes.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents. Study data is entered into the electronic CRFs in the MTN-043 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 Research Triangle Institute (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 Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf).

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 *Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites* https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf.

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 visit the site to do the following:

- 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.

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, OHRP, site IRBs/ECs, 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, as per the site's Informed Consent Process SOP. Before beginning the study, the IoR will have obtained IRB/EC approval and the protocol will have been submitted to the FDA. The IoR/designee will permit audits by the NIH, IPM, the FDA, OHRP, any of their appointed agents, site IRBs/ECs, and other local, US, and international regulatory entities.

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 (RE). 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 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.

Study implementation will also be guided by the *MTN-043 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 MTN-043 Management Team.

13.4 Risk Benefit Statement

13.4.1 Risks

General
It is not expected that this study will expose human subjects to unreasonable risk, including both participant mothers and infants.

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. Using a breast pump and/or hand expression of milk may lead to discomfort, but pumping and/or hand expression should never be painful, result in sore or irritated nipples, or cause bleeding. 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 discharge from the vagina; pain, burning, or itchiness in the vagina; vaginal bleeding in between usual periods; and urinary traction infection. Less common side effects include pelvic inflammatory disease, cervix erythema, cervix edema, cervicitis, urinary incontinence, dyspareunia, headache, decreased neutrophil count, abnormal weight loss, and dysmenorrhea. 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. In the first study of dapivirine exposure during lactation, MTN-029, 16 healthy women were enrolled who had already weaned their infants but were still able to express breast milk. In this study, dapivirine VR use was associated with lower concentrations of detectable dapivirine in milk and plasma as compared to CVF, and a favorable safety profile in lactating women. No prospective data is available for DPV VR use for breastfeeding infants and therefore there may be some risk to breastfeeding infants from their mother using a product whose full safety profile is unknown. However, the maternal benefits of using this HIV prevention method are anticipated to outweigh the risks for the breastfeeding infants targeted for this study, who live in regions with high HIV incidence.

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 selection of NNRTI resistance has not been observed in clinical research studies.

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.[13]

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

The use of antiretroviral drug combinations may lead to changes in body fat, some of which include: increased fat at the waist and stomach area; increased fat on back of the neck; thinning of face, legs and arms; and breast enlargement.

Available data for Truvada tablet use during lactation/breastfeeding by HIV-negative women is reassuring. Breastfeeding benefits of using this HIV prevention method are anticipated to outweigh the risks for the breastfeeding women targeted for this study and their infants, who live in regions with high HIV incidence.

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

DPV VR as tested in MTN-020 (ASPIRE) and IPM 027 (The Ring Study) was well-tolerated and showed a ~30% risk reduction of HIV-1 infection and is being considered for potential regulatory approval. Furthermore, Truvada is an FDA and EMA approved 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 safe and effective interventions to prevent HIV acquisition in breastfeeding women. Participants may also appreciate the opportunity to contribute to the field of HIV prevention research.

Participant mothers will receive HIV/STI risk reduction counseling, HIV and STI testing, physical

examination, pelvic examination, and routine laboratory testing. Contraceptives will also be available to participating mothers. Maternal 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. Routine postnatal and infant care 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.

Participant infants will receive direct benefit via their mother's access to HIV prevention interventions during the study. Mothers who use oral PrEP or the dapivirine vaginal ring as prescribed have a reduced likelihood of acquiring HIV if the mothers are exposed to HIV during the postpartum period, a period of increased susceptibility to HIV infection. Averting maternal infection in the postpartum period benefits the infant as mothers who acquire HIV during the postpartum period are more likely to transmit HIV to their infant during this time. Additionally, infant monitoring through feeding assessments and targeted physical examinations may lead to early referrals for potential health issues. Infants may also benefit from counseling that participant mothers receive on breastfeeding and appropriate timing of complementary feeding.

13.5 Informed Consent Process

Written informed consent will be obtained from all participants as per US, international and local regulations and sites' Informed Consent Process SOP. Informed consent is required prior to initiation of MTN-043 procedures. Written informed consent also will 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, US and other international 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 Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials https://www.niaid.nih.gov/sites/default/files/sourcedocappndx.pdf and the site's Informed Consent Process SOP. 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-043 SSP Manual*.

The informed consent process will cover all elements of informed consent as required by the OHRP, applicable local research regulations and the site's Informed Consent Process SOP. 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-043 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-043 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

Women who test positive for pregnancy at the Screening or Enrollment Visit will not be eligible to participate in this study. Should a participant test positive for pregnancy after Enrollment, study product will be discontinued. Participant will be discontinued from the study per Section 7.5.2. During the informed consent process, participants will be informed that the study VR and tablets are not effective methods of contraception and that evidence on the effects of the study drugs on a developing human fetus in HIV negative populations is limited.

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-043 study products and procedures, the MTN-043 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 46.405, children may be involved in research of greater than minimal risk but presenting the prospect of direct benefit to the individual subjects, or by a monitoring procedure that is likely to contribute to the subject's well-being, if all 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 mother and infant participants. The products being used in this study have been shown to be safe and effective in adults when used as instructed, but the DPV VR has not been approved in the countries where the implementation of this study is planned, and Truvada for oral PrEP has not yet been made widely accessible in these countries. Infant participants may receive a direct benefit from the study's monitoring procedures (e.g., counseling the mother for PrEP adherence to prevent HIV acquisition which in turn reduces the risk of the infant acquiring HIV from breastfeeding, and infant monitoring such as infant feeding assessments and targeted physical exams that may lead to early referral for issues and rapid referral for HIV management if necessary). Therefore, this research holds out the prospect of direct benefit to the health and well-being of both adult and infant MTN-043 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-043 participation is acceptable for a safety study of HIV chemoprevention products, which are not currently available to breastfeeding 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-043 will follow an IRB/EC-approved informed consent process as part of enrollment procedures for the breastfeeding participants at the time of enrollment for this study, as verified per site SOPs, as well as their infants.

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 because 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 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 participant mothers 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 9.5.

13.11 Study Discontinuation

This study may be discontinued at any time by NIH, the MTN, IPM, Gilead Sciences, Inc., the US FDA, the US OHRP, other local or international 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	Visits 3,4 (Week 1, 2)	Visits 5, 6 (Month 1, 2)	Visit 7 (Month 3 PUEV)	Visit 8 SEV (2 weeks after PUEV)	Early Termination Visit
ADMINISTRATIVE AND REGULATORY							
Obtain/confirm informed consent	^	X					
Assess and/or confirm eligibility	X	X					
Collect demographic information	X						
Randomization		X					
Collect/review/update locator information	X	X	X	X	X	X	X
Assign a unique PTID number	X						
Obtain signed medical records release and pediatric care provider information	X						
Provide reimbursement	X	X	X	X	X	X	X
Schedule next visit/contact	*	*	X	X	X	*	*
BEHAVIORAL							
HIV pre-/post-test counseling	X	X	*	X	X		X
HIV/STI risk reduction counseling	X	X	*	X	X	*	X
Contraception counseling	X	X	*	X	X	X	X
Behavioral assessment		X	X	X	X		X
Product acceptability assessment		X	X	X	X		X
Protocol adherence counseling		X	X	X	X		
Social harms assessment			X	X	X	X	X
In-depth interview (IDI) (subset)					♦		X
PrEP counseling						X	X
CLINICAL							
Infant feeding assessment	X	X	X	X	X		X
Concomitant medications and vaginal products	X	X	X	X	X	X	X
Review/update medical history	X	X	X	X	X	X	X
Physical exam (Targeted after Screening Visit)	X	X	*	*	X	*	X
Pelvic exam	X	X	*	*	X	*	X
Collect AEs			X	X	X	X	X
Treat STIs/RTI/UTI	*	▼	*	*	*	*	*

		Visit 1 SCR	Visit 2 ENR	Visits 3,4 (Week 1, 2)	Visits 5, 6 (Month 1, 2)	Visit 7 (Month 3 PUEV)	Visit 8 SEV (2 weeks after PUEV)	Early Termination Visit
Disclose available test results		X	X	X	X	X	X	X
LABORATORY								
URINE	Pregnancy test	X	X	*	*	X	*	X
	Urine dipstick and/or culture	*	*	*	*	*	*	*
BLOOD	HIV-1 testing	X	X	*	X	X	*	X
	AST/ALT	X		*	*	X	*	X
	Creatinine clearance	X		*	*	X	*	X
	Complete blood count (CBC) with platelets	X		*	*	X	*	X
	Syphilis serology	X	*	*	*	*	*	*
	Plasma archive		X					
	HBsAg	X						
	Plasma for DPV drug levels (DPV group)			X	X	X	X	X
	DBS for FTC-TP & TFV-DP drug levels (Truvada group)		X (Both DPV & Truvada groups)	X	X	X	X	X
BREAST MILK	Breast milk for DPV drug levels (DPV group)			X	X	X	X	X
	Breast milk for FTC and TFV drug levels (Truvada group)			X	X	X	X	X
PELVIC	NAAT (GC/CT/TV)	X	*	*	*	*	*	*
	Wet prep/KOH wet mount for candidiasis and/or BV	*	*	*	*	*	*	*
	Vaginal pH	*	*	*	*	*	*	*
	Vaginal swab(s) for microbiota		X			X		X
	Vaginal Gram stain		X			X		X
	Vaginal swab(s) for biomarkers		X			X		X
STUDY PRODUCT	Adherence Assessment: Returned study VR				X	X		X
STUDY PRODUCT								
Provide study VR or study tablets			X		X			

	Visit 1 SCR	Visit 2 ENR	Visits 3,4 (Week 1, 2)	Visits 5, 6 (Month 1, 2)	Visit 7 (Month 3 PUEV)	Visit 8 SEV (2 weeks after PUEV)	Early Termination Visit
Provide product use instructions		X		X			
Insertion/removal of study VR at the clinic (clinician to check VR placement) or DOD of first study tablets		X		X			
Remove and/or collect study VR or unused study tablets				X	X		X
Offer male condoms	X	X	X	X	X	X	X

^ Informed consent can be separate or combined for Screening & Enrollment; depending upon site criteria

* If indicated and/or per local standard of care

▼ Enrollment delayed until symptoms resolved if treatment is indicated

♦ May be scheduled any time between PUEV and SEV

APPENDIX II: Table of Visits and Study Procedures – Infants

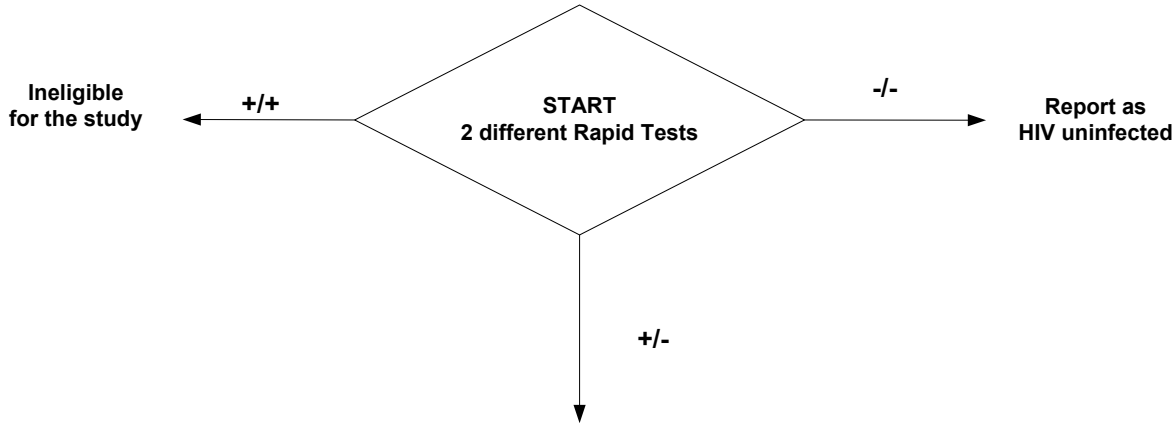
	Visit 1 SCR	Visit 2 ENR	Visits 3,4 (Week 1, 2)	Visits 5, 6 (Month 1, 2)	Visit 7 Month 3 (PUEV)	Visit 8 SEV (2 weeks after PUEV)	Early Termination Visit
ADMINISTRATIVE AND REGULATORY							
Obtain/confirm informed consent	^	X					
Assess and/or confirm eligibility	X	X					
Collect demographic information	X						
Assign a unique PTID number	X						
CLINICAL							
Review pediatric care records	▲	X	X	X	X	X	X
Review/update concomitant medications	X	X	X	X	X	X	X
Review/update medical history	X	X	X	X	X	X	X
Physical exam (Targeted after Screening Visit)	X	X	*	*	X	*	X
Collect AEs			X	X	X	X	X
LABORATORY							
Plasma for DPV drug levels (DPV group)			X (V4 only)	X	X	X	X
DBS for FTC-TP and TFV-DP drug levels (Truvada group)			X (V4 only)	X	X	X	X

^ Informed consent can be separate or combined for Screening & Enrollment; depending upon site criteria

* If indicated and/or per local standard of care

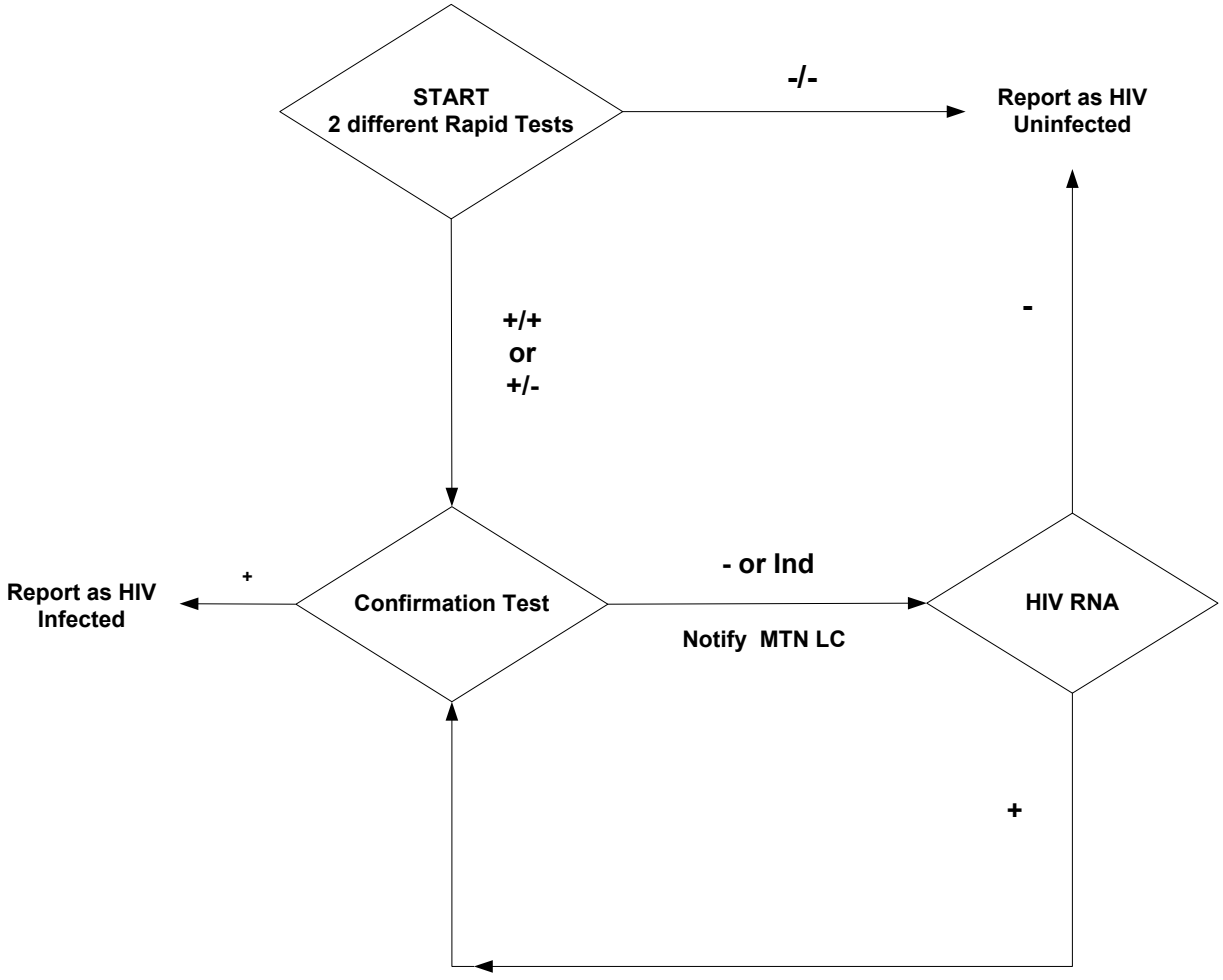
▲ Review pediatric care records as available once all required permissions have been obtained

APPENDIX III: Algorithm for HIV Testing – Screening/Enrollment



Notify the MTN Laboratory Center for follow-up.

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 & INFANT

SAMPLE INFORMED CONSENT FORM DIVISION OF AIDS, NIAID, NIH

MTN-043

Each **adult participant** must receive, read and sign (themselves or representative) this document **before** any study-related procedure

Study Title: Phase 3B, Randomized, Open-Label, Safety, and Drug Detection Study of Dapivirine Vaginal Ring and Oral TRUVADA® in Breastfeeding Mother-Infant Pairs

Version 1.0, July 24, 2019

Principal Investigators: ***[Site to insert]***

Daytime and After-Hours Telephone Number (s): ***[Site to insert]***

Short Title for the Study: B-PROTECTED**:** Mother-Infant Pair Study of Dapivirine Ring and PrEP in Breastfeeding

INFORMED CONSENT

You and your infant 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). This consent is for both you and your infant. For this consent, we will use the word 'baby' for the word 'infant'. Two products are included 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 for you and your baby's participation in the study:

- The study products to be used by you, the mother, in this research study each contain a different anti-HIV medication:
    - The vaginal ring containing 25 mg of dapivirine (DPV). The ring is inserted in the mother's vagina and worn continuously for approximately one month, to be replaced every month. We will refer to it as the ring in this document.
    - The oral tablet, Truvada, contains 200 mg emtricitabine (FTC) and 300 mg tenofovir disoproxil fumarate (TDF). It is taken once a day by mouth by the mother. 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 by the mothers is safe - for themselves and their breastfed babies. Also, the study will determine how much drug in the ring and tablet can be detected in the mother's plasma, blood and breast milk and the baby's blood when mothers use the ring or the tablet during breastfeeding.
- It is unknown if taking the study drugs will reduce the risk of passing HIV to the baby while breast feeding. We know that these drugs are found in breastmilk in small amounts. Existing safety data supports the use of the tablet in breastfeeding women who are at continuing substantial risk of HIV infection. However, the tablet may have side-effects that no one knows about yet. More data are needed on FTC and TDF safety during breastfeeding. To date, no formal studies with the ring have

been conducted in women who are breastfeeding. However, in the first study of dapivirine exposure during lactation, the maternal blood and breast milk samples showed very low drug levels which rapidly decreased upon removal of the ring by the mothers. Data are needed on the ring's safety during breastfeeding.

- If you decide that you and your baby want to join the study, we will first do some tests to see if you both qualify. If either you or your baby do not qualify for this study, neither of you can enter the study. If you both qualify to participate in this study, you, the mother, will be randomly assigned to use one of the two study products for approximately three months.

  Note: It is important that you know if you do not intend to exclusively breastfeed your baby for the duration of the study, you will not be able to join this study.

- You and your baby will come in together for eight (8) study visits, including the visit today. Study visits will take place at this study clinic or at mutually agreed upon locations. You and your baby's participation in this study will take about 4.5 months (18 weeks).
- At some of the clinic visits, you will be asked to complete the following: a physical exam, a pelvic exam, blood draw, urine and vaginal fluid collection, several short interviews (and possibly selected to complete a longer interview at one or more visits), and you will be asked permission to access your medical records and contact your health care provider. At some visits, a physical exam and blood will be drawn from your baby. You will be asked permission to access your baby's medical records and contact your baby's health care provider. Most procedures done in this study are routine medical procedures, with little risk to you and your baby.
- Some common risks or discomforts from the ring include: vaginal irritation, discharge, and/or discomfort, and allergic reaction. One serious but rare side-effect is toxic shock syndrome caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacterium.
- Some common risks or discomforts from the tablet include: nausea, abdominal pain, diarrhea, vomiting, flatulence, headache, dizziness, tiredness, and inability to sleep. More serious but rare side-effects include: rash, liver problems, kidney problems, allergic reaction, and lactic acidosis. 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.
- You will be using a study product that may prevent you from getting HIV if you use it consistently. 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 and your baby do not have to participate, and you can stop both of your participation in the study at any time.
- If you decide that you and your baby cannot join this study, there are currently available methods you can use to prevent acquiring HIV and passing it to your baby: 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 have you and your baby join the study. If you are willing to take part in the study, you will sign/mark this form for yourself and on your baby's behalf. A copy of this form will be offered to you. Signing/marking this form does not mean you and your baby will be able to join the study. You and your baby must first complete the screening tests and exams to see if you both are eligible. It is important to know that you 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

The ring is being evaluated in adults for the prevention of HIV infection. It has been tested and found to be well-tolerated for use by adolescent (15-17 years old) and adult (18 years and older) women. The ring works by stopping HIV from making copies of itself. It was found to reduce HIV infection in women ages 22-45 when used consistently. Researchers believe that younger women were not protected from getting HIV because they did not use the ring consistently. The ring has not been approved by regulatory groups like the Food and Drug Administration (FDA) or European Medicines Agency (EMA) to prevent HIV.

The tablet, called Truvada, is an approved drug for adults in many settings for the prevention of HIV infection, called oral pre-exposure prophylaxis (PrEP). Truvada is composed of the two drugs tenofovir (TDF) and emtricitabine (FTC). The tablet works by stopping HIV from making copies of itself. The tablet is also approved for the treatment of HIV-1 for both adults and pediatric patients (12 years of age and older and weighing greater than or equal to 35 kg) when combined with other drugs.

Neither study product is effective against common sexually transmitted diseases other than HIV.

Who will be in this research study?

Two hundred (200) healthy breastfeeding women who are 18 or older and their healthy babies between six and twelve weeks old will be enrolled in the study across various sites in Malawi, South Africa, Uganda, and Zimbabwe.

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

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 three women who will receive the ring, there will be one 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, with your baby, one week, two weeks, and four weeks after your Enrollment Visit, then every four weeks for the following eight weeks. You both will also come to the clinic two weeks after that for your final study visit. You will allow study staff to access you and your baby's medical records. You and your baby will come to the clinic for a total of eight (8) visits including the visit today and will be in the study for approximately 4.5 months (18 weeks). Each visit will take about *[SITES TO INSERT THE APPROXIMATE LENGTH OF TIME]*.

Do I or my baby have to be in this study?

You and your baby do *not* have to be in this study. You both 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 and your baby no longer wish to participate. If you do not join the study, your baby cannot join the study.

Study Procedures:

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 and your baby can join this study and will take about *[SITES TO INSERT THE APPROXIMATE LENGTH OF TIME].*

If it seems like you both can join, you and your baby 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 to which study group you have been assigned.

The following things will happen to you during your study visits:

- We will ask you questions about your health, any medications you may be taking, and any vaginal products you may be using. 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 study medical records.
- We will talk with you about what you need to do to be in the study, how to use the study products, how to protect yourself from getting an infection, including HIV, and how to keep from getting pregnant. 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.
- At some study visits, we will give you a pelvic exam to check for infections and to make sure you are healthy. 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, using a swab (e.g., Q-Tip or earbud). We may give you a pelvic exam at other visits, if needed. We will also collect blood to make sure you are healthy and to test you for HIV and other STIs.
- At some study visits, we will draw up to 30 mL (about two 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 study products. More blood may be collected if you become ill.
- At some visits, we will collect a urine sample to test you for some STIs.
- At some visits, we will give you a physical exam to make sure you are healthy.
- 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, we will collect breast milk to test to see if the study product is in the milk.
- At some visits, we may ask you to undergo a pregnancy test.
- At some visits, we may ask you questions regarding your baby's eating/feeding activities.
- 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 longer interview with study staff. You may choose not to do the interview. During the interview, 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. 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, we will give you either another ring to use, or another month of tablets to take. The insertion/removal of the ring will occur at the clinic and will be checked by the study clinician.
- At all visits, we will ask you of any issues that you may be experiencing as a result of the study products, or as a result of procedures performed during your visits.

- 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.
- 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, you will be asked to abstain from sexual practices, tampon use and other non-study products for 24 hours prior to your clinic visits.

Activity:	***Not Permitted for How Long?***
Receptive sexual practices, including: • Penile-vaginal intercourse • Penile-anal intercourse • Receptive oral intercourse • Finger stimulation	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: • Female condoms • Diaphragms • Menstrual cups • Cervical caps or any other vaginal barrier method	For 24 hours before each clinic visit

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

The following things will happen for your infant's participation during the study visits:
- Ask for access to your baby's medical records and to contact your baby's healthcare provider(s).
- At all visits, we will ask about your baby's health and any medicines he/she may be taking.
- At some visits, we will give your baby a physical exam to make sure he/she is healthy.
- At some visits, we will draw up to X mL (about X tablespoons) of blood [Sites to insert local amount] to learn if the study drug enters his/her blood.

It is important for you and your baby 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 and/or your baby 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 and/or your baby experience any changes in your physical condition, including symptoms of infection (urinary or sexually transmitted). If you discontinue breastfeeding your baby, you will continue to receive study product and continue with all regularly scheduled visits

What if I become infected with HIV?
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 pass it on to your baby. If you or your baby become HIV-positive, you will stop using the study products. In both cases, we will ask you to continue to have monthly study visits (approximately 4.5 months [18 weeks] duration) but with modified procedures. If you become HIV-positive during the study, your baby will have additional HIV testing for 3 months (12 weeks) after confirmation of you being infected. This study does not provide medication for treatment of HIV. If you and/or your baby become infected with HIV, the study staff will refer you for

medical care and other available services for both of you. If you and/or your baby 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. We will do a blood test to find out if you and/or your baby have drug resistance. These results can help us know which drugs would be best to treat your and/or your baby for 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/AMMEND 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].*

What if I become pregnant?
The ring and the tablet are not family planning methods and will not prevent pregnancy. We do not know what effect the study products have on pregnancy, including any effect on the unborn babies. Because of this, pregnant women may not join this study. Also, you must use an effective family planning method (e.g., oral contraceptive pills, contraceptive implants, intrauterine device, injectable progestin, and surgical sterilization) even if you are not currently sexually active.

If you become pregnant during the study, study staff will refer you to available medical care and other services. The study does not pay for this care. You will stop using study products and will discontinue the study. We will stay in contact with you until the end of your pregnancy to find out about the health of your pregnancy and baby and will contact you again 12 months after delivery.

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws
You and your baby may feel discomfort or pain when blood is drawn. You and your baby may feel dizzy or faint. You and your baby may have a bruise, swelling, or small clot where the needle is inserted. Rarely, drawing blood can cause an infection where the needle is inserted.

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 Breast Pump Use or Hand Expression (If applicable)
You may feel discomfort when you start using the breast pump and/or hand express milk, but pumping and/or hand expression should never be painful, result in sore or irritated nipples, or cause bleeding. These may be signs of an injury, problems with your breast pump, or errors with your technique. If you experience these, or any other symptoms you are concerned about, please consult a member of the study staff.

Risks of the DPV Ring
We do not yet know all the side-effects of the ring. Some women who used the ring in other studies have had discharge from the vagina; pain, burning, or itchiness in the vagina; vaginal bleeding in between their usual periods and urinary tract infection. Less common side effects include pelvic inflammatory disease, cervix erythema, cervix edema, cervicitis, urinary incontinence, dyspareunia (difficult or painful sexual intercourse), headache, decreased neutrophil count, abnormal weight loss, and dysmenorrhea (pain and cramping during periods).

Although rare, the ring can cause some side-effects, such as 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 DPV ring use may be different in women who are breastfeeding, or that the side-effects may resemble normal symptoms post-pregnancy. 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 babies. However, there is not enough information to know for sure. There is currently no reason to suspect that using the ring will change the amount or taste of milk for 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.

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. Individuals with hepatitis B virus who suddenly stop taking the tablet may get a “flare” or worsening of hepatitis symptoms

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, weakness and liver failure. This serious side-effect has been seen more often in women taking the tablet in combination with other drugs. Also, in rare cases, some people with HIV who take the tablet in combination with other drugs may get an enlarged and fatty liver which may result in liver failure, other complications and death. The liver complications and death have been seen more often in women on these 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: increased fat at the waist and stomach area; increased fat on back of the neck; thinning of 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 breastfeeding, or that the side-effects may resemble normal symptoms post-pregnancy. 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.

The medicines in the tablet are often used to treat women with HIV infection. Existing safety data supports the use of the tablet in pregnant and breastfeeding women who are at continuing substantial risk of HIV infection. We know that these medicines can be found in breastmilk in small amounts. Data shows that the drug levels found in the breast milk of breastfeeding mothers is very low. A recent study in 50 HIV-uninfected breastfeeding African mother-infant pairs, suggests Truvada could be safely used during breastfeeding with minimal exposure for the baby. After using Truvada for ten days, the milk samples from the mothers showed the drug levels of FTC and TDF were very low. In the babies' blood samples, no amount of TDF could be detected and the amount of FTC was very low. There were no serious effects for the mothers and breastfeeding babies during the study or in the follow-up to the study. There is currently no reason to suspect that taking Truvada will change the amount or taste of milk for babies.

Truvada may have side-effects that no one knows about yet. It is still possible that breastfeeding mothers taking the tablet may cause some problems in the baby when they are older from the study product exposure in the breastmilk.

Risks of HIV and Sexually Transmitted Infection (STI) Testing
HIV and STI testing may make you feel anxious regardless of the test results. Denial is a risk associated with disclosure of HIV-positive status. 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 you and your baby's participation in this study, and because of this, may treat you and your baby unfairly or discriminate against you both. There also is a risk to your privacy or the privacy of your baby if someone else taking part in this study knows 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 and your baby 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 baby'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 and your baby from getting HIV if you use it consistently. Information learned from this study may help us learn how to prevent HIV in women and their babies. You and your baby will receive medical exams and tests to check both of your overall health. You will also receive counseling and testing for HIV and STIs.

This study cannot give you and your baby general medical care. Study staff will refer you both 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 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 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 breastfeeding. 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 https://www.ClinicalTrials.gov, as required by US 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 and 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, the Institutional Review Board (IRB)/Ethics Committee (EC), or by other international government or regulatory authorities. An IRB/EC is a committee that watches over the safety and rights of study participants.
- You are not able to keep appointments.
- You (as the mother) leave the study
- Other reasons that may prevent you and/or your baby from completing the study successfully.

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

- Become pregnant.
- Acquire an HIV infection.
- Acquire a hepatitis B infection (Truvada users only).
- Confirmation of ≥ Grade 2 creatinine clearance (for Truvada group only).
- Confirmation of ≥ Grade 2 glycosuria (presence of sugar in the urine) or proteinuria (presence of abnormal amount of protein in the urine) (for Truvada group only).
- Use drugs for HIV prevention beyond what the study gives you.
- Use drugs to prevent infection after being exposed to HIV. In such a scenario, the use of antiretroviral medication (post-exposure prophylaxis [PEP]) is encouraged, however it does lead to discontinuation of the study product.
- Use injectable drugs for reasons other than treating disease.
- 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 for reasons other than pregnancy, we will ask that you and your baby to 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, with your baby, 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 your baby is removed from the study or you choose to stop his or her participation, we will ask you to bring your baby 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]: You and your baby 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 you and your baby's 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. We can also 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 your and your baby's 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 interview(s) with staff, you will receive [*SITES TO INSERT AMOUNT* $xx].

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

Study visits will take place in private. We will keep the information about you and 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 both of your information into computers protected by passwords and will not include information that could identify you both. We will only record both of 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 and your baby for this study will be kept for at least two years after either the vaginal ring is approved for use or research on the vaginal ring is stopped.

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

The study staff may use you and your baby's personal information to verify that you both 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 you and your baby's name or identify you both personally in any publication.

You and 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 ring
- Gilead Sciences, Inc., the company that supplies the tablets
- Study monitors
- Site IRB/EC
- Study staff

[Sites to remove/amend the following if instructed by their local IRB/IEC:]
The researchers will do everything they can to protect you and your baby's privacy. In addition to the efforts of the study staff to help keep you and your baby's personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This Certificate protects study investigators from being forced to tell people who are not connected with this study, such as the court system, about you and your baby's participation or information you give for study purposes. With limited exceptions, researchers may not disclose names, information or documents containing information you give for study purposes. This Certificate does not expire.

However, if the study staff learns of possible infant abuse and/or neglect or a risk of harm to you, your baby or others, they will be required to tell the proper authorities. Also, we may have to release information about you and your baby if the organization that is funding this study, [*Funding Agency*], requests the information, or if the FDA, EMA or other regulatory body tells us to release this information. This Certificate does not prevent you from releasing information about you and your baby's participation in the study.

RESEARCH-RELATED INJURY
It is unlikely that you and your baby will be injured by being in this study. The US 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 and your baby become ill or injured because of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you and 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 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/your baby used other medicine during the study that you did not tell us about.
- Any injury that happens because you/your baby 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 for you and your baby not to join this study or leave this study at any time. If you choose for you and your baby not to join or to leave the study, you both 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 and your baby 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 you and 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]*.

INFORMED CONSENT FORM – MOTHER (18 years or older)

WRITTEN PERMISSION FOR PARTICIPATION OF ADULT MOTHER IN THE MTN-043 STUDY:

I, _____ (Name of Participant) hereby confirm that I have been informed by _____ (Name of Study Staff) about the nature, conduct, benefits and risks of the clinical study.

- I have received, read and been told the above written information (Informed Consent) regarding this study.
- I have been told about the study procedures that I will be involved in if I agree to participate; in addition to routine standard of care procedures.
- I have been told that I may, at any stage, without prejudice, refuse to continue participation in the study.

I have had the study explained to me. I have had my questions answered satisfactorily.

□ **NO** (please tick), I **DO NOT** agree to participate in this study

If NO, please stop all enrollment processes at this point.

□ **YES** (please tick), I **DO** agree to participate in this study.

For each visit that I miss:

I may be contacted via telephone up to *[X]* times by the researchers. □ **YES** □ **NO** (please tick)

If the researchers cannot contact me by telephone they may do *[X]* home visits. □ **YES** □ **NO** (please tick)

Participant:

Printed Name & Surname of Research Participant | Signature | Date and Time

If Applicable: WITNESS

_____

Designation of Witness

Printed Name & Surname of Witness | Signature | Date and Time

Study Staff Conducting Consent Discussion):

I**, (Study Staff)** _____, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above research study.

Printed Name & Surname | Signature | Date and Time

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.

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

INFORMATION SHEET AND INFORMED CONSENT FORM – STORAGE OF BLOOD, BREAST MILK, AND/OR VAGINAL FLUIDS FROM MOTHERS

ONLY FOR MOTHERS WHO ARE ENROLLED IN THE MTN-043 STUDY.
Each **participant** must receive and sign (themselves or representative) this document **before** any study-related procedure.

[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, breast milk, and/or vaginal fluids left over after we have done all the study related testing on you. We would like to store your leftover body fluids for future work that could include testing for drug products and testing for HIV risk. 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 of 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 that we cannot store your blood, breast milk, and/or 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

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

INFORMED CONSENT FORM – INFANT PARTICIPANT

WRITTEN PERMISSION FOR PARTICIPATION OF INFANT IN THE MTN-043 STUDY:

I, _____ (Name of Participant), biological mother of _____
(Name of baby), hereby confirm that I have been informed by _____
(Name of Study Staff) about the nature, conduct, benefits and risks of the clinical study.

- I have also received and read the above written information (Informed Consent) regarding this study.
- I have been told what study procedures my baby will be involved in if I agree to let him/her participate. I have also been told about the routine standard of care procedures that the baby will receive.
- I have been told that I must be enrolled in the study for my baby to be enrolled in the study.
- I have been told that I may, at any stage, and without prejudice, refuse to allow my baby to continue to be a part of the study.

Please show your choices regarding your baby's participation in the study (tick the boxes that show your choice):

I have had the study explained to me. I have had my questions answered satisfactorily.

□ **NO** (please tick), I **DO NOT** agree to let my baby participate in this study

If NO, please stop here

□ **YES** (please tick), I **DO** agree to let my baby participate in this study

If the baby tests HIV-positive at any point during the study:

□ **YES** (please tick), I **DO** agree to allow the study team to continue to collect important information on my baby at each of our study visits including the baby's weight, height, head circumference, information (including blood results) and details of regular vaccines.

□ **NO** (please tick), I **DO NOT** agree to allow the study team to continue to collect information on my infant at each of our study visits.

Participant:

Printed Name of Research Participant (Baby) Baby's Date of Birth

Printed Name & Surname of Mother Signature Date and Time

If Applicable: WITNESS (IF PARTICIPANT IS UNABLE TO UNDERSTAND ENGLISH/X/X):

Designation of Witness

Printed Name & Surname of Witness Signature Date and Time

Study Staff Conducting Consent Discussion:

I**, (Study Staff)** _____, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above research study.

Printed Name & Surname	Signature	Date and Time

INFORMATION SHEET AND INFORMED CONSENT FORM – STORAGE OF LEFTOVER BLOOD FROM INFANTS

ONLY FOR INFANTS WHO ARE ENROLLED IN THE MTN-043 STUDY.
The mother of each infant **participant** must receive and sign (themselves or representative) this document **before** any study-related procedure.

[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 the study-related testing on your baby. We would like to store this leftover blood for future work that could include testing for study products and testing for HIV risk. 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 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

_____ Initials or Mark Date	I DO agree to allow my baby's biological specimens and health data to be stored and used in future research studies.
_____ Initials or Mark Date	I DO NOT agree to allow my baby's biological specimens and health data to be stored and used in future research studies.

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