MTN-042

Phase 3b, Randomized, Open Label Safety and Pharmacokinetic Trial of Dapivirine Vaginal Ring (VR) and Oral FTC/TDF Use in Pregnancy

Microbicide Trials Network

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

Grant Numbers:
UM1AI068633, UM1AI068615, UM1AI106707

DAIDS Protocol ID: 38544

IND Sponsor:
DAIDS

IND #: TBD

Pharmaceutical Company Collaborators:
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Version 0.2

March 29, 2018

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LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	Audio Computer-Assisted Self-Interviewing
ADAPT	Alternative Dosing to Augment PrEP Pill Taking
AE	adverse event
AIDS	acquired immunodeficiency 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
AST	aspartate aminotransferase
ATN	Adolescent Trials Network
AVAC	Global Advocacy for HIV Prevention
BID	*bis en die* (twice a day)
BRWG	Behavioral Research Working Group
BSWG	Biomedical Science Working Group
BV	bacterial vaginosis
CAB	Community Advisory Board
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CASI	Computer-Assisted Self-Interviewing
CBC	complete blood count
CDC	U.S. Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHAMPS	Choices for Adolescent Prevention Methods for South Africa
C_{max}	maximum concentrations
C_{min}	minimum concentrations
CMRB	Clinical Microbicide Research Branch
CONRAD	Contraception Research And Development
CRF	case report form
CRMS	Clinical Research Management System
CROI	Conference on Retroviruses and Opportunistic Infections
CRS	clinical research site
CT	Chlamydia trachomatis
CTA	clinical trial agreement
CTU	clinical trials unit
CVF	cervicovaginal fluid
CVL	cervicovaginal lavage
CWG	Community Working Group
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of Acquired Immunodeficiency Syndrome
DAPY	di-aminopyrimidine
DLV	delavirdine
DMPA	depot medroxyprogesterone acetate
DNA	deoxyribonucleic acid

DOD	directly observed dosing
DPV	dapivirine
DREAMS	Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe women
DSMB	Data and Safety Monitoring Board
EAE	expedited adverse event
EC	Ethics Committee
EC_{50}	50% effective concentration
EFV	efavirenz
FDA	Food & Drug Administration (U.S.)
FGD	focus group discussion
FHCRC	Fred Hutchinson Cancer Research Center
FTC	emtricitabine
FTP	File Transfer Protocol
g	grams
GC	*Neisseria gonorrhoeae*
GCP	Good Clinical Practice
GMP	good manufacturing practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HEENT	Head, Eye, Ear, Nose and Throat
HHS	Department of Health and Human Services (U.S.)
HIV-1	human immunodeficiency virus-1
HPTN	HIV Prevention Trials Network
HPV	human papilloma virus
HSV	herpes simplex virus
IAS	International AIDS Society
IATA	International Association of Air Transport
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICRC	International Clinical Research Center
IDI	in-depth interview
IIDMM	Institute of Infectious Disease and Molecular Medicine
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
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
JKUAT	Jomo Kenyatta University of Agriculture and Technology
KEMRI	Kenyan Medical Research Institute
KOH	potassium hydroxide
3TC	lamivudine
LC	Laboratory Center
LCDR	lieutenant commander
LDMS	Laboratory Data Management System
LMP	last menstrual period

LOC	Leadership and Operations Center
µg	microgram
µM	micromolar (10^{-3} mol/m^3)
mg	milligram
mL	milliliter
MCAZ	Medicines Control Authority of Zimbabwe
MCC	Medicines Control Council (South Africa)
MO	Medical Officer
MSC	Mail Stop Code
MSM	men who have sex with men
MTD	maximum tolerated dose
MTN	Microbicide Trials Network
MU-JHU	Makerere University – John Hopkins University Research Collaboration
MVC	maraviroc
NAAT	nucleic acid amplification test
NDA	National Drug Authority (Uganda)
ng	nanogram
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
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
PID	pelvic inflammatory disease
PK	pharmacokinetic
PoR	Pharmacist of Record
PPB	Pharmacy and Poisons Board (Kenya)
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/Early Termination Visit
QD	*quaque die* (once daily)
RE	regulatory entity
REACH	Reversing the Epidemic in Africa with Choices in HIV Prevention
RHI	Reproductive Health and HIV Institute
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
SAE	serious adverse event

SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	Statistical Data Management Center
SIV	Simian Immunodeficiency Virus
SMC	Study Monitoring Committee
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
TMC-120	dapivirine
UCSF	University of California- San Francisco
UCT	University of Cape Town
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children's Fund
UPMC	University of Pittsburgh Medical Center
USA	United States of America
UTI	urinary tract infection
VOICE	Vaginal and Oral Interventions to Control the Epidemic
VR	vaginal ring
WHO	World Health Organization
ZDV	zidovudine

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MTN-042

Phase 3b, Randomized, Open Label Safety and Pharmacokinetic Trial of Dapivirine Vaginal Ring (VR) and Oral FTC/TDF Use in Pregnancy

INVESTIGATOR SIGNATURE FORM

Version 0.2; March 29, 2018
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: TBD)

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

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

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

_____
Name of Investigator of Record (print)

_____ _____
Signature of Investigator of Record Date

MTN-042

Phase 3b, Randomized, Open Label Safety and Pharmacokinetic Trial of Dapivirine Vaginal Ring (VR) and Oral FTC/TDF Use in Pregnancy

PROTOCOL SUMMARY

Short Title:	Safety and PK of Dapivirine VR and Oral PrEP in Pregnancy
IND Sponsor:	DAIDS
Funders:	Division of AIDS, NIAID, NIMH, NICHD, US NIH
Protocol Chair:	Katherine Bunge, MD Bonus Makanani, MBBS, FCOG(SA)
Protocol Co-Chair:	Lee Fairlie, MBChB, FCPaeds
Sample Size:	Approximately 750 women and their newborns
Study Population:	Healthy, HIV-uninfected pregnant females, 18-45 (inclusive) years old, with an uncomplicated singleton pregnancy who are willing to be randomized to study product, and their newborn infants
Study Sites:	MTN-042 site(s) selected by the MTN Executive Committee
Study Design:	Phase 3b, two-arm, open label, multi-site, randomized (2:1) trial (DPV VR, oral FTC/TDF tablet), with onset of dosing period to occur within the following gestational age (GA) ranges: Cohort 1: 36 0/7 weeks – 37 6/7 weeks 150 women Cohort 2: 30 0/7 weeks – 35 6/7 weeks 150 women Cohort 3: 20 0/7 weeks – 29 6/7 weeks 150 women Cohort 4: 12 0/7 weeks – 19 6/7 weeks 300 women
Study Duration:	The total duration of study participation for each participant will vary depending on gestational age at time of enrollment and length of pregnancy prior to pregnancy outcome, and may range from approximately 12 weeks or less for Cohort 1 to approximately 36 weeks or less for Cohort 4. Infants born to MTN-042 participants will be followed for approximately 6 weeks.
Study Products:	• Silicone elastomer matrix vaginal ring (VR) containing 25 mg of dapivirine (DPV) • Oral tablets containing 200 mg emtricitabine/300 mg tenofovir disoproxil fumarate (FTC/TDF)
Study Regimen:	Within each cohort, participants will be randomized to the above study products in a 2:1 ratio (VR:tablet). Participants randomized to the DPV

Commented [DL1]: To recruit Cohorts 1 and 2, will need to ensure an ultrasound is done no later than at 28 weeks, and preferably at 18-22 weeks. Dating US could be done at or arranged by the sites if participants do not have it already. Will build in a pre-screening with an US and make the screening to enrollment window long enough for Cohorts 1 and 2 to have a 2nd TM US, especially since many women will likely not know when was their last menstrual period.

VR will use one ring continuously for up to one month, replacing the ring each month. Participants using FTC/TDF tablet will take one tablet orally per day. Participants will use their assigned study product until the outcome of their pregnancy.

Figure 1: Study Visit Schedule by Cohort across Gestational Age Ranges

Cohort 1 Enrollment Window 36 0/7 weeks – 37 6/7 weeks	Screening
	Enrollment
	Every 2 weeks until pregnancy outcome, with phone contact every other week
	Within 1 week of pregnancy outcome and at approximately 6 weeks after (home or clinic)
Cohort 2 Enrollment Window 32 0/7 weeks – 35 6/7 weeks	Screening
	Enrollment
	1-week (phone)
	2-week
	4-week
	Every 2 weeks until pregnancy outcome, with phone contact every other week
	Within 1 week of pregnancy outcome and approximately 6 weeks after (home or clinic)
Cohort 3 Enrollment Window 20 0/7 weeks – 29 6/7 weeks	Screening
	Enrollment
	1-week (phone)
	2-week
	4-week and every 4 weeks until Week 36
	Every 2 weeks after Week 36 until pregnancy outcome, with phone contact every other week
	Within 1 week of pregnancy outcome and approximately 6 weeks after (home or clinic)
Cohort 4 Enrollment Window 12 0/7 weeks – 19 6/7 weeks	Screening
	Enrollment
	1-week (phone)
	2-week
	4-week and every 4 weeks until Week 36
	Every 2 weeks after Week 36 until pregnancy outcome, with phone contact every other week
	Within 1 week of pregnancy outcome and approximately 6 weeks after (home or clinic)

Primary Objective:

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

Primary Endpoints:

Commented [DL2]: "All serious AEs" covers maternal dealths, neonatal deaths, NICU/ICU admissions, and congenital anomalies.

Maternal Safety (composite)

- All serious adverse events
- 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])

- For AEs categorized as complications of pregnancy, all Grade 2 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])

Commented [DL3]: DAIDS AE Grading Table specifically lists "stillbirth (≥20 weeks)", "preterm birth (Grade 1 = <37 weeks, Grade 2 = <34 weeks, Grade 3 = <28 weeks, Grade 4 = <24 weeks)" and "spontaneous abortion or miscarriage" under the category "Pregnancy, Puerperium, and Perinatal". Deleted those from 2ry endpoints for pregnancy outcome.

Infant Safety (composite)
- All serious adverse events
- 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

Secondary Objectives:

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

Pharmacokinetics: To describe the pharmacokinetic profile of study products used during pregnancy

Adherence: To characterize adherence to open label use of the dapivirine vaginal matrix ring (25 mg) and oral FTC/TDF in pregnant women

Acceptability: To characterize acceptability of open label use of the dapivirine vaginal matrix ring (25 mg) and oral FTC/TDF in pregnant women

Secondary Endpoints:

Pregnancy Outcome
- Therapeutic/elective abortion, peri-partum hemorrhage, chorioamnionitis, post-partum endometritis, prolonged admission for baby, premature rupture of membranes (PROM), infant size relative to gestational age, low birth weight (<2500g)

Pharmacokinetics
- Maternal plasma and peripheral blood mononuclear cell (PBMC) tenofovir (TFV) concentrations
- Maternal plasma DPV concentrations
- Infant blood TFV and DPV concentrations

Commented [DL4]: Edited maternal PK endpoints per CWH, and edited infant PK endpoints per Annual Meeting discussion (heelstick, not venipuncture, for infants).

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

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

Commented [DL5]: Added per AVS.

Exploratory Objective:

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

Commented [DL6]: Edited to be more in line with how other objectives are written in this protocol.

Exploratory Endpoints:

Genital microenvironment

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

Commented [DL7]: Edited to be more in line with how these endpoints are written in MTN-008.

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	Phase 3b, Randomized, Open Label Safety and Pharmacokinetic Trial of Dapivirine Vaginal Ring (VR) and Oral FTC/TDF Use in Pregnancy
Protocol Number:	MTN-042
Date:	March 29, 2018

1.2 Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 Microbicides, Oral Pre-exposure Prophylaxis (PrEP) and Human Immunodeficiency Virus (HIV) Prevention

In 2016, 1.8 million people became newly infected with human immunodeficiency virus (HIV) and one million people lost their lives to acquired immunodeficiency syndrome (AIDS). AIDS-related illnesses remain the leading cause of death among women of reproductive age (15-49 years) globally.[1] According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) Global Report, the estimated number of individuals living with HIV is 36.7 million globally. In Eastern and Southern Africa, young women (15-24 years) accounted for 26% of new HIV infections, despite making up just 10% of the population. Female controlled prevention options remain a global priority given the high rates of HIV infection among women. The development of safe, effective and acceptable HIV prevention technologies for women in low and middle income countries remains a public health priority.

Between 1990 and 2004, HIV prevalence among pregnant women who attended public sector health care facilities in South Africa increased from 0.8% to 30.2%, staying at that level through 2010.[2] It was estimated that 70.4% of all maternal deaths in South Africa in 2011 were related to HIV infection, along with half of all deaths for children under five years old, prompting the scale-up of existing programs for prevention of mother-to-child transmission (PMTCT).

Pregnant and breastfeeding women in areas with high HIV incidence rates, particularly in sub-Saharan Africa (SSA), are at high risk of acquiring HIV.[3] It is possible that biological factors during pregnancy and breastfeeding may increase susceptibility to HIV infection; for example, elevated hormonal levels and changes in the vaginal microbiome associated with genital or cervical inflammation, as well as nutritional deficiency and lowered immunity. Social and behavioral factors during pregnancy and breastfeeding may also increase exposure and susceptibility to HIV infection; for example, untreated sexually transmitted infections (STIs), reduced condom use and increased intimate partner violence (IPV). Furthermore, pregnant and breastfeeding women who acquire HIV at this time have a greater risk of transmitting HIV to their infant than women who became infected with HIV before pregnancy because recent seroconversion leads to HIV viremia.[4]

Unprotected heterosexual intercourse is currently the leading mode of HIV acquisition among women. Correct and consistent use of latex condoms is one proven method of preventing HIV acquisition. However, condoms are widely regarded as inadequate prevention options for women because many women are unable to negotiate condom use with their partners. This is likely more difficult for women during pregnancy and breastfeeding, when contraception is not a motivating factor for condom use and male partners may be more resistant to use them during sex. Thus, developing HIV prevention options that women, particularly pregnant and breastfeeding women, can use remains a global concern.

In 2014, the World Health Organization (WHO) developed recommendations for offering oral pre-exposure prophylaxis (PrEP) containing the antiviral drug tenofovir disoproxil fumarate (TDF), alone or in combination with emtricitabine (FTC), to select key populations at high risk of HIV infection.[5,6] The WHO further expanded these recommendations in 2015 to include all persons at high risk of HIV infection, and then in 2016 stated that the benefits of PrEP for pregnant and breastfeeding women at risk of HIV infection outweighed any potential risks from side effects.[5,6] These guidelines were then followed by the inclusion of PrEP in the 2016 WHO recommendations on antenatal care, which stated that “oral pre-exposure prophylaxis containing tenofovir disoproxil

Commented [DL8]: Background section still in development, and references still need to be updated and formatted.

Focus the background section more towards the importance of research in pregnancy and what gaps exist in our understanding of PrEP in pregnancy. Add known info re: these products in pregnancy, the importance of research in pregnant women, and an ethical argument for benefit to both mother and fetus.

Consider opening statement on high fertility rates (and long lactation periods) in SSA.then move on to HIV in pregnancy (and breast feeding).

fumarate should be offered as an additional prevention choice for pregnant women at substantial risk of HIV infection as part of combination prevention approaches." The expansion of the WHO recommendations' scope was supported by mounting evidence that oral PrEP regimens containing TDF, when followed consistently, were safe, cost-effective, and highly efficacious in reducing HIV infection risk regardless of age, gender, PrEP regimen, or sexual exposure method.[5-7] However, gaps still exist in our understanding of how best to systematically implement oral PrEP with a number of populations, including the need for additional safety, acceptability and adherence data for HIV-uninfected pregnant and breastfeeding women.

Vaginal microbicides, which are self-initiated and controlled, offer women a critically needed biomedical prevention tool to complement existing HIV prevention strategies. With successful proof-of-concept that antiretroviral (ARV)-based microbicides reduce the risk of HIV-1 acquisition, confirmatory work and further trials involving different ARV compounds, formulations, and dosing strategies are required to improve upon the level of product effectiveness and to provide a range of options that will meet the needs of all potential end-users.

For a microbicide or other PrEP strategy to be effective, it is essential that it be used correctly and consistently, and that it be acceptable to the user. A product used independently of sex could be more convenient for women and provide long-term protection during anticipated and unanticipated sexual intercourse. Higher adherence to a product can translate into higher effectiveness of the product. It is likely that products that can be applied less frequently or products that can remain *in situ* for an extended duration will be more acceptable and will achieve better adherence. Vaginal rings (VRs) that need to be replaced monthly may have benefits over dosage forms that need to be used more frequently.

Multiple clinical trials have evaluated the safety of dapivirine in VRs, gels and in an oral formulation. These clinical trials support the favorable safety profile and tolerability of dapivirine in general and specifically in vaginal delivery formulations. Two recently completed Phase 3 safety and efficacy trials of the dapivirine VR, MTN-020 (ASPIRE) and IPM 027 (the Ring Study), found the VRs to be safe and effective in reducing HIV-1 infection in healthy female adults in SSA when used for one month and replaced monthly. These results indicate the need to expand studies of the dapivirine VR to additional populations, including pregnant and breastfeeding women.

2.2 Description of Microbicides and Oral PrEP

2.2.1 Dapivirine VR

Dapivirine (also known as TMC-120), a non-nucleoside reverse-transcriptase inhibitor (NNRTI), is a substituted di-amino-pyrimidine (DAPY) derivative with potent antiviral activity against HIV-1. Dapivirine is chemically described as 4-[[4-[(2,4,6-trimethylphenyl)amino]-2-pyrimidinyl]amino]benzonitrile.[22] The dapivirine matrix VR (Ring-004) is a flexible ring containing 25 mg of drug substance dispersed in a platinum-catalyzed cured silicone matrix. When delivered via VR, dapivirine has demonstrated favorable safety and pharmacokinetic (PK) profiles as described below.

Dapivirine was originally developed by Janssen Research and Development (formerly Tibotec Pharmaceuticals Ltd.), a subsidiary of Johnson & Johnson, as an oral ARV compound for treatment of HIV/AIDS and was tested in Phase 1 and 2 clinical trials in more than 200 participants.[22] However, dapivirine is also a promising topical microbicide candidate due to its proven *in vitro* and *in vivo* efficacy and favorable safety profile as well as its physical and chemical properties. Dapivirine has potent activity against wild-type HIV-1 strains and strains harboring

different resistance-inducing mutations. Dapivirine'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 dapivirine 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. Dapivirine does not have any contraceptive properties.[22] Detailed information on dapivirine is available in the Dapivirine VR Investigator's Brochure (IB).[22]

The International Partnership for Microbicides (IPM) has investigated a wide range of dosage forms for the development of topical microbicide products, including vaginal gels, rings, films, tablets and soft gel capsules. However, the dapivirine silicone elastomer VR has now been prioritized over all other dosage forms for the following reasons:

- Clinical trials have demonstrated sustained delivery of high levels of dapivirine throughout the cervicovaginal vault for up to 1 month;
- Since the ring is able to deliver drug for at least 1 month, the burden of user-dependent adherence is lower than for once daily products;
- Product acceptability studies and the experience gained from marketed VR products have established a high level of acceptance and adherence from women using VR with similar physical characteristics;
- The overall cost for the VR is relatively low;
- Minimal storage space is required for the VR when compared with once daily products

2.2.2 Truvada® Oral Tablet

FTC/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).[23]

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 and has become the most-prescribed ARV in the United States. Gilead Sciences, Inc. received US FDA approval in 2012 for once-daily oral 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; this is known as PrEP.[15] Truvada® for oral PrEP has also been approved for use by adults at high risk of sexually acquiring HIV-1 infection in a number of other countries, including two countries anticipated to participate in MTN-042, South Africa and Zimbabwe.[16]

FTC/TDF does not protect against common STIs such as gonorrhea, syphilis or chlamydia; therefore, it is recommended that it be used in conjunction with condoms.[26] However, a secondary analysis[27] within the Partners PrEP trial 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. FTC/TDF does not have any contraceptive properties, and animal studies have not found evidence that Truvada alters female fertility.[23] Detailed information on FTC/TDF is available in the package insert.[23]

Truvada® for oral PrEP has become an important part of large-scale HIV-prevention efforts for the following reasons[5-7]:

- Clinical trials have demonstrated that oral PrEP containing TDF reduces HIV infection risk in a wide variety of settings and populations;
- ARV drugs are becoming safer, more efficacious, and more affordable;
- New and improved HIV testing technologies offer greater opportunities to monitor and detect acute HIV infection, reducing the chances of promoting TDF-resistant HIV strains;
- The overall cost-effectiveness of targeted oral PrEP is relatively high; and
- Daily tablet regimens have high acceptability among most providers and target populations.

2.3 Mechanism of Action

2.3.1 Dapivirine Vaginal Ring (VR)

Dapivirine is an NNRTI; NNRTIs bind to the HIV reverse transcriptase (RT) enzyme thereby preventing viral replication and therefore the production of an infectious virus.[22]

2.3.2 FTC/TDF Tablet

FTC/TDF is a fixed-dose combination of antiviral drugs emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF). FTC and TDF are nucleoside reverse transcriptase inhibitors (NRTIs), which act by blocking RT enzyme, preventing HIV from multiplying and reducing the amount of HIV in the body.[23]

2.4 Strength of Study Products

2.4.1 Dapivirine Vaginal Ring (VR)

The dapivirine VR (Ring-004) contains 25 mg of dapivirine. Ring-004 is a matrix VR in which the drug substance is dispersed in a platinum-catalyzed cured silicone.[22]

2.4.2 FTC/TDF Tablet

The once-daily film-coated FTC/TDF oral tablet contains 200 mg of FTC and 300 mg of TDF, equivalent to 245 mg of tenofovir disoproxil, as active ingredients. Choice of the FTC/TDF oral tablet strength is based on the available strength of Truvada®, a US FDA approved medication with the indications of treatment and prevention of HIV-1 infection. Dosages used in MTN-034 are the same as licensed doses, and the safety profile has been assessed as part of FDA licensure.[23]

2.5 Nonclinical Studies

2.5.1 *In vitro* Studies of Dapivirine

Anti-HIV-1 Activity

The activity of dapivirine 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 HIV-1 isolates encoding one or more known NNRTI resistance mutations.[28,29]

The anti-HIV activity of dapivirine was also confirmed in an *ex vivo* model of human cervical explant cultures and a humanized severe combined immunodeficient mouse model.[28,29] Pre-treatment of tissue with dapivirine for 2 or 24 hours inhibited HIV-1 infection when challenged with virus on Days 0, 2, 4 and 6 post drug removal. Dapivirine 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, dapivirine (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]).

Dezzutti et al.[30] evaluated dapivirine gel for gel product attributes, efficacy, and safety. Dapivirine gel was safe toward ectocervical and colonic mucosal tissue. The dapivirine gel fully protected ectocervical tissue when 8 µM of dapivirine gel was added to the ectocervical explant cultures while 0.8 µM of dapivirine gel added to colonic explant cultures was needed. These data provide additional safety and efficacy results of dapivirine when used topically at either mucosal site.

Resistance

HIV-1 breakthrough in the presence of dapivirine was initially evaluated in studies in which cells were infected with wild-type HIV-1 laboratory strains at a high multiplicity of infection and in the presence of increasing concentrations of dapivirine. At a dapivirine concentration of 40 nM, virus breakthrough occurred between 4 and 7 days; at 200 nM, breakthrough occurred between 7 and 10 days; and at 1 µM, virus breakthrough took up to 30 days to occur. In all cases, mutations were present. Virus that selected for the Y181C mutation was resistant to dapivirine. Subsequently, cells were infected with wild-type HIV-1 at low multiplicity of infection and were exposed to very low concentrations of dapivirine to mimic the extremely low systemic concentrations observed in the first clinical trial of one formulation of topical dapivirine (Gel-001).[22]

In the first experiment, population sequencing performed following prolonged exposure of HIV-1_{LAI}-infected MT4 cells to low concentrations of dapivirine for a period of approximately 30 days identified several NNRTI resistance-associated mutations, including Y181C, at dapivirine concentrations of 10 nM and 100 nM, but not at 1 nM and 0.1 nM concentrations. However, both Y181C and V179I were detected when single viral genomes were analyzed by end-point dilution at 1 and 0.1 nM concentrations. The frequency of Y181C was 10-12% both at 1 and 0.1 nM.[22]

In a second series of experiments using the same and lower dapivirine concentrations, population sequencing identified the Y181C mutation at 1 nM, but not at lower concentrations. Analysis using a more sensitive end-point dilution technique in which the genotypic sequence of 25 to 30 individual viral genomes was determined indicated the presence of Y181C at 0.1 nM, and possibly 0.01 nM (approximately 10-fold lower than the EC_{50} for dapivirine).[22]

The significance of Y181C in a single clone at 0.01 nM in the 31-day culture is not clear. It is possible that the sensitive single genome sequencing technology detected some of the pre-existing natural variants present in a virus population in the absence of selective pressure. It was concluded that prolonged exposure to low concentrations of dapivirine can result in selection of viruses carrying NNRTI resistance-associated mutations, but the clinical relevance of these *in vitro* data is not known.[22]

Experiments comparing the selection of resistant viruses following exposure to dapivirine with that following exposure to the NNRTIs UC781, MIV-160, NVP and EFV, showed that dapivirine

demonstrated a high genetic barrier to resistance development in three viral isolates from subtypes B, C, and CRF02_AG. Fully resistant viruses took 12 weeks to emerge, whereas reduced susceptibility to the NNRTIs UC781, EFV and NVP was detected within 5 weeks. Unlike UC781 and MIV-160, dapivirine did not select for mutations common to all three isolates, although the subtype C VI829 and CRF02_AG MP568 viruses contained the mutations L100I and E138K. Other mutations selected under dapivirine pressure included E138Q, K101E, V108I, K103N, Y181C, V179M/E and F227Y.[22]

To evaluate whether the presence of resistance mutations impaired replication fitness, p2/p7/p1/p6/PR/RT/INT-recombinant NNRTI-resistant viruses were constructed and viral growth evaluated. Only four out of 15 resistant viruses showed impairment in replicative fitness; however, one of them was a dapivirine-resistant form of VI829.[22]

Cross-resistance

In comparison with NVP, DLV, EFV and emivirine, dapivirine 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.[22]

When tested against 433 clinical isolates with phenotypic resistance to at least one of the NNRTIs (NVP, DLV, EFV, or dapivirine), dapivirine 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 dapivirine-resistant strains were inhibited by EFV.[22]

Dapivirine cross-resistance was also evaluated *in vitro* against subtype C HIV-1 with at least one NNRTI mutation from individuals failing ART with high viral loads (HIV-1 RNA > 10,000 copies/mL). Recombinant HIV-1_{LAI} containing bulk-amplified, plasma-derived, full-length reverse transcriptase were generated. Fold change (FC) values were calculated compared with a composite 50% inhibitory concentration (IC_{50}) from 12 recombinant subtype C HIV-1_{LAI} plasma-derived viruses from treatment-naive individuals in South Africa. Of 100 samples, 91 exhibited ≥3-fold cross-resistance to DPV. Nine of 100 samples were susceptible to DPV (FC <3). Mutations L100I and K103N were significantly more frequent in samples with >500-fold resistance to DPV compared to samples with a ≤500-fold resistance. Although the majority of NNRTI-resistant HIV-1 from individuals on failing first-line ART in South Africa exhibited >3-fold cross-resistance to DPV, the very high genital tract DPV concentrations from DPV ring could still block viral replication from both wild-type and cross-resistant viruses.[31]

2.5.2 *In vitro* studies of Emtricitabine (FTC) and Tenofovir Disoproxil Fumarate (TDF) in Combination

Animal Studies

The prophylactic activity of the FTC/TDF oral tablet taken daily was evaluated in a controlled study of macaques inoculated once weekly for 14 weeks with Simian Immunodeficiency Virus (SIV)/HIV-1 chimeric virus applied to the rectal surface. Of the 18 control animals, 17 became infected after a median of 2 weeks. In contrast, 4 of the 6 animals treated daily with oral FTC/TDF remained uninfected and the two infections that did occur were significantly delayed until 9 and 12 weeks and exhibited reduced viremia. An M184I-expressing FTC-resistant variant emerged in 1 of the 2 macaques after 3 weeks of continued drug exposure.[23]

Anti-HIV-1 Activity and Mitochondrial Toxicity

No antagonism was observed in combination studies evaluating the in vitro antiviral activity of

FTC/TDF. More information regarding anti-HIV-1 activity and mitochondrial toxicity studies can be found in the Truvada package insert.[23]

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.[23]

Cross-Resistance
Cross-resistance among certain NRTIs has been recognized. The M184V/I and/or K65R substitutions selected in vitro by the combination of FTC and unformulated TDF are also observed in some HIV-1 isolates from subjects failing treatment with TDF in combination with either lamivudine (3TC) or FTC, and other ARVs. More information regarding cross-resistance studies can be found in the Truvada package insert.[23]

2.6 Condom Compatibility Studies (Dapivirine Gel)

Chemical compatibility studies with different dapivirine-containing gel formulations have been conducted on the following types of condoms:[22]

- Non-lubricated latex condoms (male condom);
- Silicone lubricated latex condoms (male and female condoms);
- Aqueous lubricated latex condoms (male condom);
- Silicone lubricated polyurethane condoms (male and female condoms); and
- Silicone lubricated nitrile condoms (female condom).

The results of condom compatibility testing indicate that dapivirine-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 ring 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.

2.7 Clinical Studies

2.7.1 Clinical Studies of Dapivirine Vaginal Rings

To date, a total of 29 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted, with all but two completed:[22]

- Eight trials of dapivirine VRs (containing 25 mg loads); a total of 298 participants were assigned to receive dapivirine VRs,
- Eight trials of dapivirine vaginal gel; a total of 491 participants were assigned to receive dapivirine vaginal gel,

- Eleven trials of oral dapivirine; a total of 211 participants were assigned to receive oral dapivirine,
- Two trials of dapivirine vaginal film; a total of 71 women were assigned to receive dapivirine vaginal film.

Additionally, two recently completed Phase 3 trials, MTN-020 (ASPIRE) and IPM 027 (The Ring Study), evaluated long-term safety and efficacy of the 25 mg dapivirine vaginal Ring-004, in which the VR was replaced with a new VR after approximately 28 days of use. A total of 4588 participants were enrolled between the two studies, with 2620 assigned to receive dapivirine VRs.[13,14]

Clinical Pharmacokinetics (PK)

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

The clinical PK profile of Ring-004 dapivirine VR formulation evaluated in IPM 013 showed a rapid increase in plasma and vaginal fluid concentrations of dapivirine after ring insertion.[22] Maximal dapivirine plasma concentrations were achieved in plasma by Day 7 post VR insertion and maximal dapivirine concentrations in cervicovaginal fluids (CVF) were achieved between Day 1 and Day 14 post VR insertion. Dapivirine concentrations decreased steadily over the remainder of a 28-day or 35-day ring use period. Plasma dapivirine concentrations did not exceed 1 ng/mL, and were therefore well below concentrations at the maximum tolerated dose (MTD) for multiple oral dapivirine doses. For dapivirine in CVF, the highest dapivirine concentration was observed in the area where the ring was placed, followed by the cervix, with the lowest concentrations near the introitus.

Data from post-use analysis of residual levels of dapivirine in Ring-004 (IPM 015, in which a ring containing dapivirine 25 mg was inserted once every 28 days over a 12-week period) indicate that, on average, 4 mg of dapivirine were released over approximately one month of ring use.[22] The mean remaining amounts of dapivirine in the used VR were similar for Weeks 4, 8 and 12 (post-insertion), at 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 dapivirine and corresponding plasma concentrations (i.e., at scheduled ring removal). Dapivirine plasma concentrations below approximately 200 pg/mL were generally associated with above-average ring residual amounts, while plasma concentrations above 200 pg/mL were generally associated with relatively constant residual levels (between approximately 20 and 22 mg).

Safety

Table 1: Phase 1-3 Clinical Trials of Dapivirine Vaginal Rings

Trial Details			Number of Participants				
Trial Number	**Description**	**Country**	**Ring-001 reservoir (200 mg)**	**Ring-002 reservoir (25 mg)**	**Ring-003 matrix* (25 mg)**	**Ring-004 matrix** (25 mg)**	**Placebo Ring**
IPM 001	Safety and PK in women; 7 days	Belgium	12	--	--	--	12 (crossover)
IPM 008	Safety and PK in women; 7 days	Belgium	--	10	--	--	3

Trial Details			Number of Participants				
Trial Number	**Description**	**Country**	**Ring-001 reservoir (200 mg)**	**Ring-002 reservoir (25 mg)**	**Ring-003 matrix* (25 mg)**	**Ring-004 matrix** (25 mg)**	**Placebo Ring**
IPM 013	Safety and PK in women; 56/57 days	Belgium	--	--	--	36	12
IPM 015	Safety and PK in women; 84 days	Multiple Countries in Sub-Saharan Africa	--	--	--	140	140
IPM 018	Safety and PK in women; 28 days	Belgium	--	8	8	--	8
IPM 024	Safety and PK in women; 28 days	Belgium	--	--	--	8	8
MTN-013/ IPM 026***	Safety and PK in women; 28 days	United States	--	--	--	12	12
IPM 028	Drug-drug Interaction (miconazole nitrate); 28 days	Belgium				36	0
IPM 034	Safety and PK in women; 7, 14, 28, 56, or 84 days	Belgium				40	0
IPM 027	Safety and efficacy in women; 24 months	Multiple Countries in Sub-Saharan Africa	--	--	--	1307****	652
MTN-020	Safety and effectiveness in women; 2 years	Multiple Countries in Sub-Saharan Africa	--	--	--	1313	1316
MTN-024/ IPM 031	Safety in post-menopausal women; 12 weeks	United States	--	--	--	72	24
MTN-023/ IPM 030	Safety in adolescents; 24 weeks	United States	--	--	--	72	24
TOTAL = 5235 participants			**12**	**18**	**8**	**3036**	**2211**

*Tin-catalyzed matrix ring.
**Platinum-catalyzed matrix ring
***MTN-013/ IPM 026 was the first in human clinical trial of a VR containing maraviroc (MVC) alone, dapivirine alone or a combination of the two (dapivirine/MVC) compared to placebo. The dapivirine VR arm included 12 participants. It should be noted, however, that the dapivirine VR was similar to Ring-004, but of slightly different composition.
****One participant randomized to Ring-004 did not receive the investigational product (IP) and had to withdraw from the trial prior to ring insertion.

Across all clinical trials conducted in healthy participants evaluating multiple ring configurations, the dapivirine VR was generally safe and well-tolerated.[22]

The first dapivirine VR tested in humans, Ring-001, consisted of two reservoir cores containing a total of 200 mg dapivirine surrounded by a controlled-release outer sheath of silicone elastomer. Ring-001 was tested in a Phase 1, open-label, crossover trial in 12 healthy, sexually abstinent, HIV-uninfected women at a single research center in Belgium (IPM 001).[33] Women used the placebo ring for 7 days followed by the dapivirine ring for seven days. No SAEs were reported during the trial, and few treatment-emergent adverse events (TEAEs) were observed. The

Dapivirine Ring-001 ring was considered to be safe based on the results of this trial in healthy participants.

Ring-002, a similar formulation with a single dapivirine reservoir core containing 25 mg dapivirine, was tested in a Phase 1, randomized, placebo-controlled trial conducted in 13 healthy, sexually abstinent, HIV-uninfected women at a single research center in Belgium (IPM 008).[33] Ten women used the Dapivirine Ring-002 and three women used a placebo ring for seven continuous days. No SAEs were reported during the trial and few TEAEs were observed. The trial results showed that the Dapivirine Ring-002 was safe in healthy participants.

Ring-003, a dapivirine matrix VR containing 25 mg of drug substance dispersed in a tin-catalyzed-cured silicone matrix, was compared with Ring-002 in a Phase 1, randomized, placebo-controlled trial conducted at a single research center in Belgium (IPM 018).[34] Twenty-four healthy, HIV-uninfected women, 18 to 35 years of age, were randomly assigned (1:1:1) to dapivirine matrix ring, dapivirine reservoir ring, or placebo ring for 28 consecutive days. No SAEs were reported during the study. No TEAEs were determined to be definitely or probably related to the ring, and similar percentages of participants in the dapivirine and placebo ring groups had TEAEs considered possibly related to the ring.

Ring-004, the current formulation, is a dapivirine matrix VR containing 25 mg of drug substance dispersed in a platinum-cured silicone matrix. It has been evaluated in five completed clinical trials.[22]

The first clinical trial of Ring-004, IPM 024, was conducted in Belgium and enrolled 16 healthy, HIV-uninfected, sexually abstinent women between 18 to 40 years of age.[22] The women were randomly assigned to a dapivirine (25 mg) matrix ring or a placebo ring for 28 consecutive days. No SAEs were reported in the dapivirine VR group. No AEs were judged by the investigator to be related to the study agent. Most dapivirine VR group participants, 87.5% (7/8), experienced at least one TEAE. Of the women in the dapivirine VR group who experienced a TEAE, 50% (4/8) reported headache. Of the participants using dapivirine VRs, 50% experienced Grade 1 or Grade 2 metrorrhagia, 38% experienced vulvovaginal discomfort and 25% experienced nasopharyngitis. One participant experienced a Grade 1 vaginal hemorrhage in the dapivirine VR group.

IPM 013 was a Phase I, randomized, double-blind, placebo-controlled trial conducted over 3 months at one research center in Belgium (IPM 013).[22] Forty-eight healthy, HIV-negative, sexually active women between 18 to 40 years of age were assigned in groups of eight to one of two groups, Group A or Group B (unblinded assignment). Within each group, participants were randomized in a blinded manner, in a 3:1 ratio, to either the dapivirine ring or placebo ring, for a total of four treatment arms. In Group A, the first VR was removed on Day 28, and a second VR inserted after 3 days, on Day 31, for another 28 days. In Group B, the first VR was removed on Day 35, and a second VR was inserted after 3 days, on Day 38, for another 21 days. A third VR was inserted immediately following removal of the second ring on Day 59, and was inserted for 24 hours. No SAEs were reported during the trial. One participant discontinued the trial due to a TEAE of generalized pruritus; the event was not considered serious, of Grade 2 (moderate) intensity, and regarded by the investigator as possibly related to use of the dapivirine ring. No TEAEs were assessed by the investigator as definitely or probably related to the dapivirine ring, and a similar percentage of participants in the dapivirine and placebo ring groups had TEAEs considered to be possibly related to the VR.

IPM 015 was a double-blind, randomized, placebo-controlled Phase 1/2 trial conducted at 10 research centers in Kenya, Malawi, Tanzania and South Africa.[35] The trial was performed in 280

healthy, HIV-negative women who inserted a VR once every 21-35 days over a 12-week period. Five SAEs occurred during the trial, of which four occurred in placebo participants. None of the SAEs were judged to be related to product. No TEAEs related to study product led to premature discontinuation of ring use. In IPM 015, two vaginal bleeding events were reported; both occurred in the placebo ring arm.

IPM 028, the fourth trial of Ring-004 was a Phase I open-label, randomized, 3-period, 2-sequence, cross-over trial, to assess the drug-drug-interaction potential between Ring-004 and miconazole nitrate, administered as a single dose (1200 mg) vaginal capsule (Gyno-Daktarin®) in HIV-negative women, 18 to 40 years of age.[22] The trial was conducted at a Phase I unit in Belgium and enrolled 36 women, randomly assigned to one of two treatment sequences, ABC or BAC, during which they received three treatments, each separated by a washout period of 3 weeks: Treatment A = Dapivirine Vaginal Ring-004 inserted for 28 days; Treatment B = Dapivirine Vaginal Ring-004 inserted for 28 days along with a single dose of miconazole nitrate on Day 0; Treatment C = a single dose of miconazole nitrate inserted on Day 0. One SAE (fracture of the right acetabulum) was reported in a participant during the washout period who had been assigned to initial treatment with the dapivirine ring and miconazole vaginal capsule (Treatment B). The event was assessed as severe (Grade 3) and regarded by the investigator as unrelated to the IP. One TEAE was considered by the investigator as related to IP use during the trial. The participant was enrolled in Treatment Sequence ABC and experienced moderate (Grade 2) vulvovaginal candidiasis during the ring use period of Treatment A, two days before the scheduled ring removal. Based on all safety evaluations performed, no overall clinically significant differences were observed between treatment with the dapivirine VR alone, in co-administration with miconazole, or miconazole alone.

IPM 034, the fifth trial of Ring-004 was a Phase I open-label, parallel group trial, to assess the release profile of Ring-004 over extended periods of ring use in HIV-negative women, 18 to 40 years of age.[22] The trial was conducted at a Phase I unit in Belgium and enrolled 40 women in five groups (Groups A, B, C, D and E) of eight women each. Each woman was administered one dapivirine ring and instructed to use the ring continuously for a period of 7, 14, 28, 56, or 84 days (1, 2, 4, 8, or 24 Weeks). One SAE (thoracic vertebral fractures following a motor vehicle accident) was reported in a participant using the dapivirine ring in Group C. The event was assessed as severe (Grade 3) and regarded by the investigator as unrelated to the IP. Product-related TEAEs were reported for four women during the trial of whom three experienced mild vaginal discharge (one woman with a 56-day ring use period and two women with an 84-day ring use period) and one experienced moderate bacterial vaginosis (BV) (84-day ring use period). Based on all safety evaluations performed during the trial, no overall clinically significant differences were observed between the different ring use periods.

MTN-013/IPM 026, a Phase 1 safety and PK study of dapivirine VR, MVC VR, dapivirine/MVC VR and placebo VR, enrolled approximately 48 women between the ages of 18-40.[36] The participants were randomized in a 1:1:1:1 ratio to one of the four products, with all groups assigned to 28 days of continuous study VR use. Over the course of 52 days, 14 follow-up visits occurred. No statistically significant difference in the number of participants with genitourinary AEs was noted between placebo arm and any other treatment arms. Twenty-two women experienced 33 grade 1 and one grade 2 related genitourinary AEs. Two grade 2 AEs were determined to be related to study product. At Day 28, dapivirine vaginal fluid levels were 14.9 µg/mL in women assigned to the dapivirine only ring.

MTN-024/IPM 031, a multi-center, two-arm, randomized, double blind, placebo-controlled Phase 2a trial, enrolled 96 healthy, HIV-uninfected, post-menopausal females, 45-65 (inclusive) years of

age.[37] Participants were randomized in a 3:1 ratio to one of the following study groups: placebo VR or dapivirine (25 mg) VR. Each enrolled participant was followed for approximately 13 weeks (12 weeks on study product and a final phone call one week after end of study product use). Dapivirine VRs were safe and well tolerated in postmenopausal women. There was no difference in the number of women with related Grade 2 or higher reproductive system AEs in the dapivirine vs placebo arms (6/72 (8%) vs 3/24 (13%), p=.68), and no statistical difference in Grade 3 or higher AEs in the dapivirine vs placebo arms (4/72 (6%) vs 0/24 (0%), p=0.57). One grade 3 AE, vaginal pain, was deemed related to study product. There were 6 protocol-required product holds for 5 women, all due to AEs which resolved; 2 women in the dapivirine arm declined to restart product. Median dapivirine concentrations in plasma and vaginal fluid showed no significant change over 12 weeks. The median residual drug level for returned VRs across all visits was 21.1 mg, consistent with adherence to VR use.

MTN-023/IPM 030 was a double-blind, randomized, Phase 2a clinical trial designed to assess the safety of a VR containing 25mg of dapivirine in HIV-uninfected adolescent females (ages 15-17 years old, inclusive) in the United States.[38] Ninety-six participants were randomized 3:1 to use either the dapivirine ring or a placebo ring every four weeks over approximately 24 weeks. The trial was initiated at the request of the US FDA to collect safety data for the dapivirine VR when used by an adolescent population, and results were presented at the 2017 International AIDS Society (IAS) Conference in July 2017. The dapivirine VR was safe to use by adolescent females. The mean age of the 96 participants enrolled was 16.3 years; 59% were black and 34% white. There were no differences in safety outcomes between study arms.

Extended Safety and Efficacy

In March of 2012, IPM 027, also known as The Ring Study, was initiated. IPM 027 is a randomized, double-blind, placebo-controlled efficacy and long-term safety study that enrolled 1959 healthy, HIV-uninfected women, ages 18-45. Approximately 1762 women in South Africa and 197 in Uganda were randomized in a 2:1 ratio to receive either a dapivirine ring or a placebo ring. Study participants used either the dapivirine ring or the placebo ring every four weeks over approximately two years. The main goals of The Ring Study are to evaluate the long-term safety and efficacy of the dapivirine ring for the prevention of HIV-1 as compared to a placebo ring, when used by healthy, HIV-negative women over a two-year period. Additional goals include measuring the incidence of curable STIs, HIV-2 and pregnancy; monitoring ring acceptability (how well women liked using the ring) and adherence (if women used the ring as intended) as reported by the study participants; and tracking the development of any HIV-1 drug resistance in participants who become HIV positive during the study.[12,13]

The median age at enrollment was 25 years, and 91% were unmarried. At the data cut-off point, the total number of person years of follow-up was 2805, 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 dapivirine ring (incidence 4.08 per 100 person-years) and 56 among women assigned to placebo (incidence 6.10 per 100 person-years). The dapivirine 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.[12,13]

No clinically significant differences in the frequency of TEAEs were detected between the dapivirine and placebo treatment groups, and the majority (>80%) were assessed as moderate (Grade 2) or mild (Grade 1) in severity as per the current Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events or Female Genital Grading Table for use in Microbicide Studies at the time of diagnosis. Product-related AEs in both treatment groups

included metrorrhagia, menometrorrhagia, pelvic discomfort/pain, suprapubic pain and application site pain, and all were assessed as mild (Grade 1) in severity by the Investigator. There were no statistically significant differences in the frequency of the primary safety endpoints between the study arms. Further, there was no overall difference between NNRTI resistance profiles.[22]

MTN-020, A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), was a Phase 3 clinical trial designed to assess the efficacy and safety of a ring containing 25 mg of dapivirine for the prevention of HIV-1 acquisition in women. The double-blind, randomized controlled trial was conducted in HIV-uninfected women, between the age of 18 and 45. A total of 2629 women from Malawi, South Africa, Uganda, and Zimbabwe enrolled in the trial. Participants replaced the ring monthly for a minimum of one year. MTN-020 aimed to determine the safety and efficacy of the dapivirine ring in preventing HIV-1 infection among healthy sexually active HIV-uninfected women when inserted vaginally once every 4 weeks. Additional goals of MTN-020 included the assessment of participant acceptability and adherence to the investigational product, HIV-1 drug resistance mutations among participants who acquired HIV-1 infection and establishing steady state drug concentrations in the study population. Results were presented at the February 2016 CROI[11] and published that same month in the New England Journal of Medicine[14].

A total of 168 HIV-1 infections occurred: 71 among those assigned the dapivirine VR and 97 among those assigned the placebo ring (incidence 3.3 and 4.5 per 100 person-years, respectively). Dapivirine ring 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 that 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, with objective markers of adherence lower in this subgroup compared to women older than 21.[14]

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 as per the current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events or Female Genital Grading Table for use in Microbicide Studies at the time of diagnosis. Finally, among those acquiring HIV-1, detection of NNRTI mutations did not differ by study arm (8/68 assigned dapivirine and 10/96 assigned placebo, p=0.80).[22]

The dapivirine ring was safe and effective in preventing HIV infection in both ASPIRE and The Ring Study. Results suggest the dapivirine ring could be an important HIV prevention option for women at risk of HIV infection. Two open label studies are currently under way to evaluate the VR's effectiveness in a more real-world setting as the VR moves through the marketing approval process.

MTN-025, the HIV Open-label Prevention Extension (HOPE) trial, is a multi-site, open-label, randomized, Phase 3b trial currently being implemented in the ASPIRE trial research sites. Eligible HIV-uninfected ASPIRE participants will receive the same VR used in MTN-020, a silicone

elastomer VR containing 25 mg of dapivirine, to be replaced monthly, for a total period of 12 months of use. Study follow-up visits will occur monthly for the first 3 months and quarterly thereafter, reflecting a transition to a more real-world type of follow-up (versus a clinical trial approach). The study will evaluate the safety of and participant adherence to the dapivirine (25 mg) VR in the context of an open-label extension trial, reflecting a transition to a more real-world type of product use where the participants know they are getting an active product that has been shown to be safe and effective when used as indicated. The HOPE sample size will be contingent upon how many former ASPIRE participants are interested in enrolling, are HIV- negative and otherwise eligible to enroll.

IPM 032, the Dapivirine Ring Extended Access and Monitoring (DREAM) study, is a multi-site, open-label follow-on trial to The Ring Study currently being implemented in six of the IPM 027 sites. Approximately 1700 eligible HIV-uninfected former Ring Study participants, as well as ring-naive women aged 18-25, will receive the same VR used in The Ring Study. Like the HOPE study, DREAM study participants will be asked to use the VR for a total period of 12 months, replacing it monthly, and to attend monthly study follow-up visits for the first 3 months and quarterly thereafter. In addition to offering former Ring Study participants access to the VR and evaluating the safety of and participant adherence to the dapivirine VR in the context of an open-label extension trial, the DREAM study will also explore when, how and why young women use the ring, as well as how adherence may affect the VR's efficacy and ways to support effective VR use.

2.7.2 Clinical Studies of FTC/TDF Tablet (Truvada®)

Clinical Pharmacokinetics

A PK study was conducted to establish the bioequivalence of the FTC 200 mg/TDF 300 mg fixed-dose combination tablet relative to administration of FTC capsules and TDF tablets in their individual dosage forms.[23,39] The steady state PK of FTC and TFV were unaffected when FTC and TDF were administered together as compared to when each agent was dosed alone.

Truvada® may be administered with or without food.[23] *In vitro* and clinical PK drug-drug interaction studies have shown that the potential for CYP450 mediated interactions involving FTC and TFV with other medicinal products is low. FTC and TFV are primarily excreted renally by a combination of glomerular filtration and active tubular secretion. No drug-drug interactions due to competition for renal excretion have been observed; however, coadministration of FTC/TDF 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.

Clinical Studies of FTC with TDF in HIV Infection

Several studies have assessed the safety and efficacy of FTC (Emtriva®) with TDF (Viread®), albeit none using the fixed dose combination. Four-hundred and forty-seven HIV-1 infected patients have received combination therapy with FTC and TDF with either a NNRTI or protease inhibitor for 48 weeks in clinical studies. AEs and laboratory abnormalities observed in clinical trials were generally consistent with those seen in other studies in treatment-experienced or treatment-naïve patients receiving FTC and/or TDF.

Gilead Study 934 was a Phase 3, randomized, open-label, noninferiority, multicenter study designed to compare a regimen of TDF 300 mg + FTC 200 mg + EFV QD with a regimen of ZDV 300 mg/3TC 150 mg BID (as FD Combivir®) + EFV QD in ARV-naïve, HIV-1-infected participants.[40] The 48-week data demonstrated that using the time to loss of virologic response

as the primary analysis (where missing, switch, or early termination is counted as a failure), the proportion of participants with plasma HIV-1 ribonucleic acid (RNA) levels < 400 copies/mL in an intent-to-treat (ITT) population (n = 487) was 84% in the TDF + FTC group compared with 73% in the ZDV/3TC group (P = 0.002). The proportion of participants with plasma HIV-1 RNA levels < 50 copies/mL was 80% in the TDF + FTC group versus 70% in the ZDV/3TC group (p = 0.020). Safety analysis, based on 511 participants who received any study medication, showed that discontinuation due to AEs occurred more frequently in the ZDV/3TC group (9%) than in the TDF + FTC group (4%) (P = 0.02). The most common AE resulting in discontinuation related to study drug was anemia for the ZDV/3TC group (14/254) and NNRTI-associated rash (2/257) for the TDF+FTC group. Renal safety was similar in the two groups, and no participant discontinued study medication because of renal events. All participants with confirmed >400 copies/mL of HIV-1 RNA at week 48 or early discontinuation were analyzed for genotypic resistance. Genotype data were limited to 23 participants on ZDV/3TC and 12 participants on TDF + FTC, and showed mostly M184V/I (3% in ZDV/3TC participants vs. 1% in TDF + FTC participants) and/or EFV-resistance mutations (7% in ZDV/3TC vs. 4% in TDF + FTC participants), with no participants developing the K65R mutation.

Exacerbations of hepatitis B virus (HBV) have been reported after discontinuation of TDF and FTC. HIV-infected persons co-infected with HBV may have increased values on liver function tests and exacerbation of hepatitis symptoms when TDF or FTC is stopped.[23] Usually symptoms are self-limiting; however, serious complications have been reported. Causal relationship to TDF or FTC discontinuation is unknown. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with use of nucleoside analogues alone or in combination, including FTC, TDF, and other ARVs. However, the incidence of many of these complications is lower with TDF/FTC than with other NRTI ARVs such as d4T, ddI and ZDV.[41]

A review[42] of seven completed PrEP randomized clinical trials with a combined 18,747 female and male participants, including the iPrEX (Iniciativa Profilaxis Pre-Exposición), PartnersPrEP, 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) trials, evaluated safety, efficacy, adherence and potential barriers to 'real-world' uptake. Across all trials, reduction in HIV risk provided by oral TDF alone or in combination with FTC ranged from 0%–75%. While adherence to daily pill-taking assessed by pill counts and self-report was high at 84%–95%, the proportion of participants in the PrEP arms with detectable serum drug levels was lower, ranging from 24%–82%. Regarding safety, TDF-based oral PrEP did not increase rates of serious (grade 3 or 4) AEs in any studies. In some studies the risk of nausea, vomiting, diarrhea, unexplained weight loss, fatigue, and dizziness was higher than with placebo. Side effects were generally mild, infrequent (affecting 1%–10% of participants), and disappeared after 1 to 2 months of use. Drug resistance was rare among participants who were HIV-negative at enrollment but became infected during follow-up (0%–12% of incident cases); however, resistance was frequently observed in those who started PrEP while already infected (up to 100% of such cases).

Effectiveness of Truvada® as PrEP in Studies that Enrolled Women

On July 16, 2012, the US FDA approved the use of Truvada® to be taken once daily in combination with safer sex practices, to reduce the risk of sexually acquired HIV-1 infections in adults who are at high risk of becoming infected with HIV-1. In late 2015, both the South African MCC and the Kenyan PPB also approved Truvada® for use as oral PrEP by adults at high risk of sexually acquiring HIV-1 infection.[25]

Below is a summary of data completed prior to the US FDA's consideration of Truvada® for the HIV prevention indication:

MTN-003 (VOICE)
VOICE was a Phase 2b, multi-site, five-arm, randomized, controlled trial. A total of 5,029 predominantly young, unmarried women were randomized in a 1:1:1:1:1 ratio to one of five regimens: oral TDF (300 mg) and TDF-FTC placebo, oral TDF-FTC (300 mg of TDF and 200 mg of FTC) and TDF placebo, oral TDF placebo and oral TDF-FTC placebo, vaginal 1% TFV gel, or vaginal placebo gel. The VOICE trial was unique within the HIV prevention field as it was designed to provide parallel comparisons of oral and topically (vaginal) applied ARV strategies for prevention of HIV infection in women.[43]

All participants completed study follow-up on 13 August 2012, with an overall study retention rate of 91% during 5509 person-years of follow-up. Findings showed that there were no statistically significant differences in rate of new infections when each study product arm was compared to placebo. Excluding 22 cases of acute HIV infection detected at enrollment, the overall incidence of HIV-1 infection was 5.7 per 100 person-years. In the modified ITT analysis, the effectiveness was −4.4% with TDF-FTC (hazard ratio, 1.04; 95% CI, 0.73 to 1.49). Elevations of serum creatinine levels were seen more frequently among participants randomly assigned to receive oral TDF-FTC than among those assigned to receive oral placebo (1.3% vs. 0.2%, P=0.004). Following Data and Safety Monitoring Board (DSMB) reviews, the oral TFV tablet study arms and the vaginal TFV gel and corresponding placebo arms were stopped due to futility. No other significant AE differences were observed. The results may be due, in part, to low adherence to study products.[43]

Partners PrEP
Partners PrEP, a study of TDF or FTC/TDF in serodiscordant heterosexual couples in Kenya and Uganda reported high efficacy against HIV acquisition, and the DSMB overseeing the trial recommended stopping the placebo arm early.[44] The team enrolled a total of 4,758 HIV serodiscordant couples. Participants were randomized in a 1:1:1 ratio, to TDF, FTC/TDF, and a matched placebo. 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 FTC/TDF 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 FTC/TDF PrEP efficacy estimates ranged from 64% to 84%.[45]

Additional analyses from the Partners PrEP data relevant to MTN-034 were findings for: the efficacy of TFV-containing PrEP in reducing HSV-2 incidence,[27] efficacy in women on depot medroxyprogesterone acetate (DMPA) contraception,[46] safety in early pregnancy,[47] the low incidence of drug resistance in PrEP users detected by sensitive assays,[48] and the low incidence and reversibility of renal glomerular changes.[49]

TDF2 Study
The Botswana TDF2 Study[50] was a double-blind, randomized study that enrolled 1,219 HIV-uninfected, sexually active, heterosexual males and females (45.7% women) ages 18-39 in Gabarone and Francistown. Participants were randomized to either daily TDF/FTC PrEP or placebo (1:1) once daily, with monthly follow-up visits for a median of about 1 year. The trial was ended early due to low retention. PrEP was found to be effective in this population, reducing the risk of acquiring HIV infection by approximately 62%. Adherence and risk reduction counseling, condoms, and STI testing/treatment were also provided. The level of protection was strongly related to adherence to the daily pill regimen. Limiting analysis to HIV infections that occurred within 30 days after a participant's last reported dose indicated that TDF/FTC reduced the risk of

HIV infection by 78%, and participants who became HIV-infected had far less drug in their blood than matched participants who did not become infected. Although the study had limited power for gender sub-analysis, among young female participants known to have a supply of study drug, the efficacy of daily oral PrEP was high. There were 3 infections among those receiving TDF/FTC and 13 infections among those receiving placebo, translating into a statistically significant HIV risk reduction of 75.5 percent (CI 23.8 to 94.4; p=0.021). Additional information about the study can be found in Section 2.9.2.

FEM-PrEP

The FEM-PrEP Study[51] was a Phase 3, randomized, placebo-controlled trial of the effectiveness of daily oral FTC/TDF for HIV prevention among HIV-uninfected women in Kenya, South Africa and Tanzania. The FEM-PrEP study enrolled HIV-negative women between the ages of 18 and 35 who were at higher risk for HIV. Higher risk was defined as: 1) has had at least one vaginal sex act in the last two weeks, or 2) has had more than one sexual partner in the last month. All participants in the study were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for STIs. This trial was stopped early for futility by the Independent Data Monitoring Committee on April 18, 2011. HIV infections occurred in 33 women in the FTC/TDF group (incidence rate, 4.7 per 100 person-years) and in 35 in the placebo group (incidence rate, 5.0 per 100 person-years). Adherence, measured by blood plasma drug concentrations, was low with less than 40 percent of a representative sample of HIV-negative participants recently taking study product. The study was unable to detect if FTC/TDF use could prevent HIV infection.

Corneli et al. (2015)[52] sought to identify participants' reasons for adhering or not to the study regimen by conducting qualitative, semi-structured interviews with 88 FEM-PrEP participants assigned to 3 adherence interview groups: high, moderate and none/scarce. Quantitative Audio Computer-Assisted Self-Interviews (ACASIs) were conducted with 224 participants. Five thematic factors facilitating adherence that often stressed personal motivations were identified: participants' support for the research, HIV risk reduction, routine formation and use of tools (pill boxes, calendars), adherence counseling, and partner awareness/support. Among ACASI participants who reported having taken a study pill, wanting to help answer the research question was the most often stated reason for taking the pills.

Bangkok Tenofovir Study

Demonstration and other projects indicate that at-risk individuals are motivated and able to use PrEP effectively when they receive counseling about its efficacy. The Bangkok Tenofovir Study[53] was a Phase 3, randomized, placebo-controlled trial of the effectiveness of daily oral TFV PrEP for HIV prevention among HIV-uninfected Thai men and women at higher risk for HIV. The study enrolled injection drug users ages 20-60 (N=2,411 evaluable participants; 20% female). Participants chose either daily directly observed treatment or monthly visits and were permitted to switch at monthly visits. They received monthly HIV testing and individualized risk-reduction and adherence counseling, quarterly blood safety assessments, and were offered condoms and methadone treatment. Adherence was higher in participants ages 40 and older and (controlling for age) higher in females than males. When combined with other HIV prevention services at the drug treatment clinics from which participants were recruited, once-daily oral TFV decreased the risk of HIV infection by 48.9%. The frequency of deaths, SAEs, Grade 3-4 laboratory results, and increased creatinine concentrations were similar in the TFV PrEP and placebo groups. Similar to other trials, nausea and vomiting were reported more frequently in the TFV group than the placebo group; a difference which resolved by Month 2 of follow-up. Grade 1-2 increases in alanine aminotransferase (ALT) concentrations were more common in the TFV group than placebo; the median difference at monthly visits was 1–5 U/L and did not increase over time. Participants

randomized to TDF did not exhibit higher rates of kidney disease or increased creatinine. The number and severity of other reported AEs were similar between groups. This study was the first to show that oral PrEP, when combined with other HIV prevention strategies, reduces the risk of HIV infection among injection drug users.

Uptake, adherence and efficacy of open label FTC/TDF in African women

The Partners Demonstration Project
ART and PrEP are potential prevention options for HIV-1 serodiscordant couples, Assessing potential delivery approaches to achieve maximal individual and public health benefits is critical. For HIV-1 serodiscordant couples, HIV-1 risk is greatest prior to and during the first months after ART initiation by the HIV-1 infected partner, before viral suppression is achieved. PrEP could offer substantial benefit prior to and during early ART. In a prospective implementation study of 1013 newly-recruited, high-risk heterosexual HIV-1 serodiscordant couples in Kenya and Uganda, PrEP was offered to the HIV-uninfected partner as a 'bridge' until the HIV-infected partner initiated ART and was on ART for at least 6 months, which is sufficient time for viral suppression. An estimated 95% reduction in HIV incidence was achieved in the Partners Demonstration Project.[54] Adherence and acceptability results can be found in Section 2.9.2. The study was concluded in July 2016.

HPTN 067 ADAPT
Additional research is needed to develop delivery strategies which emphasize both maximizing adherence and meeting the needs of all females in Africa. The HIV Prevention Trials Network (HPTN) 067/ADAPT (Alternative Dosing to Augment PrEP Pill Taking) Study[55,56] was a Phase II, randomized, open-label trial of varying oral FTC/TDF PrEP dosing strategies which included a cohort of 179 South African women in Cape Town. The study investigated whether a nondaily versus daily regimen of oral FTC/TDF resulted in equivalent prophylactic coverage of sex events, less tablets required, and fewer side effects. Following 6 weeks of directly-observed dosing (DOD), women (aged 18-52 [median 26]), 80% of whom were unmarried, were assigned to one of three PrEP regimens for 24 weeks of self-administered dosing: daily; twice weekly with a post-intercourse boost; or before and after intercourse. Adherence was highest in the daily dose arm. See Section 2.9.2 for acceptability and additional adherence results from the study.

HPTN 082
HPTN 082 is a Phase IV, randomized, open-label, multi-site prospective study that will assess PrEP acceptance and adherence among HIV-uninfected young women ages 16-25 years in South Africa (Cape Town and Johannesburg) and Harare, Zimbabwe. All participants will be offered once-daily oral FTC 200 mg/TDF 300 mg. The study will recruit approximately 400 young women who adopt PrEP at enrollment and up to 200 young women who are eligible and interested in PrEP but decline PrEP at enrollment, who will continue to be offered PrEP after enrollment. All women who accept PrEP will be randomized 1:1 to receive enhanced adherence counseling based on feedback from observed drug levels or standard adherence support. A subset of up to ~25 women per site (maximum 75), will participate in qualitative assessments of facilitators and barriers for PrEP acceptance, adherence and continuation. The primary study objectives are to assess the proportion and characteristics of young HIV-uninfected women who accept vs. decline PrEP at enrollment, and to assess the difference in PrEP adherence using counseling based on drug levels from the 4 and 8 week visits in participants randomized to the enhanced versus standard arms. Participants will be followed for 12 months. The trial began enrollment in October 2016.[57]

CHAMPS Pilot Study B: 'PlusPills'
CHAMPS: Choices for Adolescent Prevention Methods for South Africa, Pilot Study B: 'PlusPills' was a Phase II, open-label, demonstration, single group assignment study assessing PrEP acceptability and use among 149 healthy, HIV-uninfected young males and females, 15-19 years of age in South Africa (Cape Town and Soweto). All participants were followed for 12 months, and all participants took Truvada® (FTC 200 mg/TDF 300 mg) once daily by mouth for the first 12 weeks of the study. After Week 12 of the study, only participants who indicated a willingness to use Truvada® PrEP and who did not have any contraindicating medical reasons continued to receive the Truvada® tablets through Week 52. In addition to PrEP, an HIV prevention package including HIV testing, management of STIs, risk reduction counseling, access to condoms, post-exposure prophylaxis (PEP), and circumcision counseling/referral for male participants was provided. Between Months 11 and 12, some participants were randomly selected to participate in focus groups to discuss their experiences while taking PrEP. The study concluded in Q1/Q2 2017. Early data suggests side effects are minimal and early adherence reasonable, with most adolescents persisting with PrEP. It is hoped the study will help researchers understand use patterns and appropriate support measures for this important population.[58]

IMPAACT 2009
IMPAACT (International Maternal, Pediatric, Adolescent AIDS Clinical Trials Group) 2009: Feasibility, Acceptability and Safety of Oral PrEP for Primary HIV Prevention During Pregnancy and Breast Feeding in Adolescents and Young Women is a parallel, observational cohort study of HIV-uninfected pregnant adolescents and young women (aged 16-24). The study is designed to characterize adherence over time among women who initiate once-daily oral PrEP during pregnancy and continue in the first 6 months following delivery, and to compare pregnancy outcomes among participants who take PrEP and participants who decline PrEP during the antenatal period. As of Q4 2017, the trial is in development and sites have been selected in Zimbabwe, Malawi, Uganda and South Africa.[59]

2.8 Prevalence of Primary Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) and NRTI Resistance Mutations

2.8.1 Dapivirine Vaginal Ring (VR)

Primary NNRTI resistance from a WHO threshold surveillance study conducted between 2005-2009 categorized KwaZulu Natal as having 5-15% NNRTI resistance.[60] MTN-009 found 6.5% NNRTI resistance amongst participants screening for VOICE who were already HIV positive, with 87% of those with NNRTI resistance having HIV-1 with Y181C and/or K103N.[61] In the Stanford University HIV Drug Resistance Database, which compiled data through August 2015 from over 19,500 HIV-1 subtype C, A and D sequences from treatment-naïve and NNRTI-treated persons, the following was found:[62,63]

Table 2: Frequency of K103N

	Treatment-Naïve	NNRTI-experienced
Subtype C	77/8621 (0.9%)	1488/3392 (42%)
Subtypes A	33/3547 (0.9%)	157/543 (29%)
Subtype D	17/1320 (1.0%)	94/421 (22%)

(one isolate per person)

Table 3: Frequency of Y181C

	Treatment-Naïve	NNRTI-experienced

Subtype C	19/8672 (0.2%)	536/3977 (14%)
Subtypes A	5/4192 (0.1%)	120/747 (16%)
Subtype D	3/1600 (0.2%)	86/430 (20%)

(one isolate per person)

Proportion of HIV-1 seroconverters with antiretroviral resistance in the ASPIRE study, by randomization arm[14]

Plasma samples for HIV-1 antiretroviral resistance testing were obtained at the visit at which HIV-1 seroconversion was detected (at which time study medication was withdrawn). Resistance testing was successfully completed on plasma from 170/174 (98%) participants, which included 3/3 participants acutely infected at enrollment, 164/168 HIV-1 seroconverters while on study product, and 3/3 participants who seroconverted after their product use end visit. Overall, 4 participants did not have a resistance result, 3 because of insufficient copies of HIV-1 RNA for extraction (<200 copies/mL) and 1 because of polymerase chain reaction (PCR) amplification failure.

RNA extracted from plasma was reverse transcribed and HIV-1 pol was PCR amplified and sequenced using an in-house Sanger sequencing-based population genotyping assay optimized for non- B HIV-1 subtypes. Population sequences spanned from protease codon 1 through reverse transcriptase codon 335. Mutations in HIV-1 Group M subtype were identified using the Stanford HIV-1 Drug Resistance Database version 7.0.

The frequency of all NNRTI mutations were evaluated as mutations of potential clinical significance for resistance to dapivirine. Of the 164 participants with successful viral resistance results within the intention-to-treat cohort (i.e., excluding acutely infected participants and participants that seroconverted after cessation of product use), 10 out of 96 (10.4%) in the placebo arm had any NNRTI resistant strain, and 8 out of 68 (11.8%) in the dapivirine arm had any NNRTI resistant strain. The overall occurrence of NNRTI mutations was not different by arm (Fisher's Exact Test: 0.19, p=0.80).

Additional analyses examined the frequencies of a subset of four NNRTI resistance mutations including L100I, K103N, E138K and Y181C because of their potential relationship to dapivirine resistance based on in vitro selection studies.10 No subjects had HIV-1 with the E138K, L100I or Y181C detected. Four subjects had HIV-1 with the K103N mutation however the frequency of K103N detection did not differ by arm. Other NNRTI mutations detected included V90I, K101E, K103S, V106M, V108I, E138A/G, V179D/I/T and H221Y but the frequency of detection of these mutations also did not differ by arm. Several NNRTI mutations were observed to occur in combination, including E138A or G with V179D/I/T (n=2), V108I (n=1) or K101E (n=2); K103S with V106M (n=1) and V90I with K103N (n=2), but the frequency of more than one NNRTI mutation was not different between study arms.

2.8.2 FTC/TDF Tablet

Resistance to FTC-TDF is relatively infrequent.[64] Resistance to TDF is conferred by the relatively uncommon RT K65R and/or K70E mutations. Little baseline resistance to TDF is exhibited in TDF-naïve patients. FTC combined with TDF may offer a somewhat higher barrier to drug resistance.[65]

Resistance in individuals seroconverting while taking FTC/TDF tablet has been assessed from 5 placebo-controlled, Phase III trials. 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.[43,44,51,66,67] Resistance to TFV and FTC was found to be infrequent (3%) from use of TDF/FTC tablet for PrEP if HIV-1 infection is not present at the time PrEP is started (5 cases in 160 seroconverters assigned to TDF/FTC in 5 PrEP trials). Resistance to TFV and FTC is much more common (41%) if TDF/FTC PrEP is started during undiagnosed acute HIV-1 infection (7 cases in 17 participants).[48,68-72] The risk of resistance with FTC/TDF tablet is low if acute HIV-1 infection is excluded before starting PrEP.[73]

2.9 Behavioral Studies

2.9.1 Acceptability and Adherence: Dapivirine VR

MTN-013/IPM 026
MTN-013/IPM 026 was a Phase 1, multi-site, double-blind, randomized, placebo-controlled, 4-arm trial conducted at two US sites with 48 female, HIV-negative participants (mean age 29.6 ± 6.2 years) that evaluated VRs containing: 25 mg dapivirine (DPV) and 100 mg maraviroc (MVC); DPV only; MVC only; and placebo used continuously for 28 days.[36] It was the first study to include a combination VR (DPV/MVC). Adherence was primarily assessed by self-report; however, assessments included both Computer-Assisted Self-Interviewing (CASI) and face-to-face interview, and responses by CASI are expected to be less susceptible to social desirability bias.

All 4 VRs were found to be safe, well-tolerated, and women were highly adherent. Since this was a PK and safety study, participants were asked to abstain from penetrative intercourse and receptive oral sex throughout the study. Despite these restrictions limiting generalizability, study retention and adherence to VR use were high. Almost all women (94%) were fully adherent with 28 days of VR use by self-report. Residual VR drug levels supported these data. Mean residual DPV concentrations were 20.6 ± 0.8 mg (n=8) and 21.6 ± 1.6, n=8) in the DPV and DPV/MVC arms, respectively, representing 82% and 86% of the loaded doses. Mean residual MVC concentrations were 95.7 ± 8.0 mg (n=8) and 95.0 ± 7.6 mg in the MVC and DPV/MVC arms, respectively, representing 96% and 95% of the loaded dose. These residual drug levels are comparable to a previous study conducted by IPM that also found approximately 4 mg DPV released from the VRs (Ring-004) over 28 days, thus the rings were likely used as instructed. The high adherence displayed in this study is promising for further development of VRs given the impact of low adherence of daily microbicides on microbicide efficacy. However, since CVF and cervical tissue DPV levels rapidly decrease after ring removal, continuous use of the VR will likely remain important for efficacy.

IPM 011
IPM 011 assessed the acceptability of the dapivirine VR and the placebo VR in 170 women.[74,75] The trial was conducted across multiple sites in Tanzania and South Africa. The study participants found the ring to be very comfortable (95%), very easy to insert (94%) and remove (92%), and rarely were the rings felt during daily activities. All questionnaire respondents, when asked if they would be willing to use the VR if shown to be effective for HIV prevention, replied that they would use the VR. In IPM 011, 11% of the women experienced expulsions or removal, with the most common reason being 'menses related'. In the majority of cases (64%), the VR was washed and re-inserted.

IPM 015
In IPM 015, at Week 12, 97% of African women reported that the dapivirine VR was comfortable

and that they were willing to use the VR if it was found to be effective.[35] Women preferred to use the VR every day (97%) and reported that the ring did not interfere with their daily activities (89%). In terms of the male partner acceptability, 63% of women reported that their partner did not feel the ring during sex. Of those participants who reported that their partner felt the ring, only 1% reported that this might be or definitely was a problem. In IPM 015, perfect adherence was reported by 92% of the female participants. Perfect adherence was defined as never having the VR out for more than an entire day. Of the women who reported that the ring was out, the most common activity for expulsion was urination/defecation. The most common reason reported by participants for VR removal was to clean the VR. As the study progressed, more women reported removing the VR prior to sexual intercourse, 17% at week 2 and 36% by week 12.

MTN-024/IPM 031
MTN-024/IPM 031 also assessed adherence and acceptability of the dapivirine VR in 96 postmenopausal women across multiple sites in the United States.[76] Over three months of use, almost all study participants found the VR easy to use (99%), felt comfortable with the ring inside every day (97%), and liked the ring (93%). Most study participants felt the VR was easy to insert (85%), easy to remove (80%), and most (81%) kept the VR inside every day except for protocol-instructed removals; this last finding was confirmed by objective adherence markers. Over one third (36%) of study participants reported some change in their vagina over three months of use, with the majority of those not feeling bothered by those changes. Two thirds (65%) of study participants preferred the VR over condoms, and most participant worries about ring use decreased significantly after three months of use. Overall, the VR was very acceptable to study participants, and most were able to use the ring consistently.

MTN-023/IPM 030
MTN-023/IPM 030 also assessed adherence and acceptability of the dapivirine VR in 96 adolescent females across multiple sites in the United States.[38] Adherence to study visits was 97%. By self-report, 42% (95% CI: 32%-52%) of participants reported that they never removed the ring except to replace it monthly. In the dapivirine group, drug levels indicated adherence in 87% of plasma samples and 95% of rings. Participants noted no discomfort due to the ring at 87% of visits and "liking" the ring at 93% of visits. The most frequently cited concern (28%) involved their primary sex partner feeling the ring during sex.

2.9.2 Acceptability and Adherence: FTC/TDF Tablet as PrEP

MTN-003 (VOICE)
The MTN-003 (VOICE) trial is introduced in Section 2.7.2. Although adherence rates were high by self-report (88-90%) and returned product counts (86%), analysis of plasma drug levels showed that fewer than 30% of women enrolled in VOICE used their assigned study product. Lower adherence, as assessed by measurement of TFV levels in plasma, was associated with characteristics that predicted a higher risk of HIV acquisition. Results were consistent with those of the FEM-PrEP trial (Section 2.7.2), in which daily TDF-FTC 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 (Sections 2.7.2 and 2.9.2), which displayed a significant reduction in risk of HIV-1 acquisition. Of note was that VOICE participants who were most likely to adhere were similar in terms of age and marital status to women in the Partners PrEP trial.[43]

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. Despite the use of multiple measures to assess adherence, including ACASIs, fewer than half the participants disclosed non-adherence or barriers to use, and in fact products were returned in a manner consistent with high adherence. The VOICE trial 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.[43]

HPTN 067 ADAPT

Acceptability of and barriers and facilitators to adherence to various randomly assigned oral FTC/TDF PrEP dosing regimens (daily, twice weekly with a post-sex dose, and pre/post-sex dosing) were assessed via in-depth interviews (IDI) and focus groups among a subgroup of 179 Cape Town, South African women participating in the HPTN 067 ADAPT study. Encouragingly, in this cohort in which half were ≤25 years old, PrEP adherence was high. Adherence was highest in the daily dosing arm (92.5% of women at week 10, and 79.3% at week 30 who had reported sex in the week prior had detectable TFV in plasma).[56] Adherence was assessed via Wisepill dispenser data, plasma and PBMC (for TFV, FTC and metabolites) and was found to be highest in the daily PrEP arm. Prophylactic coverage of sex acts was also higher in the daily arm. The investigators concluded these findings may be attributable to better habit formation and more forgiveness for missed doses with a daily dosing regimen.[56]

Acceptability enhancers were found to include interpersonal support, personal belief in PrEP's efficacy, cellphone and other reminders, and keeping pills at hand. Dosing timed to sex was found to be a poor fit to usual post-sex routines (resting with partner, being away from home).

Similarly, Amico et al.[77] explored 60 HPTN 067 ADAPT participants' experiences via IDI and focus groups. These IDIs and focus groups explored facilitators and barriers to females' dosing regimen, experiences using PrEP and taking part in a PrEP study, and their level of engagement with the study. The team identified 5 common themes as facilitators of PrEP adherence: social support, understanding of regimen, efficacy beliefs, concrete strategies (such as reminder alarms), and need for protection (e.g., in case of rape). Five factors facilitating study participation were commitment/alignment (desire to help one's community, interest in the research), lived experiences (relatives who passed away due to AIDS), package of care (appreciation for testing and other clinic services), financial (study reimbursement), and feelings towards the team (their kindness and caring). Three themes presenting challenges to uptake or consistent adherence were safety concerns (e.g., side effects), community stigma/distrust, and negative clinic experiences (being asked highly personal or repetitive questions). Four themes presenting challenges to adherence were privacy/non-disclosure (e.g., to a partner), attributes of PrEP (e.g., odor), side effects (particularly nausea/vomiting), and PrEPs status as an ARV (concern that others would see the pills). While community stigma and personal distrust of PrEP led some women to discontinue use, the authors identified a subgroup, the 'PrEP Ubuntu' or 'PrEP champions', who in an effort to foster community acceptance of and trust in PrEP, purposefully disclosed their study participation and PrEP use. Additional details about HPTN 067 ADAPT may be found in Section 2.7.2.

Partners PrEP

Adherence was high as assessed via pill counts; 98% of dispensed pill bottles were returned, and 97% of dispensed tablets were taken. Study medication was used during 92.1% of the study follow-up time, after accounting for missed visits, various reasons for nondispensation of medication, and nonadherence to dispensed pills,. Consistent with these data, TFV was found in 82% of samples from randomly selected participants.[44] In a subgroup case-cohort analysis of participants in the active PrEP arms (29 seroconverters and 196 randomly selected controls who did not seroconvert), blood concentrations (plasma TFV) were used to assess adherence. Among

controls, 71% of visits had TFV concentrations >40 ng/mL, consistent with steady-state daily dosing, compared with 21% of cases at the visit when HIV was first detected; controls displayed consistent patterns of TFV concentrations throughout follow-up. TFV concentrations >40 ng/mL were associated with older age and shorter time on study; lower concentrations were associated with periods during which participants reported no sex with their partner. Pill count data indicated that 96% of nonseroconverting controls and 66% of seroconverting cases had >80% adherence for these same visits.[78]

Data from Partners PrEP[78] and other Phase 3 PrEP trials (i.e., iPrEx,[79] and VOICE[43]) indicate that adherence at early time points (as measured by assays such as TFV-DP levels in dried blood spot [DBS], or TFV in plasma) predict adherence over the next one to two years, suggesting that adherence-focused interventions should occur as soon as possible after initiation of PrEP. Additional information about Partners PrEP can be found in Section 2.7.2.

TDF2 Study
In the Botswana TDF2 study (details in Section 2.7.2, above) adherence as measured by pill counts was found to be similar between groups (84.1%, TDF/FTC group; 83.7%, placebo group) as was self-reported adherence for the preceding 3 days (94.4% and 94.1% respectively).[67] Adherence as measured by pill count was high among both study groups, at approximately 84%.

Phase 1 Pilot PrEP Study in Kenya
A Phase 1 pilot trial to evaluate safety, acceptability and adherence to either intermittent (2x weekly and within 2 hrs post-coitally) or daily PrEP was conducted in an at-risk Kenyan population (adult female sex workers and MSM [men who have sex with men]). The trial showed high acceptability. Post-trial qualitative assessments conducted with 51 of 72 participants found that oral PrEP would be feasible and acceptable regardless of dosing schedule, and also indicated that PrEP might be more acceptable than other HIV prevention methods in Kenya and other highly religious regions because it does not contain a contraceptive.[80]

Partners Demonstration Project
The Partners Demonstration Project is a completed open-label demonstration project among African heterosexual HIV serodiscordant couples that evaluated integrated delivery of PrEP and ART. Daily oral PrEP in HIV-uninfected partners was offered as a bridge until their HIV-infected partner initiated ART and completed 6 months of ART. Among 1,013 couples evaluated (20% of whom are <25 years old), PrEP uptake was high (95% at enrollment), PrEP adherence was high (86% with detectable TFV), ART initiation was high (80% by 12 months with 90% viral suppression), and HIV incidence was reduced by 95% compared to a counterfactual HIV incidence.[54]

ATN 110 Study
The Adolescent Trials Network (ATN) 110 study is a completed open-label demonstration project and Phase 2 safety study of oral PrEP use among young MSM aged 18-22 years old across multiple urban sites in the United States.[81] The study enrolled 200 participants, who attended HIV risk reduction behavioral interventions and were provided TDF/FTC tablets for daily use. Participants were on oral PrEP for 48 weeks, with monthly study visits during the first twelve weeks and quarterly visits for the remainder of their participation. PrEP adherence was assessed at each study visit by DBS, and PrEP acceptability and participant risk behaviors were assessed at each study visit by behavioral questionnaires.

STI rates were high at baseline (22% of participants) and remained high throughout the study, while condomless sex was reported by most participants (>80%). At the first follow-up visit (Week

4), over half of participants (56%) had protective drug levels indicative of consistent adherence (≥4 pills/week). However, by the end of the study (Week 48) only a third of participants (34%) exhibited such protective drug levels, with the biggest drop-off occurring at the first study visit of the quarterly visit schedule (Week 24). Higher adherence levels were associated with condomless anal sex with last partner. Acceptability was high throughout the study, with >90% of participants liking the overall study procedures, 60% finding the daily tablet regimen acceptable, and two thirds not minding the size of the tablet, though over half of participants did not like the taste of the tablet.

ATN 113 Study

The ATN 113 study is a completed open-label demonstration project and Phase 2 safety study of oral PrEP use among young MSM aged 15-17 years old across multiple urban sites in the United States.[82] The study enrolled 79 participants, who attended HIV risk reduction behavioral interventions and were provided TDF/FTC tablets for daily use. Participants were on oral PrEP for 48 weeks, with monthly study visits during the first twelve weeks and quarterly visits for the remainder of their participation. PrEP adherence was assessed at each study visit by DBS, and PrEP acceptability and participant risk behaviors were assessed at each study visit by behavioral questionnaires.

STI rates were high at baseline (15.4% of participants), though the total number of diagnosed STIs declined by more than half over the course of study duration. Condomless anal sex with last partner was reported by 60% of participants, and participants reported an average of two sexual partners in the previous month. At the first follow-up visit (Week 4), over half of participants (60%) had protective drug levels indicative of consistent adherence (≥4 pills/week). However, by the end of the study (Week 48) less than a third of participants (28.2%) exhibited such protective drug levels, with the biggest drop-off occurring at the first study visit of the quarterly visit schedule (Week 24). Acceptability was high throughout the study, with >90% of participants liking the overall study procedures, 70% liking the daily tablet regimen and the tablet size at Week 12, and 60% still liking both at Week 48, though only 40% liked the taste of the tablet.

2.10 Rationale for Study Design

Commented [DL9]: Add more to describe value added beyond IMPAACT 2009. Highlight what 042 adds for oral PrEP data that 2009 will not, e.g., microflora. Also, this design will contribute XX more person-months of safety data for PrEP in pregnancy during the period most critical for organogenesis, and we will collect data on younger infants compared to 2009.

MTN-042 is an open-label randomized trial primarily designed to evaluate among pregnant women the safety and pharmacokinetics (PK) of two HIV prevention products found to be safe and effective when used by non-pregnant women, the monthly dapivirine VR and daily oral PrEP. The MTN-042 study will minimize risk from product exposure to this scientifically complex yet seldom-studied population by taking a carefully monitored, step-wise approach to dosing starting at later gestational ages, then progressing to earlier gestational ages once safety is confirmed. Cohorts will be filled sequentially, with pauses between cohorts to allow for interim safety review before starting recruitment for the next gestational age group. At any point during the study, the Protocol Safety Review Team (PSRT), DAIDS Medical Officer (MO), or MTN Study Monitoring Committee (SMC) may pause enrollment and/or study product dosing for further review of safety data.

The step-wise approach to the investigation of DPV VR and FTC/TDF tablet exposure during pregnancy will provide important late first trimester, second trimester, and third trimester prospective safety data rarely obtained in previous studies, particularly for the DPV VR. MTN-042 will provide necessary information on the safety of the two study products by evaluating pregnancy outcomes as well as describing the possible impact of product use on participants' vaginal microenvironment, an important area for investigation due to the potential for disruptions

in normal vaginal ecology to impact gestational age at delivery and risk for intrapartum and neonatal infection.

The MTN-042 study will also provide a unique opportunity to describe the PK, adherence and acceptability profiles associated with use of DPV VR and FTC/TDF tablets during pregnancy for HIV prevention. MTN-042 will be the first trial to provide this data for the DPV VR, and will also provide additional data for the FTC/TDF tablets. Previous trials of purposeful use of ARV drugs during pregnancy have primarily been in the context of treatment and/or PMTCT in women known to have acquired HIV, where factors influencing adherence or acceptability may differ greatly from the context of HIV prevention for uninfected women. Adherence to HIV prevention products could be higher among pregnant versus non-pregnant women due to added incentive to avoid HIV infection while on the brink of motherhood and/or concern for possible perinatal transmission. But, adherence could be lower due to cultural taboos, physical discomfort with inserting a VR and/or fear of adverse drug effects on the developing fetus. Greater attention to the mother's health and investment in the pregnancy outcome by the woman's partner and family may also impact her ability and desire to adhere. Lastly, women might be more or less tolerant of study products with side effects similar to those already occurring as normal discomforts of pregnancy, such as increased vaginal discharge or nausea.

3 OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objectives

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

Pharmacokinetics: To describe the pharmacokinetic profile of study products used during pregnancy

Adherence: To characterize adherence to open label use of the dapivirine vaginal matrix ring (25 mg) and oral FTC/TDF in pregnant women

Acceptability: To characterize acceptability of open label use of the dapivirine vaginal matrix ring (25 mg) and oral FTC/TDF in pregnant women

3.3 Exploratory Objective

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

4 STUDY DESIGN

4.1 Identification of Study Design

The MTN-042 trial is a multi-site, two-arm, randomized (2:1), open-label Phase 3b trial evaluating among pregnant women in Africa the safety, PK, adherence and acceptability profiles of two HIV prevention products found to be safe and effective when used by non-pregnant women, the monthly dapivirine VR and daily oral FTC/TDF tablet.

4.2 Summary of Major Endpoints

Primary Endpoints:

Maternal Safety (composite)

- All serious adverse events
- 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])
- For AEs categorized as complications of pregnancy, all Grade 2 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])

Infant Safety (composite)

- All serious adverse events
- 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

Secondary Endpoints:

Pregnancy Outcome

- Therapeutic/elective abortion, peri-partum hemorrhage, chorioamnionitis, post-partum endometritis, prolonged admission for baby, PROM, infant size relative to gestational age, low birth weight (<2500g)

Pharmacokinetics

- Maternal plasma and PBMC TFV concentrations
- Maternal plasma DPV concentrations
- Infant blood TFV and DPV concentrations

Adherence

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

Acceptability

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

Exploratory Endpoints:

Genital microenvironment

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

4.3 Description of Study Population

The MTN-042 study population will consist of approximately 750 healthy, HIV-uninfected, pregnant females aged 18-45 (inclusive) years old who have an uncomplicated singleton pregnancy and are willing to be randomized to study product, and their newborn infants, who meet eligibility criteria as described in Sections 5.3 and 5.4.

4.4 Time to Complete Accrual

Approximately 6 to 9 months for recruitment and enrolment for each Cohort at each site, and approximately 5 to 12 months between each Cohort to allow all enrolled participants to give birth and for interim safety analyses to be conducted before continuing to the next Cohort. See Section 10.5 for additional details.

4.5 Expected Duration of Participation

The total duration of study participation for each participant will vary depending on gestational age at time of enrollment and length of pregnancy prior to pregnancy outcome, and may range from approximately 12 weeks or less for Cohort 1 to approximately 36 weeks or less for Cohort 4. Infants born to MTN-042 participants will be followed for approximately 6 weeks.

4.6 Sites

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

5 STUDY POPULATION

5.1 Selection of the Study Population

Approximately 750 women and their newborns will be enrolled in this study. Inclusion and Exclusion Criteria, Sections 5.2 and 5.3, respectively, are used to ensure the appropriate selection of study participants for MTN-042.

5.1.1 Recruitment

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

5.1.2 Retention

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

5.2 Inclusion Criteria

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

1. Age 18 through 45 years (inclusive) at Enrollment, verified per site standard operating procedures (SOPs).

2. At Screening, evidence of a viable, intrauterine, singleton pregnancy with sonographic confirmation, including for gestational age assessment.

   Note: If adequate (per judgment of Investigator of Recoed [IoR]/designee) sonographic results are not available from medical records at Screening, an ultrasound must be performed and results be available prior to Enrollment.

3. At Enrollment, pregnancy within gestational age limits of the currently enrolling cohort (per Section 7.12).

4. HIV-uninfected based on testing performed at Screening and Enrollment (per protocol algorithms in Appendices II and III).

5. At Screening, willing to be randomized at time of enrollment to either of the two study arms, and to continue study product use until her pregnancy outcome.

6. Able and willing to comply with all study requirements and complete all study procedures.

7. Able and willing to provide the following:
   a. Informed consent for her and her infant to be screened for and to enroll in MTN-042, as defined in site SOPs.
   b. Adequate locator information, as defined in site SOPs.
   c. Adequate documentation of entry to antenatal care, as defined in site SOPs.
   d. Adequate contact information for participant's antenatal care provider, as defined in site SOPs.
   e. Permission to contact participant's antenatal and post-partum care provider(s) and to obtain copies of antenatal and post-partum care records.

Note: Potential participants who have not begun antenatal care are not eligible for enrollment in MTN-042. Rescreening after documented entry to antenatal care is permissible.

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

5.3 Exclusion Criteria

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

1. Per participant report at Screening and/or Enrollment, intends to do any of the following during the study participation period:
   a. Use oral PrEP outside the context of study participation.
   b. Relocate away from the study site.
   c. Travel away from the study site for a time period that would interfere with study participation.
   d. Deliver her baby outside of a health center or hospital.

   Note: Plans to deliver outside of a health center or hospital is exclusionary due to logistical challenges related to specimen and delivery outcome data collection in those settings.

2. At Screening or Enrollment, has a positive HIV test.

3. At Screening or Enrollment, diagnosed with urinary tract infection (UTI), pelvic inflammatory disease (PID), STI or reproductive tract infection (RTI) requiring treatment per WHO guidelines.

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

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

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

   Note: Otherwise eligible participants with exclusionary pelvic exam findings may be enrolled/randomized after the findings have improved to a non-exclusionary severity grading or resolved. If improvement to a non-exclusionary grade or resolution is documented within 35 days of providing informed consent for screening, the participant may be enrolled.

5. Participant report, clinical evidence and/or antenatal/medical care record of any of the following:
   a. Currently breastfeeding.
   b. Known adverse reaction to any of the study products (ever).
   c. Known adverse reaction to latex and polyurethane (ever).
   d. Symptoms suggestive of acute HIV infection at Screening or Enrollment.
   e. Non-therapeutic injection drug use in the 12 months prior to Enrollment.
   f. Use of HIV post-exposure prophylaxis (PEP) and/or PrEP during the current pregnancy.
   g. Sickle cell anemia (excluding sickle cell trait), chronic bleeding, blood transfusion within the past 120 days (excluding for chronic illness), or other blood dyscrasias.
   h. Bone fracture not explained by trauma.
   i. Participation in any other research study involving drugs, medical devices, vaginal products or vaccines during the current pregnancy.
   j. At Screening or Enrollment, known to have any of the following during the current pregnancy:
      - Multiple gestation
      - Placenta previa
      - Cervical cerclage
      - Abnormal fetal anatomy (in the opinion of the IoR or designee)
      - Intrauterine growth restriction
      - Pre-existing or gestational diabetes
      - Hypertensive disorder of pregnancy
      - Severe malaria
      - Treatment for preterm labor
      - Abnormal quantity of amniotic fluid (oligohydramnios or polyhydramnios)
   k. At Screening, known to have had any of the following in a previous pregnancy:
      - Intrauterine growth restriction
      - Gestational diabetes
      - Hypertensive disorder of pregnancy
      - Intrauterine fetal demise (estimated gestational age ≥20 weeks)
      - Delivery prior to 37 0/7 weeks
   l. At Enrollment, as determined by the IoR/designee, has any significant obstetrical complication or uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease that would make study participation unsafe.

6. At Screening, has any of the following laboratory abnormalities:
   a. Positive for hepatitis B surface antigen (HBsAg).
   b. Positive for malaria (at sites with capacity, where malaria is endemic).
   c. Aspartate aminotransferase (AST) or alanine transaminase (ALT) ≥ Grade 3.**
   d. Hemoglobin ≥ Grade 3.**
   e. Platelet count ≥ Grade 3.**
   f. Creatinine ≥ Grade 2.**
   g. Estimated creatinine clearance ≥ Grade 2 (Cockcroft Gault formula).**

   Note: Otherwise eligible participants with an exclusionary test (other than HBsAg) may be re-tested during the screening process; re-testing procedure details can be found in the MTN-042 Study Specific Procedures (SSP) Manual. If improvement to a non-exclusionary

grade or resolution is documented within 35 days of providing informed consent for screening, the participant may be enrolled.

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

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

5.4 Infant Enrollment

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

5.5 Co-enrollment Guidelines

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

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

- Participants may take part in ancillary studies approved by the MTN-042 Protocol Chair.
- Participants who acquire HIV may take part in observational and/or interventional studies for HIV-positive persons.
- Participants may take part in observational studies, including pregnancy registries. For both mothers and infants, enrollment in MTN-016, the HIV Prevention Agent Pregnancy Exposure Registry, will be encouraged by study sites enrolling into MTN-016.

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

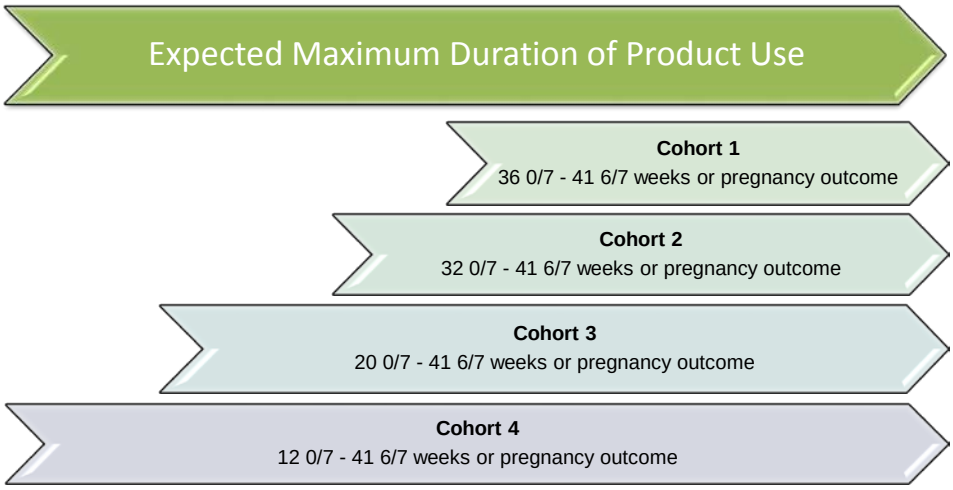
6 STUDY PRODUCT

6.1 Regimen

Each participant will be randomized (2:1) to one of two study products: a VR containing 25 mg of dapivirine to be inserted monthly or a 200 mg FTC/300 mg TDF (Truvada®) oral tablet taken daily. Participants will use one of the two study products up to their 42nd week of pregnancy, i.e., for a

maximum of approximately six (6) to thirty (30) weeks depending on their gestational age cohort and time to pregnancy outcome. Figure 2 illustrates the increasing duration of study product exposure for later enrolled groups.

Figure 2: Expected Maximum Duration of Product Use by Study Cohort



Commented [DL10]: Figure now reflects that participants will continue using either product until they go into labor.

6.2 Administration

6.2.1 Dapivirine Vaginal Ring (25 mg)

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

6.2.2 FTC/TDF 200mg/300mg Tablet (Truvada®)

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

6.3 Study Product Formulation

6.3.1 Dapivirine VR (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 ring dimensions are as follows: 56 mm and 7.7 mm, outer

diameter and cross-sectional diameter, respectively. The ring 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 dapivirine 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 FTC/TDF 200mg/300mgTablet (Truvada®)

FTC/TDF is a fixed dose combination oral tablet containing FTC and TDF. FTC is a synthetic nucleoside analogue of cytidine. One FTC/TDF tablet contains 200 mg FTC plus 300 mg of TDF. FTC/TDF should be stored at 25°C (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

Dapivirine VR (25 mg)
IPM (Silver Spring, MD) will oversee the manufacture of the study VRs and analyze/release the rings under Good Manufacturing Practices (GMP).

FTC/TDF 200mg/300mgTablet (Truvada®)
FTC/TDF tablets are supplied by Gilead Sciences, Inc. (Foster City, CA, USA).

6.4.2 Accountability

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

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

6.4.3 Study Product Dispensing

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

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

During study product use, participants will receive a new ring or a supply of tablets monthly. Product will be dispensed in quantities sufficient to last until the next scheduled study visit. In the event that additional study products between visits are needed, participants will be instructed to

contact the study site. If the participant is unable to attend their next scheduled visit, it is up to the discretion of the IoR/designee to allow the provision of additional study product. The IoR/designee will document approval of this additional dispensation.

6.5 Retrieval of Study Product

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

Table 4: Retrieval of Study Product

Condition	Timeframe for Retrieval
Permanent discontinuation due to potential HIV infection or Grade 3 or higher renal or hepatic toxicity	Within 24 hours
Permanent discontinuation for any other reason or IoR discretion	Within 5 working days
Temporary hold for reasons with expected duration of at least 7 days	Within 7 working days

Participants will be instructed to return all study product (used or unused) prior to exiting the study. Specifically, for each participant, all VRs and/or oral tablets remaining in the participant's possession should be retrieved at the visit immediately following the outcome of their pregnancy. If the participant does not bring her study product to this visit, study staff must arrange to retrieve the VR and /or oral tablets within 5 business days. If the study product is not retrieved within that timeframe, the MTN-042 PSRT must be informed.

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, medications used to treat AEs, non-study vaginal products and/or practices, vitamins and nutritional supplements, and herbal preparations will be recorded as concomitant medications on a case report form (CRF) designated for that purpose.

6.7 Prohibited Medications

Concomitant use of medications for PEP and PrEP outside the context of study participation is prohibited.

6.8 Condoms

All participants 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 visit and evaluations schedule is provided in Appendix I. Presented below is additional information on visit-specific study procedures. Detailed instructions to guide and standardize operating procedures across sites as well as information regarding the study visit windows are provided in the MTN-042 SSP Manual available at http://www.mtnstopshiv.org/studies.

Figure 3: Study Visit Schedule by Cohort across Gestational Age Ranges

Cohort 1 Enrollment Window 36 0/7 weeks – 37 6/7 weeks	Screening
	Enrollment
	Every 2 weeks until pregnancy outcome, with phone contact every other week
	Within 1 week of pregnancy outcome and approximately 6 weeks after (home or clinic)
Cohort 2 Enrollment Window 32 0/7 weeks – 35 6/7 weeks	Screening
	Enrollment
	1-week (phone)
	2-week
	4-week
	Every 2 weeks until pregnancy outcome, with phone contact every other week
	Within 1 week of pregnancy outcome and approximately 6 weeks after (home or clinic)
Cohort 3 Enrollment Window 20 0/7 weeks – 29 6/7 weeks	Screening
	Enrollment
	1-week (phone)
	2-week
	4-week and every 4 weeks until Week 36
	Every 2 weeks after Week 36 until pregnancy outcome, with phone contact every other week
	Within 1 week of pregnancy outcome and approximately 6 weeks after (home or clinic)
Cohort 4 Enrollment Window 12 0/7 weeks – 19 6/7 weeks	Screening
	Enrollment
	1-week (phone)
	2-week
	4-week and every 4 weeks until Week 36
	Every 2 weeks after Week 36 until pregnancy outcome, with phone contact every other week
	Within 1 week of pregnancy outcome and approximately 6 weeks after (home or clinic)

7.1 Pre-Screening

As part of participant outreach and recruitment strategies, study staff may pre-screen potential study participants either on-site or at off-site locations. Study staff will consult with their local IRBs/ECs regarding pre-screening potential pregnant participants. If deemed acceptable, during pre-screening interactions study staff may explain the study to potential participants and ascertain elements of presumptive eligibility, to be confirmed at clinic screening visits. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants,

provided the information is collected in such a manner that it cannot be linked to potential participant identifiers. At each site, procedures and documentation will comply with local IRB/EC requirements. Potential participants may be pre-screened for the subsequent group not yet open for enrollment, with attention to the participant's gestational age, as confirmed by an ultrasound conducted no later than the 28th week of gestation, and the screening window. Any participant who at any time expresses an interest in involving her current sexual partner and/or family members in discussions about study participation will be encouraged to bring them to the clinic, where a staff member can explain the study and answer any questions they may have.

7.2 Visit 1: Screening Visit

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

NOTE: Females who fail their first screening attempt may be re-screened.

Table 5: Visit 1 – Screening Visit

Visit 1 – Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain informed consent for screening and enrollment • Obtain signed medical records release, antenatal care provider information and planned location for delivery • 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
Clinical		• Review medical history and obstetric symptoms • Review available ultrasound results and antenatal records • Review concomitant medications • Physical exam • Pelvic exam • Obstetric abdominal exam • Calculate gestational age • Treatment for RTI/UTI/STIs* • Disclosure of available test results
Laboratory	**Urine**	• Dipstick urinalysis (UA) and/or urine culture*

Visit 1 – Screening Visit		
Component		**Procedures**
	Blood	• HIV-1 testing • HBsAg • AST/ALT • Creatinine • Complete blood count (CBC) with platelets • Syphilis serology • Malaria testing (at designated sites)
	Pelvic	• Nucleic acid amplification test (NAAT) for *Neisseria gonorrhoeae* (GC)/*Chlamydia trachomatis* (CT)/*Trichomonas vaginalis* (Trich) • Wet prep/potassium hydroxide (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

7.3 Visit 2: Enrollment Visit (Day 0)

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

Table 6: Visit 2 – Enrollment Visit

Visit 2 – Enrollment Visit		
Component		**Procedures**
Administrative and Regulatory		• Re-assess and confirm eligibility • Randomization • Review/update locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling		• Baseline behavioral assessment • Baseline product acceptability assessment • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol adherence counseling
Clinical		• Review/update medical/obstetric history • Review/update ultrasound results and antenatal records • Review/update concomitant medications • Targeted physical exam* • Pelvic exam • Obstetric abdominal exam • Confirm calculation of gestational age • Treatment for RTI/UTI/STIs* • Disclosure of available test results
Laboratory	**Urine**	• Dipstick UA and/or urine culture*

Visit 2 – Enrollment Visit		
Component		**Procedures**
	Blood	• HIV-1 testing • Creatinine* • CBC with platelets* • Syphilis serology* • Plasma archive
	Pelvic	• NAAT for GC/CT/Trich* • 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 • Cervical 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 directly observed dosing (DOD) of first study tablet • Provide product use instructions • Offer male condoms

* if indicated and/or per local standard of care

7.4 Follow-up Visits/Contacts Prior to Pregnancy Outcome

7.4.1 Visit 3: 1-week Visit/Phone Contact

This visit/phone contact will occur 1 week (i.e., approximately 7 days) following enrollment for all participants. For Cohort 1, this visit/phone contact will also occur 1 week following every bi-weekly clinic visit until pregnancy outcome. For Cohorts 2-4, this visit/phone contact will also occur 1 week following their 36th week of gestation and every two weeks (i.e., approximately 14 days) after that until pregnancy outcome.

Table 7: Visit 3 – 1-week Visit/Phone Contact

Visit 3 – 1-week Visit/Phone Contact	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement (sites to reference SOPs) • Schedule next study visit/contact
Behavioral/Counseling	• Behavioral assessment • Product acceptability assessment • Protocol adherence counseling* • HIV/STI risk reduction counseling*
Clinical	• Review/update medical/obstetric history • Review/update concomitant medications • Collect AEs • Treatment for RTI/UTI/STIs* • Disclosure of available test results

* if indicated and/or per local standard of care

7.4.2 Bi-weekly Visits After 36th Week of Gestation

Participants in Cohort 1 will have a follow-up visit every two weeks (i.e., approximately 14 days) following their Enrolment Visit until pregnancy outcome. Participants in Cohorts 2-4 will have a follow-up visit every two weeks following their 36th week of gestation and every two weeks after that until pregnancy outcome. With approved SOPs and participant permission, appropriate components of these visits (e.g., not to include pelvic exam) may be completed off-site. These visits may not occur for all participants, due to proximity of delivery (especially Cohort 1).

Table 8: Bi-weekly Visits After 36th Week of Gestation

Bi-weekly Visits After 36th Week of Gestation		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• Behavioral assessment∇ • Product acceptability assessment∇ • Social harms/benefits assessment∇ • HIV pre- and post-test counseling▲* • HIV/STI risk reduction counseling▲* • Protocol adherence counseling • Contraceptive counseling
Clinical		• Review/update medical/obstetric history • Review/update ultrasound results and antenatal records • Review/update concomitant medications • Targeted physical exam* • Pelvic exam∇* • Obstetric abdominal exam • Collect AEs • Treatment for RTI/UTI/STIs* • Disclosure of available test results
Laboratory	**Urine**	• Dipstick UA and/or urine culture*
	Blood	• HIV-1 testing▲* • Creatinine* • AST/ALT* • CBC with platelets* • Syphilis serology* • Plasma and peripheral blood mononuclear cells (PBMC) for tenofovir (TFV) PK • Plasma for DPV PK

Bi-weekly Visits After 36th Week of Gestation		
Component		**Procedures**
	Pelvic	• NAAT for GC/CT/Trich* • 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 ∇ • Cervical swab(s) for biomarkers ∇
	Study Product	• Adherence assessment: Returned study VR ▲
Study Product/Supplies		• Remove and collect study VR or study tablets ▲ • Provide study VR or study tablets ▲ • Provide product use instructions ▲ • Insertion of study VR at the clinic (clinician to check VR placement) or DOD of first study tablet▲ • Offer male condoms

* if indicated and/or per local standard of care, ▲ Second bi-weekly visit only, ∇ First bi-weekly visit only

7.4.3 Visit 4: 2-week Visit (Cohorts 2-4)

This visit will occur 2 weeks (i.e., approximately 14 days) following enrollment for participant Cohorts 2-4. Participant Cohort 1 will not have this visit (see Sections 7.4.1 and 7.4.2 for Cohort 1 visit procedures prior to pregnancy outcome).

Table 9: Visit 4 – 2-week Visits (Cohorts 2-4)

Visit 4 – 2-week Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• Behavioral assessment • Product acceptability assessment • HIV pre- and post-test counseling* • HIV/STI risk reduction counseling* • Protocol adherence counseling
Clinical		• Review/update medical/obstetric history • Review/update concomitant medications • Targeted physical exam* • Pelvic exam* • Obstetric abdominal exam • Collect AEs • Treatment for RTI/UTI/STIs* • Disclosure of available test results
Laboratory	**Urine**	• Dipstick UA and/or urine culture*

Visit 4 – 2-week Visit		
Component		**Procedures**
	Blood	• HIV-1 testing* • Creatinine* • AST/ALT* • CBC with platelets* • Syphilis serology* • Plasma and PBMC for TFV PK • Plasma for DPV PK
	Pelvic	• NAAT for GC/CT/Trich* • Wet prep/KOH wet mount for candidiasis and/or BV*
Study Product/Supplies		• Offer male condoms

* if indicated and/or per local standard of care

7.4.4 Visit 5: 4-week Visit (Cohorts 2-4)

This visit will occur 4 weeks (i.e., approximately 28 days) following enrollment for participant Cohorts 2-4. For Cohorts 3 and 4, this visit will also occur every 4 weeks after Visit 5 until their 36th week of gestation. Participant Cohort 1 will not have this visit (see Sections 7.4.1 and 7.4.2 for Cohort 1 visit procedures prior to pregnancy outcome).

Table 10: Visit 5 – 4-week Visit (Cohorts 2-4)

Visit 5 – 4-week Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• Behavioral assessment • Product acceptability assessment • Social harms/benefits assessment • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol adherence counseling • In-depth interview (IDI) (subset at Visit 5 only) ♦
Clinical		• Review/update medical/obstetric history • Review/update concomitant medications • Targeted physical exam • Pelvic exam • Obstetric abdominal exam • Collect AEs • Treatment for RTI/UTI/STIs* • Disclosure of available test results
Laboratory	**Urine**	• Dipstick UA and/or urine culture*

Visit 5 – 4-week Visit		
Component		**Procedures**
	Blood	• HIV-1 testing • Creatinine • AST/ALT • CBC with platelets • Syphilis serology* • Plasma and PBMC for TFV PK • Plasma for DPV PK
	Pelvic	• NAAT for GC/CT/Trich* • 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 • Cervical swab(s) for biomarkers
	Study Product	• Adherence assessment: Returned study VR
Study Product/Supplies		• Retrieval of study VR or study tablets • Provision of study VR or study tablets • Provision of product use instructions • Insertion of study VR at the clinic (clinician to check VR placement) or DOD of first study tablet

* if indicated and/or per local standard of care, ♦ May be scheduled any time between 4-week Visit and pregnancy outcome to accommodate participant availability

7.5 Follow-up Visits Post-Pregnancy Outcome

7.5.1 1-week Visit Post-Pregnancy Outcome

All participants and their newborn infants will have follow-up visits within one week (i.e., approximately 7 days) of their pregnancy outcome. With approved SOPs and participant permission, appropriate components of these visits (e.g., not to include pelvic exam) may be completed off-site. Provided their study site is taking part in MTN-016, participants will be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study.

Table 11: 1-week Visit Post-Pregnancy Outcome

1-week Visit Post-Pregnancy Outcome	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Review/update signed medical records release, delivery care provider information and location of delivery • Provide reimbursement (sites to reference SOPs) • Schedule next visit/contact*

1-week Visit Post-Pregnancy Outcome		
Component		**Procedures**
Behavioral/Counseling		• Behavioral assessment • Product acceptability assessment • Social harms/benefits assessment • Contraceptive counseling • HIV pre- and post-test counseling* • HIV/STI risk reduction counseling*
Clinical		• Review/update medical/obstetric history • Review/update peripartum and antenatal records • Review/update concomitant medications • Review infant delivery details, anthropometry, feeding history • Collect AEs for mother and infant • Treatment for RTI/UTI/STIs* • Disclosure of available test results
Laboratory	**Urine**	• Dipstick UA and/or urine culture*
	Blood	• HIV-1 testing for mother and infant* • Creatinine for mother and infant • AST/ALT for mother and infant • CBC with platelets for mother and infant • Syphilis serology* • Maternal plasma and PBMC for TFV PK • Maternal plasma for DPV PK • Infant blood for TFV and DPV PK
	Pelvic	• NAAT for GC/CT/Trich* • Wet prep/KOH wet mount for candidiasis and/or BV*
	Study Product	• Adherence assessment: Returned study VR*
Study Product/Supplies		• Retrieval of study VR or study tablets* • Offer male condoms

* if indicated and/or per local standard of care

7.5.2 6-week Visit Post-Pregnancy Outcome

All participants and their newborn infants will have follow-up visits six weeks (i.e., approximately 42 days) after their pregnancy outcome. With approved SOPs and participant permission, appropriate components of these visits (e.g., not to include pelvic exam) may be completed off-site. Provided their study site is taking part in MTN-016, participants will be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study.

Table 12: 6-week Visit Post-Pregnancy Outcome

6-week Visit Post-Pregnancy Outcome	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Review/update signed medical records release, delivery care provider information and location of delivery • Provide reimbursement (sites to reference SOPs)

6-week Visit Post-Pregnancy Outcome		
Component		**Procedures**
		• Schedule next visit/contact*
Behavioral/Counseling		• Behavioral assessment • Product acceptability assessment • Social harms/benefits assessment • Contraceptive counseling • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • IDI (subset only) ♦
Clinical		• Review/update medical/obstetric history • Review/update peripartum and antenatal records • Review/update concomitant medications • Review/update infant health, anthropometry, feeding history • Collect AEs for mother and infant • Treatment for RTI/UTI/STIs* • Disclosure of available test results
Laboratory	**Urine**	• Dipstick UA and/or urine culture*
	Blood	• HIV-1 testing for mother • HIV-1 testing for infant* • Creatinine for mother and infant • AST/ALT for mother and infant • CBC with platelets for mother and infant • Syphilis serology
	Pelvic	• NAAT for GC/CT/Trich • 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 • Cervical swab(s) for biomarkers
Study Product/Supplies		• Offer male condoms

* if indicated and/or per local standard of care, ♦ May be scheduled any time between pregnancy outcome and study exit to accommodate participant availability

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

7.6.1 Participants Who Become Infected with HIV

If a participant acquires HIV-1 after the Enrollment Visit, she will be referred to local care and treatment services that have capacity to provide PMTCT services. She will be offered the option

to continue follow-up visits with a modified study visit/procedure schedule until her originally scheduled study exit date.

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

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

All participants at sites participating in MTN-015, the MTN Seroconverter Study, who become infected with HIV while on study product will be offered enrollment in MTN-015. Participants are offered enrollment in MTN-015 (http://www.mtnstopshiv.org/studies) at the visit when seroconversion confirmation test results are discussed with the participant.

For participants who delay or decline enrollment in MTN-015, the following procedures are being completed as part of the MTN-042 study; these procedures are discontinued immediately if the participant enrolls in MTN-015:

- Plasma collection
- CD4+ T cell count
- HIV-1 RNA PCR
- HIV-1 Genotyping (standard resistance testing)

Upon confirmation of HIV infection per the algorithm in Appendix III, the following procedures are performed at the following time points:

- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR will be performed at the clinic visit immediately following confirmation of an HIV-infection and every three months thereafter for the remaining follow-up period, or as indicated.
- 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).
- Behavioral, adherence, and product acceptability assessments will be performed at the clinic visit immediately following confirmation of an HIV-infection.

For those participants who choose to remain in MTN-042 follow-up, regardless of co-enrollment in MTN-015, protocol-specified procedures for MTN-042 will continue except the following:

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

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

7.6.2 Participants Who Temporarily Hold or Permanently Discontinue Study Product Use

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

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

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

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

Permanent Product Discontinuation for Reasons other than Seroconversion
Participants who permanently discontinue study product use for any reason (clinician-initiated or self-initiated) will be considered terminated from the study as continued study participation would be of no added benefit. Participants will, however, be asked to complete the procedures outlined in the 4-week Visit (Visit 5), if willing.

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

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

7.6.3 Interim Visits

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

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

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

7.7 Final Contact

Since participants' 6-week Visit Post-Pregnancy Outcome includes laboratory testing for HIV and other conditions, additional contacts after this Study Exit Visit may be required to provide her additional study test results, and post-test counseling, if needed. 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.

7.8 Behavioral Evaluations

Commented [DL11]: Add qualitative data management language in Sections 11 and 13.

Behavioral endpoints will be assessed via Audio Computer-Assisted Self-Interviewing (ACASI)/CASI and/or CRFs with all participants. A Baseline Behavioral Questionnaire will be administered in the clinic after initial application of their assigned study product has occurred at the Enrollment Visit. All participants 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 pregnancy, and other preliminary acceptability measures of the study product. At the 1-week Visit (Visit 3), all participants will report their use of study product, coital frequency, prevention method use and intravaginal practices, and participants in Cohorts 2-4 will also report on these at the 2-week Visit (Visit 4). At the 4-week Visit (Visit 5), participants in Cohorts 2-4 will be asked to complete the Follow-up Behavioral Questionnaire which will include the same measures as in Visits 3 and 4, acceptability questions similar to those from the Enrollment Visit, and additional questions about their experiences using the study product, including reasons for non-use, if applicable, willingness to use in the future and beliefs around use of vaginal products and/or oral medications during pregnancy, and any perceived effect on the fetus/infant. Participants in Cohort 1 will complete this Follow-up Behavioral Questionnaire at their first Bi-weekly Visit Prior to Pregnancy Outcome. For any participant whose pregnancy outcome occurs prior to administration of the Follow-up Behavioral Questionnaire, this assessment will occur at their next scheduled visit.

IDIs will also be conducted with a subset of participants in Cohorts 2-4 at the 4-week Visit (Visit 5), and with a subset of all participants at the 6-week Visit Post-Pregnancy Outcome. All IDIs will be conducted by trained and experienced facilitators to gain further insight on the 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.

7.9 Protocol Adherence Counseling

Protocol adherence counseling, including product use adherence counseling, will be provided to all participants upon enrollment into the study. Contraception counseling will be provided to all participants prior to and after their pregnancy outcome. Counseling will be provided in accordance with standard methods using a participant-centered approach to frame discussions around experiences with the trial and the prevention products. Cognitive behavioral and motivational strategies will be incorporated into the counseling sessions as desired by participants to address adherence barriers. Lastly, sites may offer additional adherence support strategies (e.g., text

messages, phone calls, peer support groups) to complement their product use adherence counseling.

7.10 Clinical Evaluations and Procedures

Physical exams will include the following assessments:

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

**May be omitted after the Screening Visit.*

Obstetric abdominal exams will include the following assessments:

- Appearance
- Palpation
- Fundal height
- Auscultation of fetal heart tones (by Doppler, fetoscope or ultrasound), including rate per minute (not measured following pregnancy outcome)

Once born, clinical evaluation of infants will include the following assessments:

- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- General appearance
- Weight
- Height
- …

Commented [DL12]: Physicians to add/modify as needed.

Pelvic Examination and Specimen Collection

Pelvic examinations will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at http://www.conrad.org/publications-13.html.

Additional clinical assessments may be performed at the discretion of the examining clinician in response to symptoms or illnesses present at the time of the exam.

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

7.11 Laboratory Evaluations

Local Laboratory

- Urine
  - Dipstick UA and/or urine culture
- Blood
  - Plasma archive (stored at site until notified by MTN LC)
  - Syphilis serology
  - HIV-1 testing
  - CBC with platelets
  - AST/ALT
  - Creatinine and calculation of creatinine clearance
  - HBsAg
  - Malaria (at sites with capacity, where women are at risk)
- Pelvic
  - NAAT for GC/CT/Trich
  - Vaginal pH
  - Wet prep/KOH wet mount for candidiasis and/or BV

Laboratory Center

- Blood
  - TFV concentrations in maternal plasma and PBMC
  - DPV concentrations in maternal plasma
  - TFV and DPV concentrations in infant blood
  - HIV-1 confirmatory testing as needed (see Appendix III)
  - HIV-1 drug resistance
- Pelvic
  - Vaginal Gram stain
  - Vaginal swabs for microbiota
  - Vaginal swabs for biomarkers
  - Cervical swabs for biomarkers

Designated Laboratory:

- VR for residual dapivirine 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.

7.12 Calculation of Gestational Age

The best obstetric estimate should be used as the measure for gestational age, rather than estimates based on the last menstrual period (LMP) alone. Per site SOPs and as needed to confirm gestational age of potential participants, ultrasound measurement of the embryo or fetus will be performed prior to enrollment but no later than their 28th week of gestation. Gestational age confirmation by ultrasound may occur during pre-screening or between the Screening and Enrollment Visits.

Ultrasound measurement of the embryo or fetus in the first trimester (up to and including 13 6/7 weeks of gestation) is the most accurate method to establish or confirm gestational age. Gestational age assessment based on measurement of the crown–rump length (CRL) has an accuracy of ±5–7 days in the first trimester. Mean sac diameter measurements are not recommended for estimating gestational age. The range of second-trimester gestational ages (14 0/7 weeks to 27 6/7 weeks of gestation) introduces greater variability and complexity, which can affect revision of LMP dating and assignment of a final estimated delivery date (EDD). With rare exception, if a first-trimester ultrasound examination was performed, especially one consistent with LMP dating, gestational age should not be adjusted based on a second-trimester ultrasound examination. Table 9 includes guidelines for redating based on ultrasonography.

Table 13. Guidelines for Redating based on Ultrasonograpy

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

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

7.13 Specimen Management

Each study site will adhere to the standards of good clinical laboratory practice in accordance with current US DAIDS Laboratory Requirements (https://www.niaid.nih.gov/sites/default/files/gclp.pdf), MTN-042 SSP Manual (http://www.mtnstopshiv.org/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.

7.14 DAIDS Laboratory Oversight

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

7.15 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 Protocol Team 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 trial, the PSRT will review safety reports and conduct calls to review the data as appropriate. The content, format and frequency of the 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.

An SMC has study oversight and is charged with reviewing participant safety data as no DSMB is planned for this study. See Section 10.7 for additional details.

8.3 Adverse Events Definitions and Reporting Requirements

8.3.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product. This definition is applied to all study participants at the time of enrollment. This definition is applied to all study groups, and is applied beginning at the time of enrollment (i.e., once a participant is randomized). The term “investigational products” for this study refers to the dapivirine VR and FTC/TDF oral tablet.

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

Study site staff will document in source documents and in the study database all AEs reported by or observed in enrolled study participants, regardless of severity and presumed relationship to study product. Study staff also will also report on CRFs all SAEs for neonates (first 30 days of life) born from pregnancies followed during MTN-042 participation.

AE severity and laboratory tests will be graded per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies; dated November 2007), except that asymptomatic BV and asymptomatic candida will not be reportable AEs. 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. 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, will not be reportable as an AE. Bleeding of greater quantity or longer duration than typical will still be reported. Decreased fetal movement is not considered an AE; however, AEs identified in the course of clinical evaluation of decreased fetal movement will be captured. Findings on electronic fetal monitoring strips are not considered AEs. Lastly, fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths) will not be reported as AEs; however, untoward maternal conditions that either result in or result from fetal losses are reported as reproductive system AEs. All fetal losses will be reported by sites on CRFs to the

SDMC and will be considered during safety reviews conducted by the SDMC, the DAIDS MO, the NICHD MO, PSRT, and SMC.

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

- Bleeding during pregnancy, prior to the onset of labor
  - Grade 0: None
  - Grade 1: Spotting or bleeding less than menses
  - Grade 2: Bleeding like menses or heavier, no intervention indicated
  - Grade 3: Profuse bleeding with dizziness or orthostatic hypertension, transfusion indicated
  - Grade 4: Potentially life-threatening profuse bleeding and/or shock

- Hypertensive disorders of pregnancy
  - Grade 0: None
  - Grade 1: Pregnancy-induced hypertension
  - Grade 2: Mild preeclampsia
  - Grade 3: Severe preeclampsia
  - Grade 4: HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, eclampsia, or life-threatening sequelae of preeclampsia (e.g., pulmonary edema)

- Gestational diabetes
  - Grade 0: None
  - Grade 1: Diet-controlled, no or minimal interference with usual social and functional activities
  - Grade 2: Medication prescribed
  - Grade 3: Evidence of adverse effects on pregnancy secondary to diabetes
  - Grade 4: N/A

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 [X] AEs uncovered at the last visit. For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis. For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log CRFs based on the re-assessments.

8.3.2 Serious Adverse Events

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

- Results in death
- Is life-threatening

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

8.3.3 Adverse Event Relationship to Study Product

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

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

8.4 Expedited Adverse Event Reporting Requirements

8.4.1 Adverse Event Reporting to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the Regulatory Support Center (RSC) website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual. 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 NIAID Clinical Research Management System (CRMS) Support at CRMSSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

This form is available on the RSC website, http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.

For questions about DAERS, please contact the National Institute of Allergy and Infectious Diseases (NIAID) CRMS Support at CRMSSupport@niaid.nih.gov. Where DAERS has not been implemented, sites will submit EAEs by documenting the information on the current DAIDS EAE Form, available on the RSC website, http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/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 VR and FTC/TDF oral tablet.

8.4.3 Grading Severity of Events

The grading of severity of events and the reporting period will be the same as for all AEs, as described in Section 8.3.1. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1, dated November 2007), will be used and is available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables.

8.4.4 Expedited AE Reporting Period

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

8.5 Social Harms Reporting

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

8.6 Regulatory Requirements

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

9 CLINICAL MANAGEMENT

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to hold study product temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified

below, the IoR/designee should immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.

9.1 Grading System

AE severity grading is described in Section 8.3.1.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

9.3 General Criteria for Temporary/Permanent Discontinuation of Study Product

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

- Acquisition of HIV-1 infection.
- Acquisition of hepatitis B infection.
- Allergic reaction to the study product.
- Reported use of PrEP for HIV prevention.
- Reported use of PEP for potential HIV exposure.
- Non-therapeutic injection drug use.
- Report of admission to care for labor and delivery management, including induction of labor and cesarean delivery.
- Pregnancy loss.

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 III, 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.
- Suspected onset of labor or rupture of membranes. If labor and rupture of membranes are subsequently ruled out, study product should be resumed.
- Participant is unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their safety and well-being by continuing product use, according to the judgment of the IoR/designee. The IoR/designee must consult the PSRT on all temporary product holds instituted for this reason for further guidance on resuming product use, continuing the temporary hold, or progressing to permanent discontinuation. If product use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the IoR/designee should consult the PSRT to resume product use at that time.

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

Grade 1 or 2

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

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

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

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

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

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

9.5 Other Clinical Findings

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

≤ Grade 2 nausea, vomiting, and/or diarrhea

- IoR/designee may treat the partipant symptomatically (e.g., diet changes, antiemetics, and/or supportive fluids).
- Unless other temporary product hold requirements apply, study product need not be held.
- If the IoR/designee chooses to hold product, the IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

≥ Grade 2 creatinine clearance

- Oral study product should be held.
- The PSRT should be notified.
- The test should be repeated within one week.
    - If a level of ≥ Grade 2 is confirmed, study product will be permanently discontinued.

- If either retesting cannot occur within one week or if retesting yields a result of ≤ Grade 1, the IoR/designee must consult the PSRT for further guidance on resuming product use.

AST and/or ALT elevations (Any grade)

- Careful assessments should be done to rule out alcohol, non-study medication-related drug toxicity, herbal medications/supplements, HELLP syndrome, or viral hepatitis as the cause of elevation in AST and/or ALT.
- The IoR/designee must carefully assess the participant for any symptoms or signs of hepatoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain or hepatomegaly.
- If hepatitis B infection is confirmed, product use must be permanently discontinued.
- Unless other temporary product hold/permanent discontinuation requirements apply, study product need not be held if a specific alternative etiology is identified.
  - If no specific alternative etiology is identified, study product should be temporarily held and the PSRT consulted.

STI/RTI requiring treatment

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

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

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

Superficial epithelial disruption (abrasion/peeling)

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

Deep epithelial disruption (ulceration)

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

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

- Continue study product use.
- Perform naked eye evaluation .

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

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

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

Unexpected genital bleeding

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

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

- Temporarily hold study product.
- Evaluate for GC/CT; consider syndromic management, pending results of testing and per clinician discretion.
- If GC/CT detected, provide or prescribe treatment.
- Reevaluate in 3-5 days. If all symptoms and signs are resolved at that time resume study product use.

Genital petechia(e)

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

Genital ecchymosis

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

9.6 HIV Infection

Commented [DL13]: Add infant HIV-related procedures such as testing, prophylaxis, etc. Infants will be followed up in 016. Women should be referred immediately for initiation of ART according to local guidelines.

A participant who has a positive test for HIV must have study product held, but will not be withdrawn from the study. If the participant is subsequently determined to be HIV-uninfected according to the algorithm in Appendix III, study product may be resumed. If HIV infection is confirmed, study product will be permanently discontinued by the IoR/designee. Participants identified as infected with HIV are managed or referred for management according to the local standard of care. These participants will also be offered the option to continue follow-up visits with

a modified study visit/procedure schedule, as per Section 7.5.1. Adult participants are also offered participation in MTN-015, the MTN Seroconverter Study, which also includes provisions for the clinical management and/or referral of participants infected with HIV.

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

At every study visit, study staff will actively follow-up on prior referrals to HIV care and support services, to determine whether the participant sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. All follow-up actions, outcomes, counseling, and plans for next steps are documented in participant study records. Results of study laboratory testing may be helpful in clinical management, and these results are provided to the participant and her medical provider (with her permission) as soon as they are available.

9.7 Hepatitis B Infection

If symptoms or signs of clinical hepatitis are present, the IoR/designee must test the participant mother for hepatitis (including HBsAg plus any other testing indicated by the local standard of care). Consideration should be given to other causes of hepatitis in pregnancy, including obstructive gall bladder or bile duct disease, severe preeclampsia, HELLP syndrome, and acute fatty liver of pregnancy. If hepatitis is confirmed, product use must be permanently discontinued. Participant mothers identified as infected with hepatitis B will be managed or referred for management according to the local standard of care.

9.8 Signs/Symptoms of Labor

Temporary product hold should be instituted at suspected onset of labor or rupture of membranes. If labor and rupture of membranes are subsequently ruled out, study product should be resumed. For the purposes of MTN-042, labor is defined as admission to care for labor and delivery management, which would also include induction of labor and cesarean delivery.

9.9 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. The PSRT must be notified of all terminations conducted per IoR discretion. Participants also may be withdrawn if NIAID, IPM, Gilead Sciences, Inc., government or regulatory authorities including the FDA and Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up. Study staff members will record the reason(s) for all withdrawals in participants' study records. In the event that participants who voluntarily withdraw from the study wish to re-join the study, they may resume product use (if applicable) and follow-up through their originally scheduled study exit date, pending consultation with the PSRT.

10 ANALYTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

The MTN-042 study is a multi-site, two-arm, randomized, open-label Phase 3b trial evaluating the safety, PK, adherence and acceptability profiles of two safe and effective HIV prevention products, the monthly dapivirine VR and daily oral FTC/TDF tablet, when used by pregnant African women. Participants (aged 18-45 years) will be randomized in a 2:1 ratio to VR:tablet. The total length of follow-up for each participant will vary depending on gestational age at time of enrollment and length of pregnancy prior to pregnancy outcome, and may range from approximately 10 weeks or less for Cohort 1 up to approximately 34 weeks for Cohort 4. Infants born to MTN-042 participants will be followed for approximately 4 weeks.

10.2 Study Endpoints

10.2.1 Primary Endpoints

Maternal Safety (composite)

- All serious adverse events
- 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])
- For AEs categorized as complications of pregnancy, all Grade 2 or higher AEs as defined by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addendum 1 (Female Genital Grading Table for Use in Microbicide Studies [Dated November 2007])

Infant Safety (composite)

- All serious adverse events
- 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

10.2.2 Secondary Endpoints

Pregnancy Outcome

- Therapeutic/elective abortion, peri-partum hemorrhage, chorioamnionitis, post-partum endometritis, prolonged admission for baby, PROM, infant size relative to gestational age, low birth weight (<2500g)

Pharmacokinetics

- Maternal and infant plasma and PBMC TFV concentrations
- Maternal and infant plasma DPV concentrations

Adherence

- Plasma TFV and DPV concentrations

- Participant report of frequency of study product use (e.g., missed doses for oral FTC/TDF and VR removal/expulsions [voluntary and involuntary] and duration without VR in vagina)
- Residual drug levels in returned VRs

Acceptability

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

10.3 Primary Study Hypotheses

- It is hypothesized that daily use of FTC/TDF oral tablet and dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks will both be generally safe and well-tolerated by the participants and their fetuses/infants.

10.4 Sample Size and Power Calculations

10.4.1 Primary Endpoints

Maternal Safety

Infant Safety

10.4.2 Secondary Endpoints

Pregnancy Outcome

Pharmacokinetics

Adherence

Acceptability

10.5 Participant Accrual, Follow-up and Retention

The accrual period for Cohorts 1-3 will be approximately 6 months at each site, while the accrual period for Cohort 4 will be approximately 9 months at each site. Participant accrual will be paused at each site once accrual goals are met for the currently enrolling Cohort to allow all enrolled participants to give birth. The duration of these accrual pauses will vary depending on the Cohort, and likely will be approximately 3 months for Cohort 1, approximately 6 months for Cohort 2, and approximately 9 months for Cohort 3. Once pregnancy outcome has been determined for all enrolled participants in the Cohort, interim safety analyses will be conducted to determine if accrual into the next Cohort can begin. The duration of these interim analyses will vary depending on the quantity and quality of data collected, but is not expected to exceed 3 months. Therefore, it is expected that approximately 5-6 months will lapse between end of accrual for Cohort 1 and beginning of accrual for the Cohort 2, 8-9 months between Cohorts 2 and 3, and 11-12 months between Cohorts 3 and 4.

Approximately 750 participants and their newborn infants will be enrolled.

10.6 Randomization

10.7 Data and Safety Monitoring Procedures

No DSMB oversight is planned for this study. The MTN SMC will conduct interim review of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or laboratory issues. These reviews will take place approximately every 6 months, or as needed. At the time of these reviews, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Safety monitoring will be done by the PSRT.

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

The SMC will review safety data collected in each cohort to look for a significantly higher rate of pregnancy complications compared to controls (e.g., approximately three times higher for events with a baseline rate of 5%). If this were noted at interim review, serious consideration would be given as to the prudence of enrolling women in subsequent cohorts.

The SMC will review rates of the following diagnoses for each cohort:

- Preeclampsia/eclampsia
- Chorioamnionitis
- Endometritis
- Maternal sepsis
- Retained placenta
- Placental abruption
- Intrauterine fetal demise
- Postpartum hemorrhage
- Delivery prior to 37 0/7 weeks
- Intimate partner violence
- Premature rupture of membranes
- Maternal death
- Congenital anomalies
- Small for gestational age
- Low birthweight
- Neonatal sepsis
- Neonatal death

10.8 Analyses

10.8.1 Primary Safety Analyses

10.8.2 Analysis of Secondary Endpoints

10.8.3 Missing Data

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

11 DATA HANDLING AND RECORDKEEPING

Commented [DL14]: Section 11 still needs adapted to be more specific to this protocol, and to include qualitative data management language.

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-042 Medidata Rave study database, a data management system compliant with International Council on Harmonization (ICH) Good Clinical Practices (GCP) and CFR guidelines, which is maintained by the MTN SDMC.

Interview and group discussion files (if applicable) generated in the field will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be uploaded and managed using a qualitative software package. RTI International will act as a hub, and manage all qualitative data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. Transcripts will be transferred to RTI International as they are completed. RTI International will save all versions of all files on a secure, password-protected server.

11.2 Source Documents and Access to Source Data/Documents

All study sites will maintain source data/documents in accordance with 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, Inc., OHRP and other local, US, and international regulatory entities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

13.1 Institutional Review Boards/Ethics Committees

Commented [DL15]: Section 13 still needs to be adapted to be more specific to pregnant women and to include qualitative data management language.

Site investigators will make every effort to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR will have obtained IRB/EC approval and the protocol will have been submitted to the FDA. The IoR will permit audits by the NIH, IPM, Gilead Sciences, Inc., the FDA, OHRP, any of their appointed agents, and other local, US, and international regulatory entities.

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 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 of the required documents have been received.

Site-specific ICFs *will* be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol

registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) *will not* be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

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

13.3 Study Coordination

DAIDS holds the Investigational New Drug (IND) application for this study. Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trial Agreement (CTA) executed by NIAID, IPM, and Gilead Sciences, Inc.

Study implementation will also be guided by the MTN-042 SSP Manual that provides further instructions and operational guidance on: conducting study visits; data and forms processing; specimen collection, processing, and shipping; AE assessment, management and reporting; dispensing study product and documenting product accountability; and other study operations. Standardized study-specific training will be provided to all sites by the MTN LOC, SDMC, LC and other designated members of the Protocol Team.

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

13.4 Risk Benefit Statement

13.4.1 Risks

General

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

Pelvic examination and procedures may cause mild discomfort, pressure and/or vaginal bleeding or spotting. Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Disclosure of HIV and STI status may cause worry, sadness or depression. Disclosure of HIV-positive status has been associated with depression, suicidal ideation, and denial as well as social isolation. Trained counselors will be available to help participants deal with these feelings. Participation in clinical research includes the risks of loss of confidentiality and discomfort with the personal nature of questions when discussing sexual

behaviors. 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) 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 vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse). 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 trials, 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.

Based on in vitro data, HIV-infected participants who have prolonged exposure to low concentrations of dapivirine by continuing to use the ring after infection may have a risk of selecting viruses carrying NNRTI resistance-associated mutations. Clinical relevance has yet to be established.

FTC/TDF

FTC/TDF 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 FTC/TDF 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 FTC/TDF. However, these were relatively infrequent (10% of users), presented in first or second month of use for oral PrEP, and did not lead to product discontinuation[23]:

- Gastrointestinal intolerance (such as nausea, abdominal pain, diarrhea, or vomiting), most commonly in the first month and typically resolves
- Flatulence (gas), most commonly in the first month and typically resolves
- Headache, dizziness, tiredness, or inability to sleep

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 FTC/TDF may get a “flare” or worsening of hepatitis symptoms

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 at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

13.4.2 Benefits

Given that the dapivirine VR as tested in MTN-020 (ASPIRE) and IPM 027 (The Ring Study) was found to be safe and effective, participants in MTN-042 will experience the direct benefit of using a product that has been found to be safe and effective in preventing HIV acquisition and will be considered for potential regulatory approval. Furthermore, FTC/TDF is a FDA licensed product that is used to treat HIV infection as well as reduce the risk of HIV infection.

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to understand issues important for broader implementation of the dapivirine ring and PrEP and/or for the development of other safe and effective interventions to prevent HIV acquisition in pregnant women. Participants may also appreciate the opportunity to contribute to the field of HIV prevention research.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, pelvic examination, obstetric abdominal examination, and routine laboratory testing. Participants will be provided with an obstetric ultrasound if not already performed as part of their routine antenatal care. Participants will be provided STI treatment in accordance with WHO guidelines free of charge. In addition, STI testing, counseling and treatment, as well as HIV testing and counseling will be available for participants' partners. For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some volunteers may have the opportunity to access expedient treatment and as a result may have decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals. Antenatal care and delivery will not be provided by the study and must be accessed in local care facilities as would have occurred in the absence of study participation.

13.5 Informed Consent Process

Written informed consent will be obtained from all participants as per US regulations and local authorities. Informed consent is required prior to initiation of MTN-042 procedures. Written informed consent 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 and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials

(https://www.niaid.nih.gov/sites/default/files/daids-sourcedoc policy.pdf). Participants will be provided with copies of the ICFs if they are willing to receive them.

In addition to ICFs, the Protocol Team will work with study staff and community representatives to develop appropriate materials about the study and a standardized approach to the informed consent process to be implemented at all study sites, which will be detailed in the MTN-042 SSP manual.

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

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

13.6 Participant Confidentiality

All study procedures will be conducted in private, and every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will implement confidentiality protections that reflect the local study implementation plan and the input of study staff and community representatives to identify potential confidentiality issues and strategies to address them. For example, participants will be counseled about keeping all study materials (e.g., study products, handouts) and communications (e.g., text messages, phone calls) confidential. In addition to local considerations, the protections described below will be implemented at all sites.

All study-related information will be stored securely at the study site. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data collection, and administrative forms will be identified by coded number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and ICFs, will be stored securely. All local databases will be secured with password protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participants' identification numbers to identifying information will be stored in a locked file in an area with limited access. All digital audio files will be stored on password-protected computers. Audio files will be translated and transcribed in English and securely stored. Please see MTN-042 SSP Manual for guidance.

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

- Representatives of the US Federal Government, including the US FDA, the US OHRP, NIH and/or contractors of the NIH, and other local, US, and international regulatory entities
- Representatives of IPM

- Representatives of Gilead Sciences, Inc.
- PPD
- Study staff
- Site IRBs/ECs

13.7 Special Populations

13.7.1 Pregnant Women

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

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

1. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
   - To date, studies of the DPV VR and FTC/TDF oral tablet have not identified significant safety risks to pregnant women and fetuses. Product safety data is included in Section 2 of this protocol.

2. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means.
   - Due to projected low exposure to either DPV or FTC/TDF for the fetus, associated risks are expected to be minimal. In addition, evidence pointing to the protective effect of both the DPV VR and the FTC/TDF oral tablet against HIV in women holds out the prospect of direct benefit to both the woman and the fetus, as primary maternal infection with HIV poses significant risk to the fetus. Product efficacy data is included in Section 2.

3. Any risk is the least possible for achieving the objectives of the research.
   - The MTN-042 study team has minimized participant risk for this study by taking a carefully monitored, step-wise approach to dosing, starting at later gestational ages, then progressing earlier in pregnancy once safety is confirmed. The rationale for the study design is detailed in Section 2.7.

4. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part.
   - The MTN-042 study includes an informed consent process consistent with all applicable requirements in the CFR.

5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
   - This section is not applicable, as there is the prospect of direct benefit to the pregnant woman from participation in the MTN-042 study.

6. Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate.
   - This information has been included in the MTN-042 Sample Informed Consent documents, will be included in site-specific informed consent documents, and will be covered thoroughly during the informed consent process, including throughout the pregnant woman's study participation. In addition, the pregnant woman will be informed of any applicable new information learned throughout this or other studies.

7. For children as defined in 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part.
   - This section is not applicable to MTN-042, as children under 18 years old who are pregnant will not be enrolled.

8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
   - Inducements to terminate a pregnancy will not be offered by MTN-042 study site staff.

9. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
   - Individuals engaged in MTN-042 will have no part in decisions as to the timing, method, or procedures used to terminate a pregnancy by participants.

10. Individuals engaged in the research will have no part in determining the viability of a neonate.
    - Individuals engaged in MTN-042 will have no part in determining the viability of a neonate.

13.7.2 Children

The NIH has mandated that children be included in research trials when appropriate. MTN-042 will enroll pregnant female participants who are age 18-45 years old at the time of enrolment for this study, as verified per site SOPs, as well as their newborn infants once their infants are born. MTN-042 will provide critical safety and PK data related to study drug exposure for the fetuses of those female participants. The risk involved in this research is considered greater than minimal risk but presents the prospect of direct benefit to both female and newborn participants. Both products being used in this study have been shown to be safe and effective in adults, but DPV has not been approved in the countries where the implementation of this trial is planned, and FTC/TDF for oral PrEP has not yet been made widely accessible in these countries. Therefore, this research holds out the prospect of direct benefit to the health and well-being of both adult and infant MTN-042 participants.

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.

13.9 Communicable Disease Reporting

Study staff will comply with local requirements to report communicable diseases identified among study participants to health authorities, including HIV-1. Participants will be made aware of reporting requirements during the informed consent process.

13.10 Access to HIV-related Care

13.10.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV-1 screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV-1 testing time point. Testing will be performed in accordance with the algorithms in Appendices II and III. Counseling will be provided in accordance with standard HIV counseling policies and methods at each site and additionally will provide information regarding the known efficacy of the study products in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1 test results to take part in this study. Condoms will be offered to participants throughout the duration of their participation.

13.10.2 Care for Participants Identified as HIV-Infected

Care for participants identified as HIV-infected is described in Section 9.6.

13.11 Study Discontinuation

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

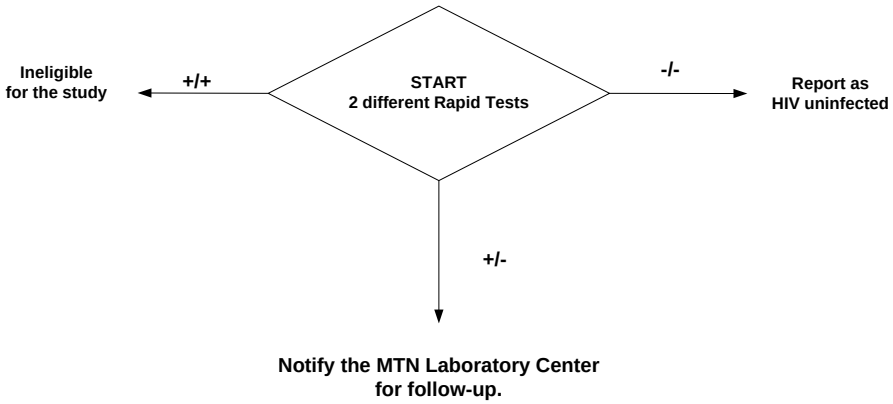
14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies and a CTA between IPM, Gilead Sciences, Inc., and NIAID, will govern publication of the results of this study. Any presentation, abstract, or manuscript will be submitted by the investigator to the MTN Manuscript Review Committee, DAIDS/NIAID, NICHD, National Institute of Mental Health (NIMH), IPM, and Gilead for review prior to submission.

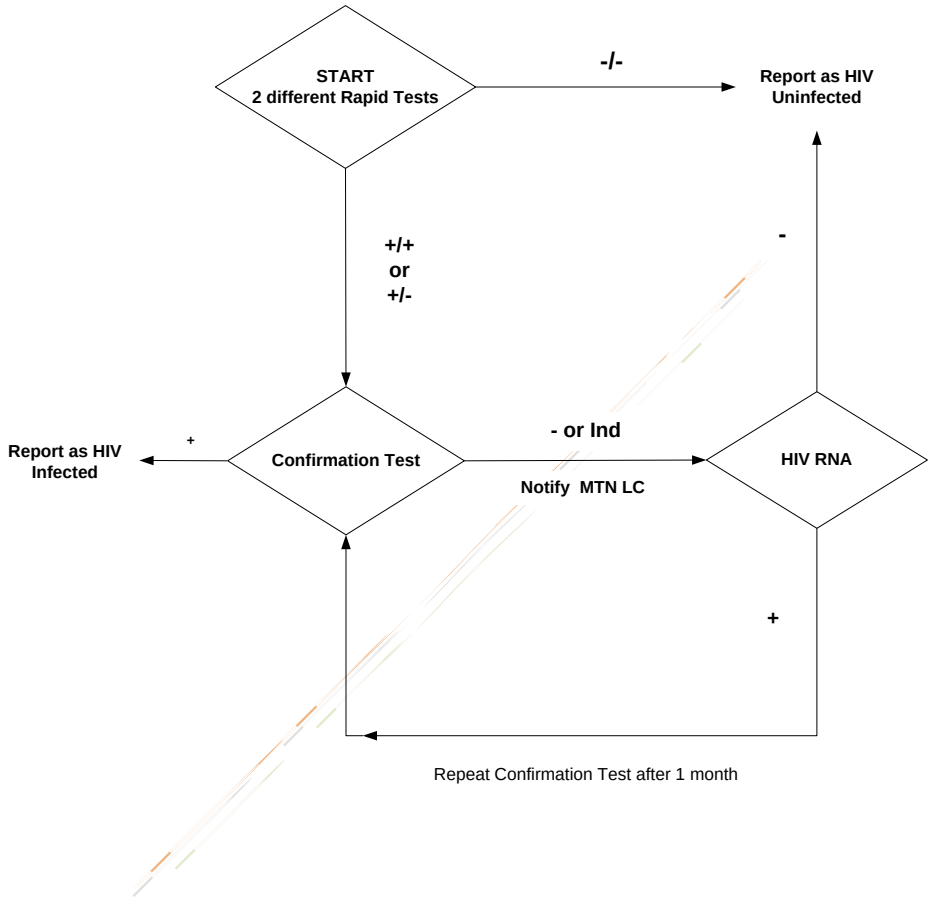
15 APPENDICES

APPENDIX I: TABLE OF VISITS AND STUDY PROCEDURES

APPENDIX II: ALGORITHM FOR HIV TESTING – SCREENING/ENROLLMENT



APPENDIX III: ALGORITHM FOR HIV TESTING – FOLLOW-UP



Ind: Indeterminate test results
LC: Laboratory Center

APPENDIX IV: SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE)

SAMPLE INFORMED CONSENT FORM
DIVISION OF AIDS, NIAID, NIH

MTN-042

Phase 3b, Randomized, Open Label Safety and Pharmacokinetic Trial of Dapivirine Vaginal Ring (VR) and Oral FTC/TDF Use in Pregnancy

Version 0.2

March 29, 2018

PRINCIPAL INVESTIGATOR: ***[Site to insert]***
PHONE: ***[Site to insert]***
Short Title for the Study: Safety and PK of Dapivirine VR and Oral PrEP in Pregnancy

INFORMED CONSENT

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