MTN-034

A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population

Microbicide Trials Network

Funding Agencies:
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DAIDS

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Pharmaceutical Company Collaborators:
Gilead Sciences, Inc.
International Partnership for Microbicides

Protocol Chair:
Gonasagrie Nair, MBChB, MPH

Protocol Co-Chairs:
Connie Celum, MD, MPH
Kenneth Ngure, PhD

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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 aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
ASCP	American Society of Clinical Pathology
ASPIRE	A Study to Prevent Infection with a Ring for Extended Use
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
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
DBS	Dried blood spot
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
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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PROTOCOL TEAM ROSTER

Protocol Chair

Gonasagrie Nair, MBChB, MPH
Protocol Chair
Emavundleni Research Centre
14 Sonwabile Drive
Crossroads7750
Cape Town South Africa
Phone: 27-21-650-5873
Email: lulu.nair@hiv-research.org.za

Protocol Co-Chairs

Connie Celum, MD, MPH
Protocol Co-Chair
University of Washington
International Clinical Research Center (ICRC), Dept. of Global Health
325 Ninth Avenue, Box 359927
Seattle, WA 98104 USA
Phone: 206-520-3824
Fax: 206-520-3831
Email: ccelum@u.washington.edu

Kenneth Ngure, PhD
Protocol Co-Chair
Jomo Kenyatta University of Agriculture and Technology (JKUAT)-College of Health Sciences
P.O. Box 19704-00202
Nairobi, Kenya
Phone: 254-722-362219
Email: kngure@uw.edu

Site Investigators

Emavundleni CRS

Linda-Gail Bekker MB ChB, FCP, PhD
CTU PI
Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine (IIDMM),
Faculty of Health Sciences, University of Cape Town (UCT),
Anzio Road, Observatory,
Western Cape Province, 7705,
Cape Town, South Africa
Phone: 27-21-650-6959
Fax: 27-21-633-0182
Email: linda-gail.bekker@hiv-research.org.za

Gonasagrie Nair, MBChB, MPH
Site Investigator of Record
Emavundleni Research Centre
14 Sonwabile Drive
Crossroads7750
Cape Town South Africa
Phone: 27-21-650-5873
Email: lulu.nair@hiv-research.org.za

The University of Zimbabwe College of Health Sciences (UZCHS) Clinical Trials Unit – Spilhaus CRS

Z. Mike Chirenje MD, FRCOG
CTU PI
UZCHS CTU
15 Phillips Avenue, Belgravia
Harare, Zimbabwe
Phone: 263-4-704-966
Fax: 263-4-704-897
Email: mchirenje@uzchs-ctu.org

Felix G. Muhlanga MBChB, MMed
Site Investigator of Record
UZCHS CTU
15 Phillips Avenue, Belgravia
Harare, Zimbabwe
Phone: 263-4-704-920
Fax: 263-4-704-897
Email: fmhlanga@uzchs-ctu.org

Wits Reproductive Health and HIV Institute (Wits RHI) CRS

Helen Vera Rees, OBE, MBBChir, MA, DRCOG, DCH
CTU Co-PI
Wits RHI
22 Esselen Street, Hillbrow
Johannesburg, 2001
Phone: 27-11-358-5300
Email: hrees@wrhi.ac.za

Ian Sanne, MD, FCP
CTU Co- PI
Helen Joseph Hospital, Perth Road, Westdene, Themba Lethu Clinic
Johannesburg, 2092 South Africa
Phone: 27-11-276-8800
Fax: 27-11-482-2130
Email: isanne@witshealth.co.za

Thesla Palanee-Phillips, M Med Sci, PhD, M Sc
Site Investigator of Record
Wits RHI
Research Centre
7 Esselen Street, Hillbrow
Johannesburg, 2001 South Africa
Phone: 27-11-358-5471
Fax: 27-86-554-1093
Email: tpalanee@whri.ac.za

Kenyan Medical Research Institute (KEMRI)/Centers for Disease Control (CDC) Kisumu CRS

Kevin Cain, MD
CRS Leader
Kenya Medical Research Institute
P.O Box 1578-40100
Kisumu, Kenya
Phone: 254-710-602786
Fax: 254-57-2022981
Email: bvz1@cdc.gov

Mitesh Desai, MD, MPH
CDC Representative
LCDR, U.S. Public Health Service
Medical Epidemiologist, Clinical Trials Team
Epidemiology Branch, Div. HIV/AIDS Prevention, CDC
Phone: (404) 639-5173
Email: gdo5@cdc.gov

Nelly Mugo,
Site Investigator of Record
Kenya Medical Research Institute
P.O Box 1578-40100
Kisumu, Kenya
Phone: 254-73-362-9665
Email: Rwamba@csrtkenya.org

Makerere University - Johns Hopkins University (MU-JHU) Research Collaboration CRS

Mary Glenn Fowler
CTU Co-PI
Johns Hopkins University School of Medicine,
600 N. Wolfe Street
Baltimore, MD 21287
Phone: 410 502 0683
Fax: 410 502 0688
Email: mgfowler@mujhu.org

Clemensia Nakabiito, MBChB, MMed
Site Principal Investigator MTN MU-JHU Research Collaboration
P.O. Box 23491
Kampala, Uganda
Phone: 256-41-541044/256-772-405332
Fax: 256-41-541044/256-41-532091
Email: cnakabiito@mujhu.org

Carolyne Akello, MBChB, MScEpi
MU-JHU Research Collaboration
P.O. Box 23491
Kampala Uganda
Phone: 256-772-530250/256-414-541044
Fax: 256-414-543002
Email: cakello@mujhu.org

US National Institutes of Health (NIH)

Roberta Black, PhD
Chief, Clinical Microbicide Research Branch
National Institute of Allergy and Infectious Diseases (NIAID), Division of AIDS (DAIDS)
5601 Fishers Lane, Room 8B62, MSC 9831
Rockville, MD 20852 USA
Phone: 301-496-8199
Email: rblack@niaid.nih.gov

Naana Cleland, MHCA
Health Specialist, Clinical Microbicide Research Branch (CMRB)
Prevention Sciences Program (PSP) DAIDS, NIAID
NIH - U.S. Department of Health and Human Services (HHS)
5601 Fishers Lane, Room 8B27
Rockville, MD 20852 USA
Phone: 240-292-4779
Email: clelandn@niaid.nih.gov

Dianne M. Rausch, PhD
Director
DAIDS Research, National Institute of Mental Health (NIMH)
5601 Fishers Lane Room 8D20, MSC 9831
Rockville, MD 20852 USA
Phone: 240-627-3874
Fax: 240-627-3467
Email: drausch@mail.nih.gov

Teri Senn, PhD
Program Chief, Psychosocial Co-morbidities of HIV Prevention and Treatment
Division of AIDS Research, NIMH
5601 Fishers Lane Room 9G29
Rockville, MD 20852 USA
Phone: 301-761-7852
Email: teri.senn@nih.gov

Lydia E. Soto-Torres, MD, MPH
DAIDS Medical Officer (MO)
NIAID, DAIDS
5601 Fishers Lane
Rockville, MD 20852 USA
Phone: 240-292-4807
Cell: 301-213-1154
Email: lsoto-torres@niaid.nih.gov

MTN Leadership and Operations Center (LOC) – Pitt

Jared Baeten, MD, PhD
Principal Investigator
University of Washington
ICRC, Dept of Global Health
325 Ninth Avenue, Box 359927
Seattle, WA 98104
Phone: 206-520-3808
Fax: 206-520-3831
Email: jbaeten@uw.edu

Katherine Bunge, MD
Protocol Safety Physician
Magee-Womens Hospital of the University of Pittsburgh Medical Center (UPMC)
300 Halket Street
Pittsburgh, PA 15213 USA
Phone: 412-641-3464
Fax: 412-641-1133
Email: kbunge@mail.magee.edu

Luis Duran, DrPH, MPIA
Project Manager
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-8539
Fax: 412-641-6170
Email: duranl2@mwri.magee.edu

Sharon Hillier, PhD
Principal Investigator
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-8933
Fax: 412-641-6170
Email: shillier@mail.magee.edu

Sybil Hosek, PhD
Consultant
Stroger Hospital of Cook County
Department of Psychiatry
1900 W. Polk Street #854
Chicago, IL 60612 USA
Phone: 312-864-8030
Fax: 312-864-9203
Email: shosek@cookcountyhhs.org or sybilhosek@gmail.com

Cindy Jacobson, PharmD
Director of Pharmacy Affairs
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-8913
Fax: 412-641-6170
Email: cjacobson@mail.magee.edu

Sharon A. Riddler, MD, MPH
Protocol Physician
UPMC, Keystone Building, Suite 510
3520 Fifth Avenue
Pittsburgh, PA 15213 USA
Phone: 412-383-1741 or 412-383-1675
Fax: 412-383-2900
Email: riddler@dom.pitt.edu

Devika Singh, MD, MPH
Protocol Safety Physician
ICRC, Dept. of Global Health
325 Ninth Avenue, Box 359927
Seattle, WA 98104 USA
Phone: 206-744-8311
Fax: 206-520-3831
Email: devika@mtnstopshiv.org

Jennifer Thomas, MSc
Protocol Development Manager
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-5579
Fax: 412-641-6170
Email: thomasj15@mwri.magee.edu

MTN Laboratory Center (LC)

Charlene S. Dezzutti, PhD
LC Principal Investigator
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-3462
Fax: 412-641-6170
Email: dezzuttics@upmc.edu

Edward Livant, BSMT (ASCP), MPH
MTN LC Research Manager
Microbicide Trials Network
204 Craft Avenue
Pittsburgh, PA 15213 USA
Phone: 412-641-3772
Fax: 412-641-5290
Email: livantew@upmc.edu

Wayne Hall, MT(ASCP)
Clinical Laboratory Representative
Microbicide Trials Network
204 Craft Ave. Room A534
Pittsburgh, PA 15213 USA
Phone: 412-641-6956
Fax: 412-641-6170
Email: hallwb@mwri.magee.edu

John Mellors, MD
Virology LC Director
University of Pittsburgh Physicians
3550 Terrace Street, Scaife Hall, Suite 818
Pittsburgh, PA 15261 USA
Phone: 412-624-8512
Fax: 412-383-7982
Email: jwm1@pitt.edu

Craig Hendrix, MD
Pharmacology LC Director
Johns Hopkins University
600 North Wolfe Street, Harvey 502
Baltimore, MD 21287 USA
Phone: 410-955-9707
Fax: 410-955-9708
Email: cwhendrix@jhmi.edu

Urvi Parikh, PhD
Virology LC Associate Director
University of Pittsburgh
3550 Terrace Street
S804 Scaife Hall
Pittsburgh, PA 15261 USA
Phone: 412-648-3103
Fax: 412-648-8521
Email: ump3@pitt.edu

MTN LOC – FHI 360

Morgan Garcia, MPH
Clinical Research Manager
FHI 360
359 Blackwell St., Suite 200
Durham, NC 27703 USA
Phone: 919-544-7040 x11367
Fax: 919-544-0207
Email: mgarcia@fhi360.org

Tara McClure, MPH
Clinical Research Manager
FHI 360
359 Blackwell St., Suite 200
Durham, NC 27703 USA
Phone: 919-544-7040 x11012
Fax: 919-544-0207
Email: tmcclure@fhi360.org

Sherri Johnson, MPH
Senior Clinical Research Manager
FHI 360
1825 Connecticut Avenue, NW
Washington, DC 20009 USA
Phone: 202-884-8000, Ext. 18677
Fax: 202-884-8844
Email: sjohnson@fhi360.org

Lisa Levy, MPH
MTN Associate Project Director
FHI 360
1825 Connecticut Avenue, NW
Washington, DC 20009 USA
Phone: 202-884-8480
Fax: 202-884-8000, Ext. 18480
Email: llevy@fhi360.org

Rhonda White, RH Ed
Senior Community Program Manager
FHI 360
359 Blackwell St., Suite 200
Durham, NC 27701 USA
Phone: 919-544-7040 Ext. 11515
Fax: 919-544-0207
Email: rwhite@fhi360.org

MTN Statistical Data Management Center (SDMC)

Karen Patterson, MPH
Program & Portfolio Manager
Fred Hutchinson Cancer Research Center (FHCRC) – Statistical Center for HIV/AIDS Research and Prevention (SCHARP)
1100 Fairview Avenue North, E3-129
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7052
Fax: 206-667-4812
Email: karenp@scharp.org

Barbra Richardson, PhD
Faculty Statistician
FHCRC-SCHARP
1100 Fairview Ave. North, M2-C200
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7788
Fax: 206-667-4812
Email: barbrar@uw.edu

Daniel Szydlo, MS
Statistical Research Associate
FHCRC - SCHARP
1100 Fairview Avenue North, M2-C200
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7451
Fax: 206-667-4378
Email: dszydlo@scharp.org

Jennifer Berthiaume, MSW, MPH
Clinical Data Manager
FHCRC-SCHARP
1100 Fairview Ave. North, J5-000
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-1230
Email: jberthia@scharp.org

Jennifer Schille
Clinical Data Manager
FHCRC-SCHARP
1100 Fairview Ave. North, J5-000
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7892
Email: jens@scharp.org

MTN Behavioral Research Working Group (BRWG)

Barbara Friedland, MPH
BRWG Co-representative
Population Council
1 Dag Hammarskjold Plaza
New York, NY 10017 USA
Phone: 212-327-7045
Fax: 212-755-6052
Email: bfriedland@popcouncil.org

Kenneth Ngure, PhD
BRWG Co-representative
JKUAT-College of Health Sciences
P.O. Box 19704-00202
Nairobi, Kenya
Phone: 254-722-362219
Email: kngure@uw.edu

Sarah T. Roberts, PhD
Research Analyst
RTI International
351 California Street, Suite 500
San Francisco, CA 94104 USA
Phone: 415-848-1335
Email: sroberts@rti.org

Ariane van der Straten, PhD, MPH
BRWG Co-representative
RTI International
351 California Street, Suite 500
San Francisco, CA 94104 USA
Phone: 415-848-1324
Fax: 415-848-1330
Email: ariane@rti.org

MTN Community Working Group (CWG) Representative

Charles Chasakara
CWG Representative
UZ-UCSF Research Programme
10 Routeledge Road Milton Park
Harare, Zimbabwe
Phone: 263-4-291-5421
Fax: 263-4-704-897
Email: cchasakara@uz-ucsf.co.zw

MTN Biomedical Science Working Group (BSWG) Representative

Betsy Herold, MD
BSWG Representative
Albert Einstein College of Med.,
1300 Morris Park Avenue, Van Etten 6A-04A
Bronx, NY 10461 USA
Phone: 718-839-7460
Fax: 718-862-1833
Email: betsy.herold@einstein.yu.edu

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INVESTIGATOR SIGNATURE FORM
Version 2.0; December 7, 2017
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 Holder:
DAIDS (DAIDS Protocol ID: 12066)

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

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PROTOCOL SUMMARY

Short Title:	Reversing the Epidemic in Africa with Choices in HIV Prevention (REACH)
IND Sponsor:	DAIDS
Funders:	Division of AIDS, NIAID, NIMH, NICHD, US NIH
Protocol Chair:	Gonasagrie Nair, MBChB, MPH
Protocol Co-Chairs:	Connie Celum, MD, MPH Kenneth Ngure, PhD
Sample Size:	Approximately 300 participants
Study Population:	Healthy, HIV-uninfected, sexually active adolescent and young adult females, 16 - 21 years old (inclusive)
Study Sites:	Sites selected by the MTN Executive Committee
Study Design:	Phase 2a, open-label, multi-site, two-sequence, crossover, randomized trial
Study Duration:	Approximately 76 weeks of follow-up per participant with a projected accrual period of approximately 12 months at each site.
Study Product:	• Silicone elastomer vaginal matrix ring containing 25 mg of dapivirine to be replaced each month • Emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) tablets to be taken orally daily
Study Regimen:	Participants will be randomized (1:1) to one of two sequences of a vaginal ring (VR) containing 25mg of dapivirine to be inserted monthly for 24 weeks and 200 mg FTC/300 mg TDF oral tablets taken daily for 24 weeks. After completing the randomized sequence of two study product use periods, participants will

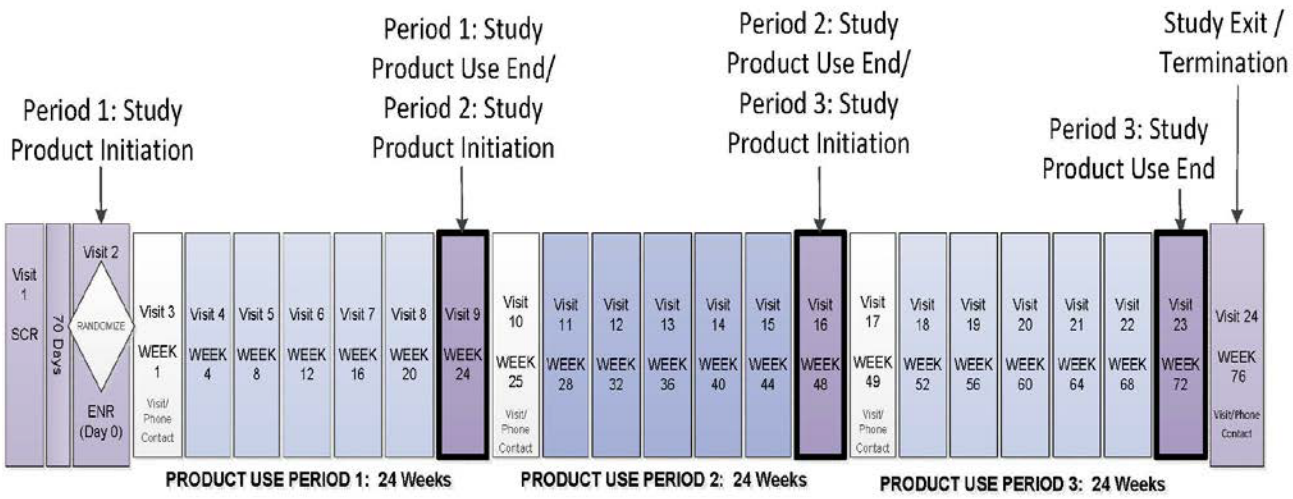
then select between the two study products to use in the final 24 weeks of the trial. Participants will be able to choose either or neither study product at any time during the third product use period.

Table 1: Study Regimen

	N	Period 1 (24 Weeks)	Period 2 (24 Weeks)	Period 3 (24 Weeks)
Sequence A	150	Vaginal (dapivirine 25 mg VR)	Oral (Daily FTC/ TDF tablet)	Free choice (dapivirine 25 mg VR or daily FTC/TDF tablet or neither)
Sequence B	150	Oral (Daily FTC/ TDF tablet)	Vaginal (dapivirine 25 mg VR)	Free choice (dapivirine 25 mg VR or daily FTC/TDF tablet or neither)

The study follow-up schedule will be approximately monthly.

Figure 1: MTN-034 Study Visit Schedule



Primary Objectives:

1. Safety
   - To compare the safety profiles of FTC/TDF oral tablet administered daily and dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population

2. Adherence
   - To compare adherence to the FTC/TDF oral tablet administered daily and to the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population

Primary Endpoints:

1. Safety
   - Grade 2 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])

2. Adherence
   - Detectable drug levels in blood
   - Residual drug levels in returned VRs

Secondary Objectives:

1. Acceptability
   - To compare the acceptability of the FTC/TDF oral tablet administered daily and the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population

2. Adherence
   - To compare study product adherence during the third study product use period when study product is chosen against the study product use period during which the study product is randomly assigned

3. Study product preference
   - Participant preference between dapivirine VR and FTC/TDF oral tablets over the course of study participation

Secondary Endpoints:

1. Acceptability
   - Participant report of acceptability

2. Adherence
   - Detectable drug levels in blood
   - Residual drug levels in returned VRs

3. Study product preference
   - Participant product selection during third product use period
   - Participant report of product preference

Exploratory Objectives:

1. HIV Incidence
   - To assess the incidence of HIV-1 infection over the course of dapivirine VR use and FTC/TDF oral tablet use

2. Vaginal Microenvironment
   - To characterize the vaginal microenvironment over the course of dapivirine VR use and FTC/TDF oral tablet use

3. Adherence
   - To assess correlates of study product adherence over the course of dapivirine VR use and FTC/TDF oral tablet use

4. Social Harms and Benefits
   - To describe the reported experiences of social harms and benefits over the course of dapivirine VR use and FTC/TDF oral tablet use

Exploratory Endpoints:

1. HIV Incidence
   - HIV-1 infection (as defined by the algorithm in Appendix III)

2. Vaginal Microenvironment
   - Vaginal microbiota
   - Evaluation of candidate biomarkers of safety and efficacy in mucosal secretions
   - Mediators of mucosal immunity at sites with capacity
   - Markers of sexual exposure

3. Adherence
   - Participant self-report of product use
   - Biomarkers of adherence to study product regimen
   - Returned VRs and pill bottles
   - Persistence with chosen product during the third product use period

4. Social Harms and Benefits
   - Participant self-report of social harms resulting from product use or study participation, including negative consequences of product use disclosure, stigma, gender-based violence, and relationship problems
   - Participant self-report of social benefits from product use or study participation, including increased confidence, intimacy, and/or self-esteem

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population
Protocol Number:	MTN-034
Short Title:	Reversing the Epidemic in Africa with Choices in HIV Prevention (REACH)
Date:	December 7, 2017

1.2 Sponsor and Monitor Identification

Funding Agencies:	US Division of AIDS (DAIDS)/National Institute of Allergy and Infectious Diseases (NIAID) National Institutes of Health (NIH) 5601 Fishers Lane Rockville, MD 20852 USA US National Institute of Mental Health (NIMH) 6001 Executive Boulevard Rockville, MD 20852 USA US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) 6100 Executive Boulevard Rockville, MD 20852 USA
Pharmaceutical Company Collaborators:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA

	International Partnership for Microbicides (IPM) 8401 Colesville Road, Suite 200 Silver Spring, MD 20910 USA
IND Sponsor:	DAIDS/NIAID/NIH 5601 Fishers Lane Rockville, MD 20852 USA
Monitor:	Pharmaceutical Product Development, Inc. (PPD) 929 North Front Street Wilmington, NC 28401-3331 USA

1.3 Medical Officer

Medical Officer:	Lydia E. Soto-Torres, MD, MPH 5601 Fishers Lane Rockville, MD 20852 USA

1.4 Clinical Laboratories

Laboratory Center:	MTN Laboratory Center (LC) 204 Craft Avenue Pittsburgh, PA 15213 USA
Pharmacology:	MTN Pharmacology LC 600 N. Wolfe Street, Osler 527 Johns Hopkins University Baltimore, MD 21287 USA

1.5 Data Centers

Data Center:	MTN Statistical Data and Management Center (SDMC) Statistical Center for HIV/AIDS Research & Prevention (SCHARP)/Fred Hutchinson Cancer Research Center (FHCRC) 1100 Fairview Avenue N., LE-400 PO Box 19024 Seattle, WA 98109-1024 USA
Qualitative Data Center:	RTI International 351 California Street, Suite 500 San Francisco, CA 94104 USA

1.6 Study Operations

Study Operations:	MTN Leadership and Operations Center (LOC) - FHI 360 359 Blackwell Street, Suite 200 PO Box 21059 Durham, NC 27701 USA

2 INTRODUCTION

2.1 Microbicides and oral PrEP in HIV/AIDS Prevention

Globally, younger women, aged 15-24 years, are disproportionately affected by the HIV epidemic compared to their male counterparts.[1,2] In 2015, the Joint United Nations Programme on Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) (UNAIDS) reported that this vulnerable demographic accounted for 20% of all new HIV infections among adults globally despite making up only 11% of the global adult population.[3] UNAIDS also reported in the same year that young women aged 15-24 years accounted for 59% of all HIV infections among 15-24 year olds globally, and in sub-Saharan Africa they were two times more likely to become HIV infected than their male counterparts.[3] According to the Centers for Disease Control & Prevention (CDC), in 2014 individuals aged 13-24 years accounted for 22% of all new HIV infections in the United States, in spite of making up only about 15% of its population.[4] Further, though HIV-related deaths globally have steadily declined since their peak in 2005, HIV continues to be the leading cause of death among adolescents between the ages of 10-19 in the African Region, and the second most common cause of death among adolescents globally.[5]

Factors influencing the risk of HIV among young female populations include a lack of awareness regarding safe sexual practices, cultural and gender incapacity to insist on male partner condom use, modes of HIV transmission, biological development, psychosexual maturation, and sociocultural context, all of which may mitigate the known benefits of proven HIV prevention methods such as condom use, oral pre-exposure prophylaxis (PrEP), male circumcision and abstinence.[6]

In 2014, the World Health Organization (WHO) developed recommendations for offering oral 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.[7,8] The WHO further expanded these recommendations in 2015 to include all persons at high risk of HIV infection.[7,8] 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.[7-9] However, despite evidence suggesting similar results for young adult and adolescent females, gaps still exist in our understanding of how best to systematically implement oral PrEP with this population, including the need for additional safety data on adolescents and for additional adherence data in real-world settings.[9]

It is predicted that utilization of microbicides that are 60 percent or more efficacious by a small proportion of women in highly HIV prevalent settings could prevent 2.5 million HIV infections over three years.[1] Vaginal rings (VR) may be one strategy to provide discreet and extended protection for women. VRs are flexible and release drug over a prolonged period of time. Studies of VR use for contraception indicate

an increase in adherence and satisfaction among adult users over time, although few contraceptive studies have confirmed or refuted such findings among adolescents.[10]

Results from two Phase 3 safety and efficacy trials of the dapivirine VR, MTN-020 (ASPIRE) and IPM 027 (The Ring Study), were presented at the 2016 Conference on Retroviruses and Opportunistic Infections (CROI). Both studies found the VR to be safe and effective in reducing HIV-1 infection in healthy female adults in sub-Saharan Africa when used for one month and replaced monthly.[11,12] In The Ring Study, dapivirine VR use reduced the risk of HIV-1 infection by 30.7% relative to placebo, and a 37.5% reduction in HIV-1 infection was observed in a subgroup analysis of women older than 21 years of age. The rate of adverse events (AEs), including product-related AEs, urogenital AEs, serious adverse events (SAEs) and deaths, was similar between treatment arms.[12,13] In ASPIRE, dapivirine VR use resulted in a 27% relative reduction in HIV-1 incidence overall, a 37% reduction in an analysis defined early in the study excluding data from two study sites with lower retention and adherence, and a 56% reduction in a post-hoc analysis among women older than 21 years of age. HIV-1 protection was not observed for women aged 18-21, and objective markers of adherence were lower in this subgroup compared to women older than 21.[11,14] More recent analyses of ASPIRE results presented at the 2016 International AIDS Conference in Durban, South Africa suggest the dapivirine VR may lead to reductions in HIV-1 incidence of 56%-65% when used consistently, and may even be as high as 75%-92% for perfect ring use.[15] The low effectiveness and adherence results observed among young women in The Ring Study and ASPIRE make it clear that gaps still exist in our understanding of how best to incorporate the dapivirine VR into the HIV-1 prevention toolkit for this population.

At a consultation meeting convened by the United Nations Children's Fund (UNICEF) during the International AIDS Society (IAS) 2015 conference, 58 scientists, researchers, government, community and development partners, and youth advocates considered the clinical, ethical and operational issues associated with implementing oral PrEP among sexually active older adolescents aged 15-19 in populations at high risk of HIV infection. They urged the inclusion of older adolescents at substantially high risk of HIV acquisition in PrEP demonstration projects as part of targeted combination HIV prevention strategies. Research areas targeted as requiring more focus included: evaluation of drug safety, acceptability and use patterns in growing adolescents under age 18 and who use PrEP in ongoing trials and demonstration projects; evaluation of long-term impact of PrEP on adolescents who undergo multiple cycles of starting/stopping the drug; development of implementation strategies in adolescent/young female subpopulations such as female sex workers; and more examination of ethical, legal and regulatory barriers to both implementation of PrEP and involving adolescents under age 18 in research.[16;17]

The consultation informed the WHO PrEP recommendations and implementation guidelines described earlier.[16,17] Subsequent consultation meetings have prompted

several sub-Saharan nations, including the MTN-034 site countries, to recognize the need for targeted HIV prevention projects focusing on key vulnerable populations such as young females. These nations have partnered with the US President's Emergency Plan for AIDS Relief (PEPFAR) and other organizations to implement a number of multi-faceted oral PrEP initiatives targeting adolescent and young adult females, collectively called the Determined, Resilient, Empowered, AIDS-free, Mentored, and Safe women (DREAMS) initiative.[18]

The substantial increase in the number of young people aged 15-24 in sub-Saharan Africa underscores the need to prioritize young people, particularly young females, in HIV prevention and PrEP research and demonstration projects. In 2015, there were 226 million individuals aged 15-24 years old in Africa, half of them females. Youth currently make up close to 20% of the continent's population and are expected to more than double by 2055.[19] Although the rate of youth population growth has slowed in the countries with the highest HIV burden[20], the youth population increases already observed will certainly test these countries' resources unless the disproportionately high HIV incidence rates in this vulnerable population are also curbed. In South Africa, the population of girls and women at risk has risen 30% since 1985. If the current incidence rate is not reduced, 30 million new infections are forecast over the next 15 years. In 2015, US President Obama proposed a prevention target of a 25% reduction in HIV incidence among adolescent and young adult women (ages 15-24) within the highest-burden geographic areas of 10 sub-Saharan African countries by the end of 2016, and a 40% reduction by 2018. While ambitious, this target was thought to be the minimum necessary to maintain the current infection rate, because the adolescent population is still growing.[21]

The International Partnership for Microbicides (IPM) and Gilead have joined with the Microbicide Trials Network (MTN) to evaluate the safety of and adherence to dapivirine VR and FTC/TDF oral tablet in an adolescent and young adult female population. MTN-034 will contribute valuable safety and adherence data for FTC/TDF oral tablet and dapivirine VR specific to adolescent and young adult females. Given the urgent need to curb the HIV epidemic in this vulnerable population and the many challenges posed by this task, it is crucial that young adult and adolescent females have as many safe and effective prevention options as can be made available to them.

2.2 Description

2.2.1 Dapivirine Vaginal Ring (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]

IPM has investigated a wide range of dosage formulations for the development of topical microbicide products, including vaginal gels, rings, films, tablets and soft gel capsules. The vaginal gel was the initial dosage form chosen for a dapivirine-based microbicide because the majority of previous microbicides evaluated in clinical trials were also vaginal gels. Therefore, a wealth of information was available on this dosage form. 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 VR 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 VRs with similar physical characteristics;
- The overall cost for the VR is relatively low; and
- Minimal storage space is required for the VR when compared with once daily products.

Summaries of the safety and tolerability of dapivirine administered orally and vaginally as evaluated in clinical studies by IPM and Jansen Research and Development (formerly Tibotec Pharmaceuticals) can be found in Section 2.7.1.

2.2.2 FTC/TDF 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 antiretroviral (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, known as PrEP.[24] Truvada® for oral PrEP was also approved for use by adults at high risk of sexually acquiring HIV-1 infection in both South Africa and Kenya, first by South Africa's Medicines Control Council (MCC) in November 2015, shortly followed by Kenya's Pharmacy and Poisons Board (PPB) in December 2015.[25]

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[7,9]:

- 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.

Summaries of the safety, acceptability and adherence of FTC/TDF administered orally as evaluated in clinical studies by Gilead Sciences, Inc. can be found in Section 2.7.2.

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 2: 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
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

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 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 3: 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 4: 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

The primary focus of MTN-034 is the collection of additional safety and adherence data in adolescent and young adult female participants in sub-Saharan Africa who will use both daily oral PrEP and dapivirine VR. MTN-034 will also examine acceptability of the VR and the daily oral tablet, which will provide valuable data to inform future rollout and issues/opportunities for product uptake.

The FTC/TDF combination pill has an established safety and efficacy profile when used as part of combined antiretroviral therapy (ART) to treat HIV infection. More recently it has been demonstrated to be effective in the prevention of HIV infection when taken daily, see Section 2.7.2. However, a paucity of safety, adherence, and acceptability data exist for adolescent and young adult females living in high-risk regions, e.g., sub-Saharan Africa, relative to that amassed on other groups such as MSM and adult females.

MTN-034 is designed to compare the safety of and adherence to two HIV prevention product formulations: a pill and a VR. The crossover design of MTN-034 will compare a daily oral tablet to a monthly VR (daily FTC/TDF oral tablet, dapivirine VR) used by the same participants. Participants will use each product for 24 weeks, and randomization to product sequence will ensure an unbiased estimate of the treatment effects. Approximately 100 adolescent (16-17 years old) and 200 young adult (18-21 years old) female participants are expected to enroll in the trial, although more than 100 adolescents may enroll if sites are able to recruit from this age group with ease. This will ensure adequate safety data is collected on adolescent females to provide evidence for both products' indication for use by adolescents, as well as valuable adherence and acceptability data for both products in adolescent and young adult females. After participants use each study product for 24 weeks (for a total of 48 weeks), they will then have the opportunity to choose either the daily pill or the monthly VR for a third 24-week product use period. Furthermore, participants will be allowed to choose either or neither study product at any time during the third product use period. This will ensure additional adherence and product preference data is collected on both products for adolescent and young adult females. It is important to note that there will not be a washout period between study product use periods as withholding an effective HIV preventative agent from this at risk population during the trial would be unethical.

While there are many facets to the future roll-out of ARV-based prevention that are worthy of study, including potential impacts on behavior, optimizing drug adherence, and implementation strategies for the public sector, all future approaches must be grounded in an evidence base for safe management of these drugs in healthy adolescent and young adult populations. MTN-034 will contribute valuable data to

this evidence base by describing the safety outcomes and adherence to ARV-based HIV prevention interventions in this adolescent and young adult female population. Safety data will be provided to regulatory entities (RE).

3 OBJECTIVES

3.1 Primary Objectives

1. Safety
   - To compare the safety profiles of FTC/TDF oral tablet administered daily and dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population

2. Adherence
   - To compare adherence to the FTC/TDF oral tablet administered daily and to the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population

3.2 Secondary Objectives

1. Acceptability
   - To compare the acceptability of the FTC/TDF oral tablet administered daily and the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks during the first 24 weeks of use of each study product in an adolescent and young adult female population

2. Adherence
   - To compare study product adherence during the third study product use period when study product is chosen against the study product use period during which the study product is randomly assigned

3. Study product preference
   - Participant preference between dapivirine VR and FTC/TDF oral tablets over the course of study participation

3.3 Exploratory Objectives

1. HIV Incidence
   - To assess the incidence of HIV-1 infection over the course of dapivirine VR use and FTC/TDF oral tablet use

2. Vaginal Microenvironment
   - To characterize the vaginal microenvironment over the course of dapivirine VR use and FTC/TDF oral tablet use

3. Adherence
   - To assess correlates of study product adherence over the course of dapivirine VR use and FTC/TDF oral tablet use

4. Social Harms and Benefits
   - To describe the reported experiences of social harms and benefits over the course of dapivirine VR use and FTC/TDF oral tablet use

4 STUDY DESIGN

4.1 Identification of Study Design

The MTN-034 trial is a multi-site, two-arm, randomized, open-label, crossover Phase 2a trial. Eligible HIV-uninfected participants will attend study visits for approximately 76 weeks. The study will assess the safety of and adherence to an oral FTC/TDF tablet and a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine.

4.2 Summary of Major Endpoints

Primary Endpoints:

1. Safety
   - Grade 2 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])

2. Adherence
   - Detectable drug levels in blood
   - Residual drug levels in returned VRs

Secondary Endpoints:

1. Acceptability
   - Participant report of acceptability

2. Adherence
   - Detectable drug levels in blood
   - Residual drug levels in returned VRs

3. Study product preference
   - Participant product selection during third product use period
   - Participant report of product preference

Exploratory Endpoints:

1. HIV Incidence
   - HIV-1 infection (as defined by the algorithm in Appendix III)

2. Vaginal Microenvironment
   - Vaginal microbiota
   - Evaluation of candidate biomarkers of safety and efficacy in mucosal secretions
   - Mediators of mucosal immunity at sites with capacity
   - Markers of sexual exposure

3. Adherence
   - Participant self-report of product use
   - Biomarkers of adherence to study product regimen
   - Returned VRs and pill bottles
   - Persistence with chosen product during the third product use period

4. Social Harms and Benefits
   - Participant self-report of social harms resulting from product use or study participation, including negative consequences of product use disclosure, stigma, gender-based violence, and relationship problems
   - Participant self-report of social benefits from product use or study participation, including increased confidence, intimacy, and/or self-esteem

4.3 Description of Study Population

Adolescent (16 to 17 years old) and young adult (18 to 21 years old) females who are healthy, HIV-uninfected, sexually active, not pregnant and meet eligibility criteria as described in Sections 5.2 and 5.3.

4.4 Time to Complete Accrual

Accrual will require approximately 12 months following site activation. See Section 10.5 for additional details.

4.5 Expected Duration of Participation

Participants will complete approximately 76 weeks of follow-up. See Section 10.5 for additional details.

4.6 Sites

Sites selected by the MTN Executive Committee.

5 STUDY POPULATION

5.1 Selection of the Study Population

Inclusion and Exclusion Criteria, Sections 5.2 and 5.3, respectively, are used to ensure the appropriate selection of study participants for MTN-034.

5.1.1 Recruitment

Participants will be recruited from a variety of sources across sites including, but not limited to, primary care health clinics, family planning clinics, HIV testing facilities, gynecology clinics, institutions of higher learning, community based youth centers, schools, and other community-based organizations. It is anticipated that all participating MTN-034 sites will have established relationships with adolescent-friendly clinics, group practices, hospitals, etc. Participants also will 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 per local requirements. 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

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

1) Age 16 through 21 years (inclusive) at Enrollment, verified per site standard operating procedures (SOPs).

2) Able and willing to provide informed consent, and if under the legal age of consent be able to provide informed assent and obtain parental or guardian permission/consent, to be screened for and to enroll in MTN-034 (as specified in site SOP).

3) Able and willing to provide adequate locator information, as defined in site SOPs.

4) Able and willing to comply with all study procedural requirements.

5) Per participant report at Screening, post-menarche.

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

7) Per participant report at Screening, history of at least one episode of sexual intercourse in participant's lifetime.

8) Negative pregnancy test at Screening and Enrollment.

9) Per participant report, use of an effective method of contraception for at least two months prior to Enrollment, and intending to continue use of an effective method for the duration of study participation; effective methods include:
   - hormonal methods (except contraceptive ring).
   - intrauterine device (IUD).

   Note: Participant must be on the same contraception method for at least the two months prior to Enrollment.

10) Per participant report at Screening, willing to abstain from inserting anything into the vagina for 72 hours prior to each study visit, including receptive intercourse.

    Note: In the event the VR has been expelled and requires reinsertion, repositioning the VR is permitted.

    Note: Participant use of tampons is permitted at any time during the study.

11) 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 Protocol Safety Review Team (PSRT).

5.3 Exclusion Criteria

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

1) Per participant report at Screening and Enrollment, intends to do any of the following during the study participation period:
   a) become pregnant.
   b) access and/or use oral PrEP outside the context of study participation.
   c) relocate away from the study site.
   d) travel away from the study site for a time period that would interfere with product resupply and study participation.

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

3) Diagnosed with UTI, PID, STI or reproductive tract infection (RTI) requiring treatment per WHO guidelines at Screening or Enrollment.

   Note: Otherwise eligible participants diagnosed during screening with a UTI, PID or STI/RTI requiring treatment per WHO guidelines — other than asymptomatic BV and asymptomatic candidiasis — are offered treatment consistent with WHO recommendations. If treatment is completed and symptoms have resolved within 70 days of obtaining informed assent/consent for screening, the participant may be enrolled. Genital warts requiring treatment also must be treated prior to enrollment. Genital warts requiring therapy are defined as those that cause undue burden or discomfort to the participant, including bulky size, unacceptable appearance, or physical discomfort.

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 non-menstrual 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 70 days of providing informed assent/consent for screening, the participant may be enrolled.

5) Participant report and/or clinical evidence of any of the following:
   a) Known adverse reaction to any of the study products (ever).
   b) Known adverse reaction to latex and polyurethane (ever).
   c) Symptoms suggestive of acute HIV infection at Screening or Enrollment.
   d) Non-therapeutic injection drug use in the 12 months prior to Enrollment.
   e) Use of HIV PEP and/or PrEP within the 3 months prior to Enrollment.
   f) Currently breastfeeding.
   g) Last pregnancy outcome within 8 weeks or less of Enrollment.
   h) Participation in any other research study involving drugs, medical devices, vaginal products or vaccines within 60 days of Enrollment.
   i) At Enrollment, as determined by the IoR/designee, has any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease.

6) Has any of the following laboratory abnormalities at Screening Visit:
   a) Positive for hepatitis B surface antigen (HBsAG).
   b) Hemoglobin Grade 2 or higher.*
   c) Calculated creatinine clearance less than 60 mL/min by the Schwartz Equation.

   Note: Otherwise eligible participants with an exclusionary test may be re-tested during the screening process; re-testing procedure details can be found in the MTN-034 Study Specific Procedures (SSP) Manual. If improvement to a non-exclusionary grade or resolution is documented within 70 days of providing informed assent/consent for screening, the participant may be enrolled.

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

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

5.4 Co-enrollment Guidelines

As indicated in Section 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-034 Protocol Chair.
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons.
- Participants who become pregnant may take part in observational studies, including pregnancy registries.

Should any participant report or should study staff discover concurrent participation in any other study after enrolling in MTN-034, 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 to one of two sequences of one VR containing 25 mg of dapivirine to be inserted monthly for 24 weeks and one 200 mg FTC/300 mg TDF oral tablet taken daily for 24 weeks. After completing the randomized sequence of two study product use periods, participants will then select between the two study products to use in the final 24 weeks of the trial. Participants will be able to choose either or neither study product during the third product use period.

Table 5: Study Product Regimen

	N	Study Product Use Period 1: 24 Weeks	Study Product Use Period 2: 24 Weeks	Study Product Use Period 3: 24 Weeks	Dose, Route and Frequency
Sequence A	150	25 mg dapivirine VR	FTC/TDF oral tablets	Choice of 25 mg dapivirine VR or FTC/TDF oral tablets or neither	One 25 mg dapivirine VR inserted vaginally each month for 24 Weeks, followed by one FTC/TDF oral tablet taken by mouth daily for 24 Weeks, followed by participant's choice of either or neither study product for 24 Weeks
Sequence B	150	FTC/TDF oral tablets	25mg dapivirine VR	Choice of 25 mg dapivirine VR or FTC/TDF oral tablets or neither	One FTC/TDF oral tablet taken by mouth daily for 24 Weeks, followed by one 25 mg dapivirine VR inserted vaginally each month for 24 Weeks, followed by participant's choice of either or neither study product for 24 Weeks

6.2 Administration

6.2.1 Dapivirine Vaginal Ring (25 mg)

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 the 24-week study period. 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-034 Pharmacist 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, except at Visit 23: Week 72 (Period 3: Study Product Use End). 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 period 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-034 PSRT must be notified.

Table 6: Retrieval of Study Product

Condition	Timeframe for Retrieval
Permanent discontinuation due to pregnancy, 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 the next product use period. Specifically, for each participant, all VRs and/or oral tablets remaining in the participant's possession should be retrieved at Visit 9: Week 24 (Period 1: Study Product Use End), Visit 16: Week 48 (Period 2: Study Product Use End), and Visit 23: Week 72 (Period 3: Study Product Use End). 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-034 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, vitamins and nutritional supplements, and herbal preparations will be recorded as concomitant medications on a case report form (CRF) designated for that purpose.

Following the Screening Visit, concomitant use of any non-study vaginal products and/or practices will be prohibited 3 days prior to each study follow-up visit. These include but are not limited to spermicides, diaphragms, vaginally applied medication, menstrual cups, cervical caps, douches, lubricants, sex toys, etc. Further, participants are expected to be sexually abstinent 3 days prior to each follow-up visit, i.e., no receptive intercourse (vaginal, anal, oral and finger stimulation).

Note: Participant use of tampons is permitted at any time during the study.

6.7 Prohibited Medications

Concomitant use of medications for PEP and PrEP is prohibited.

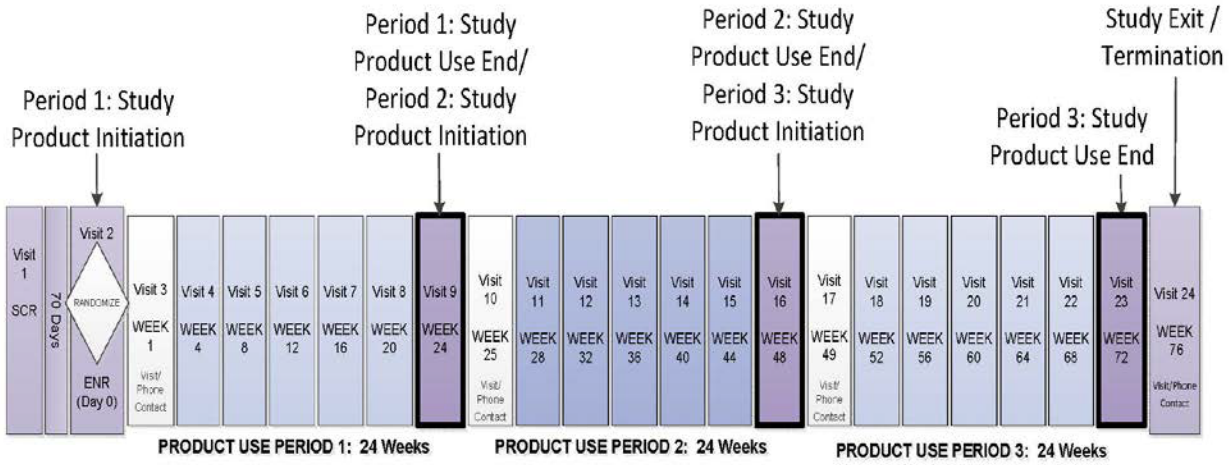
6.8 Condoms

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-034 SSP Manual available at http://www.mtnstopshiv.org/studies.

Figure 2: MTN-034 Study Visit Schedule



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 adolescent and young adult female 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 assent/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. 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 70 days prior to the Enrollment Visit. Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed assent and parental/guardian permission/consent will be obtained for all participants under the legal age of consent at the Screening Visit before any screening procedures are initiated; written informed consent will be obtained for all participants legally able to provide consent. 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 7: Visit 1 - Screening Visit

Visit 1 – Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain informed assent/consent and, as needed, parental or guardian consent/permission for screening and enrollment • Assign a unique Participant Identification (PTID) Number • Assess eligibility • Demographic information • Collect locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling		• Targeted baseline behavioral assessment • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Contraceptive counseling
Clinical		• Medical/menstrual history • Concomitant medications • Physical exam • Pelvic exam • Treatment for RTI/UTI/STIs* • Disclosure of available test results
Laboratory	**Urine**	• Human chorionic gonadotropin (hCG) • Dipstick urinalysis (UA) and/or urine culture*
	Blood	• HIV-1 testing • Hepatitis B surface antigen (HBsAG) • Blood creatinine and creatinine clearance • Complete blood count (CBC) with platelets • Syphilis serology
	Pelvic	• Rapid test for Trichomonas • Nucleic acid amplification test (NAAT) for *Neisseria gonorrhoeae* (GC)/ Chlamydia trachomatis (CT) • 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 70 days of the Screening Visit.

NOTE: Participants will be offered the HBV vaccine series as well as the human papillomavirus (HPV) vaccine series (if approved locally) starting at their enrollment visit. For enrolled participants who decline vaccination at enrollment, the vaccine series may be initiated at any time during follow-up. The HBV and HPV vaccines are not considered study products.

Table 8: 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 study visit/contact*
Behavioral/Counseling		• Baseline behavioral assessment • Baseline product preference/acceptability assessment • HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Contraceptive counseling • Protocol adherence counseling
Clinical		• Review/update medical/menstrual history • Review/update concomitant medications • Physical exam* • Pelvic exam • Treatment for RTI/UTI/STIs* • Offer and, if accepted, provide HBV and HPV vaccine series* • Disclosure of available test results
Laboratory	**Urine**	• hCG • Dipstick UA and/or urine culture*
	Blood	• HIV-1 testing • HSV-2 antibody • Blood creatinine for creatinine clearance* • CBC with platelets* • Syphilis serology* • Plasma archive
	Pelvic	• Rapid test for Trichomonas* • NAAT for GC/CT* • Wet prep/KOH wet mount for candidiasis and/or BV* • Vaginal pH • Vaginal swabs for microbiota • Vaginal Gram stain • Vaginal swab for biomarkers • Cervicovaginal lavage (CVL) for biomarkers • Cervical swab for biomarkers • Cervical cytobrush for flow cytometry (designated site(s) only)

Visit 2 – Enrollment Visit	
Component	**Procedures**
Study Product/Supplies	• Provision of study VR(s) or study tablets • Insertion of one study VR (clinician to check VR placement if problem with insertion) or directly observed dosing (DOD) of first study tablet • Provision of product use instructions • Offer male condoms

* if indicated and/or per local standard of care

7.4 Follow-up Visits

7.4.1 Visit 3, Visit 10, Visit 17: Weeks 1, 25, and 49 – Visits/Phone Contacts

The Visits/Phone Contacts are to be scheduled approximately one week after study product initiation for all product use periods. These visits may take place in-person or be conducted over the phone.

Table 9: Visit 3, Visit 10, Visit 17: Weeks 1, 25, and 49 – Visits/Phone Contacts

Visit 3, Visit 10, Visit 17: Weeks 1, 25, and 49 – Visits/Phone Contacts	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement (sites to reference SOPs) • Schedule next study visit/contact
Behavioral	• Protocol adherence counseling • Contraceptive counseling* • HIV/STI risk reduction counseling*
Clinical	• Review/update medical/menstrual history • Disclosure of available test results • Collect AEs • Treatment for RTI/UTI/STIs* • Offer and, if accepted, provide HBV and HPV vaccine series*

* if indicated and/or per local standard of care

7.4.2 Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68

Procedures listed below will occur every four weeks starting at Visit 4 (Week 4) until Visit 22 (Week 68). Prior to the initiation of the second and third product use periods, and prior to switching between study products during the third product use period, all AEs that would result in study product holds need to be managed per Sections 9.4 and 9.5. If requirements are not met for product use resumption, the PSRT should be consulted regarding progression into the next dosing period.

Further, if a participant is scheduled to initiate DPV VR use during her menses, she may choose to delay study product initiation until the completion of menses.

Lastly, participants will be presented with their previous months' product use laboratory results as part of the product adherence counseling at selected follow-up

visits. These product use disclosure counseling sessions are planned to occur on the second and fifth follow-up study visits of each study product use period; however, they may be re-scheduled for a later date if product use laboratory results are delayed for any reason.

Table 10: Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68

Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next study visit/contact
Behavioral/Counseling		• Behavioral assessment∞ • Adherence assessment∞ • Product preference/acceptability assessment∞ • Social harms/benefits assessment∞* • Qualitative activities (In-depth interviews [IDI] or focus group discussions [FGD]) (subset of participants only)♦ • Contraceptive counseling* • Protocol adherence counseling▲ • Product adherence disclosure counseling□ • HIV/STI risk reduction counseling▲ • HIV pre- and post-test counseling
Clinical		• Review/update medical/menstrual history • Review/update concomitant medications • Disclosure of available test results • Collect AEs • Targeted physical exam • Pelvic exam∞* • Treatment for RTI/UTI/STIs* • Offer and, if accepted, provide HBV and HPV vaccine series*
Laboratory	**Urine**	• hCG • Dipstick UA and/or urine culture*
	Blood	• HIV-1 testing • Blood creatinine and creatinine clearanceϕ* • HSV-2 antibody∞* • CBC with plateletsϕ* • Syphilis serology∞* • Dried blood spot (DBS) for PK • Plasma storage∞
	Pelvic	• Cervical swab for biomarkers∞ • Vaginal Gram stain∞ • Vaginal swab for biomarkers (self-collected at visits when no pelvic exam is performed) • CVL for biomarkers∞ • Cervical cytobrush for flow cytometry (designated site(s) only)∞

Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68		
Component		**Procedures**
		• Vaginal swabs for microbiota∞ (except on Visit 20) • Vaginal pH∞* • Wet prep/KOH wet mount for candidiasis and/or BV* • NAAT for GC/CT∞* • Rapid test for Trichomonas∞*
	Study Product	• Adherence assessment(s): Returned study VR(s)
Study Product/Supplies		• Retrieval of study VR(s) or study tablets • Provision of study VR(s) or study tablets • Provision of product use instructions • Insertion of one study VR (clinician to check VR placement if problem with insertion) or DOD of first study tablet • Offer male condoms

* if indicated and/or per local standard of care, ♦ = Conducted once per product use period, and may be scheduled any time between the second and last monthly clinic visit of each period, ▲ = modified if necessary, ∞ = Required at Visits 6, 9, 13, 16, and 20, ϕ = Required at Visits 9 and 16, □ = Required at Visits 5, 8, 12, 15, 19, and 22, pending lab results availability

7.4.3 Visit 23 - Week 72: Period 3 Product Use End/Early Termination Visit

Participants will undergo the following procedures at the Period 3 Product Use End/Early Termination Visit (PUEV).

Table 11: Visit 23 - Week 72: Period 3 PUEV

Visit 23 – Week 72: Period 3 PUEV		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next study visit/contact*
Behavioral		• Behavioral assessment • Adherence assessment • Product preference/acceptability assessment • Social harms/benefits assessment • FGD (subset of participants only)∇ • HIV pre- and post-test counseling • Contraceptive counseling* • HIV/STI risk reduction counseling▲
Clinical		• Review/update medical/menstrual history • Review/update concomitant medications • Physical exam • Pelvic exam • Disclosure of available test results • Collect AEs • Treatment for RTI/UTI/STIs*
Laboratory	**Urine**	• hCG • Dipstick UA and/or urine culture*

Visit 23 – Week 72: Period 3 PUEV		
Component		**Procedures**
	Blood	• DBS for PK • Blood creatinine and creatinine clearance • HIV-1 testing • HSV-2 antibody • CBC with platelets • Syphilis serology • Plasma storage
	Pelvic	• Cervical swab for biomarkers • CVL for biomarkers • Cervical cytobrush for flow cytometry (designated site(s) only) • Vaginal swab for biomarkers • Vaginal Gram stain • Vaginal pH* • Wet prep/KOH wet mount for candidiasis and/or BV* • NAAT for GC/CT • Rapid test for Trichomonas
	Study Product	• Adherence assessment(s): Returned study VR(s)
Study Product/Supplies		• Offer male condoms • Removal and collection of study VR(s) or study tablets

* if indicated and/or per local standard of care, ∇ = May be scheduled any time between Visit 20 and study exit to accommodate participant availability, ▲=modified if necessary

7.4.4 Visit 24 - Week 76: Study End Visit/Phone Contact

Participants will undergo the following procedures at the Study End Visit (SEV)/Phone Contact, which will take place approximately one month (4 weeks) after the PUEV. This visit may take place in-person or be conducted over the phone.

Table 12: Visit 24: Week 76 – Study End Visit/Phone Contact

Visit 24: Week 76 – Study End Visit/Phone Contact	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement (sites to reference SOPs) • Schedule next study visit/contact*
Behavioral	• Contraceptive counseling* • HIV/STI risk reduction counseling*
Clinical	• Review/update medical/menstrual history • Disclosure of available test results • Collect AEs • Treatment for RTI/UTI/STIs* • Offer male condoms*

* if indicated and/or per local standard of care

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

7.5.1 Participants Who Become Infected with HIV

If a participant becomes infected with HIV-1 after the Enrollment Visit, she will be referred to local care and treatment 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
- Blood creatinine for creatinine clearance
- Collection of PK and biomarker specimens

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 preference/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-034 follow-up, protocol-specified procedures for MTN-034 will continue except the following:

- HIV-1 testing
- Provision of study VR(s) or study tablets, provision of product use instructions, and retrieval and collection of study VR(s) or study tablets
- Collection of PK and biomarker specimens
- Adherence and product preference/acceptability assessments
- Provision of HIV pre- and post-test, protocol adherence, and product adherence disclosure counseling

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

7.5.2 Participants Who Become Pregnant

MTN-034 participants who become pregnant will be offered the option to continue follow-up visits with a modified study visit/procedure schedule until their originally scheduled study exit date. Participants will be referred to local health care services, as needed. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcomes are ascertained (see Section 9.7 for additional details).

The study site will make every reasonable effort to contact participants and collect infant outcomes at approximately one year after delivery for those pregnancies that result in live birth. For additional details regarding obtaining pregnancy and infant outcomes, please reference the MTN-034 SSP Manual (www.mtnstopshiv.org).

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

- HIV -1 testing, HIV pre- and post-test counseling
- CBC with platelets
- Blood creatinine for creatinine clearance
- Collection of PK and biomarker specimens
- Behavioral, adherence, and product preference/acceptability assessments

For those participants who choose to remain in MTN-034 follow-up, protocol-specified procedures will continue except the following:

- hCG urine test
- Provision of study VR(s) or study tablets, provision of product use instructions, and retrieval and collection of study VR(s) or study tablets
- Pelvic examination as well as associated procedures after 24 weeks of pregnancy, unless the participant indicates comfort with continuing vaginal procedures post 24 weeks
- Collection of PK and biomarker specimens
- Adherence and product preference/acceptability assessments
- Provision of protocol adherence and product adherence disclosure counseling

Product use may be resumed ≥8 weeks after birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff, provided the participant is not breastfeeding and after consultation with the PSRT. The aforementioned protocol procedures are to be resumed at follow-up visits once study product use has been resumed.

7.5.3 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.

Product adherence disclosure counseling will be conducted as scheduled, e.g., second and fifth follow-up visit for a given study product use period, provided the participant's data is available; otherwise, these counseling sessions are to be discontinued.

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 or Pregnancy

Participants who permanently discontinue study product use for one of the two study products for any reason (clinician-initiated or self-initiated) during the first or second study product use period may continue study participation by initiating the next (i.e., second or third) study product use period after consultation with the PSRT. Participants who permanently discontinue study product use for one of the two study products during the third product use period may continue study participation after consultation with the PSRT.

Participants who permanently discontinue study product use for any reason (clinician-initiated or self-initiated) during both the first and second product use periods will be considered terminated from the study as continued study participation would be of no added benefit. Similarly, participants who permanently discontinue use of both study products for any clinician-initiated reason during the third product use period, or at any time during the study, will be considered terminated from the study as continued participation would be of no added benefit. Participants will, however, be asked to complete the procedures outlined in the PUEV, 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.

7.5.4 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 tablet(s).
- 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., social harm.

All interim contacts and visits will be documented in participants' study records and on CRFs, if applicable.

7.6 Final Contact

Since participants' PUEV include laboratory testing for HIV, additional contacts after the Visit 24 SEV may be required to provide her additional study test results, and post-test counseling, if needed. In addition, for participants who become pregnant during study participation, additional contacts may be required to ascertain the participant's pregnancy and infant outcome (see Section 7.5.2 for details). 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.

7.7 Behavioral Evaluations

Behavioral endpoints will be assessed via CASI/ACASI and/or CRFs with all participants. IDIs and/or focus group discussions (FGDs) will also be conducted with a subset of participants at predetermined time points (see Sections 7.4.2 and 7.4.3 for schedule of predetermined IDIs and FGDs). Additional IDIs or FGDs 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.

All IDIs and FGDs will be conducted by trained and experienced facilitators to gain further insight on the following behavioral issues:

- Acceptability and attitudes towards the DPV VR and oral TDF/FTC, including preferences for DPV VR versus oral TDF/FTC
- Insights into product use, e.g., patterns of use, motivators and barriers
- Reports of product storage
- Sexual activity including condom use before and during DPV VR and oral TDF/FTC use
- Vaginal and sexual practices including evaluation of whether these change during the periods of VR use
- Understanding of partial efficacy for both DPV VR and oral TDF/FTC
- Motivations for joining the study
- Social harms and benefits stemming from DPV VR and oral TDF/FTC use

Interviews and group discussions will be audio-recorded. Depending on participant availability and visit length, it may be necessary to conduct these assessments as a separate visit. Participants scheduled for qualitative activities may have their Period 1 qualitative activity (IDI or FGD) between their Month 2 and Month 6 visit, their Period 2 qualitative activity between their Month 8 and Month 12 visit, and their Period 3 qualitative activity between their Month 14 and Month 18 visit. Participants selected for a PUEV FGD may have their FGD scheduled up to three months before or four weeks after their Month 18 visit to accommodate availability for both the site and for other study participants.

7.8 Protocol and Product Adherence Counseling

Study product adherence counseling will be provided as a component of the protocol adherence counseling to all study participants by site staff. 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 strategies will be incorporated into the counseling sessions as desired by participants to address adherence barriers. Participants will also be presented with their previous months' product use results to tailor the product adherence counseling messages. These product use disclosure counseling sessions are planned to occur on the second and fifth follow-up study visits of each study product use period; however, they may be re-scheduled for a later date if product use laboratory results are delayed for any reason. Lastly, participants will be able to choose from a menu of additional adherence support strategies (e.g., text messages, phone calls, peer support groups) that, coupled with the counseling described, will form their individualized adherence support plan.

7.9 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*
- Breasts (only applicable to 16-17 year olds)*

**may be omitted during targeted physical examinations*

Pelvic examination

- Visual inspection per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004

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.

7.10 Laboratory Evaluations

Local Laboratory

- Urine
  - hCG
  - Dipstick UA and/or urine culture
- Blood
  - Plasma archive/storage (stored at site until notified by MTN LC)
  - Syphilis serology
  - HIV-1 testing
  - CBC with platelets
  - Creatinine for calculation of creatinine clearance
  - HBsAG
  - Cytobrush for flow cytometry (at designated site(s) with capacity)
- Pelvic
  - NAAT for GC/CT
  - Vaginal pH
  - Rapid test for Trichomonas

- Wet prep/KOH wet mount for candidiasis and/or BV

Laboratory Center

- Blood
  - Drug concentration in blood
  - HIV-1 confirmatory testing as needed (see Appendix III)
  - HIV-1 drug resistance
  - HSV-2
- Pelvic
  - Cervicovaginal swabs for possible PK assessments
  - Vaginal Gram stain
  - Vaginal swabs for microbiota
  - Vaginal swabs for biomarkers
  - CVL for biomarkers

Designated Laboratory:

- VR for residual dapivirine levels
- Blood
  - Drug concentration in blood

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.

7.11 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-034 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.

7.12 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).

7.13 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. 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 Co-Chairs, DAIDS Medical Officer (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.

After the product use and the final safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the MTN-034 PSRT.

A Study Monitoring Committee (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 VR and oral tablet.

Study participants will be provided instructions for contacting the study site to report any untoward medical occurrences they may experience. In cases of potentially life-threatening events, participants will be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where a study clinician is based, and to request that the clinician be

contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to untoward medical occurrences will be obtained and required data elements will be recorded on study CRFs. All participants reporting an untoward medical occurrence will be followed clinically until the occurrence resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents and in the study database all AEs reported by or observed in enrolled study participants, regardless of severity and presumed relationship to study product.

AE severity and laboratory tests will be graded per the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and Addendum 1, (Female Genital Grading Table for Use in Microbicide Studies; dated November 2007), except that asymptomatic BV and asymptomatic candidiasis 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. In addition, changes in genital bleeding judged to be related to a woman's contraceptive use or irregular bleeding judged to be related to the adolescent menstrual cycle will not be considered an AE, nor will a pelvic exam be required for follow-up. Bleeding at the time of speculum insertion/removal or cervicovaginal specimen collection that is judged by the clinician to be within the range of 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.

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. 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 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 most current 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 (Visit 23: Week 72). 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 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. 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. 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 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/ECs 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.

Note: Given the trial design, continued study participation on to the second or third period of study product use after a permanent study product discontinuation of either the VR or the tablet during the first or second period of study product use is permitted after consultation with the PSRT, unless other temporary product hold/permanent discontinuation guidelines apply.

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 both study products (25 mg dapivirine VR and FTC/TDF oral tablet) by the IoR/designee for any of the following reasons:

- Acquisition of HIV-1 infection. 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.

- Allergic reaction to the study product.*
- Reported use of PrEP for HIV prevention.
- Non-therapeutic injection drug use.

**In the event of an allergic reaction, participants will be permanently discontinued from study product use during the first or second study product use period, but may continue study participation by initiating the second or third study product use period after consultation with the PSRT.*

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

- A reactive rapid HIV test.
- Reported use of PEP for potential HIV exposure.
- Pregnancy. A participant who has a positive pregnancy test may resume study product use after birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff, provided the participant is not breastfeeding, pending consultation with the PSRT. A pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption, in the opinion of the IoR/designee.
- Breastfeeding. Product use may resume when the participant reports complete cessation of breastfeeding.
- 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 (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.

- If the creatinine clearance is <60mL/min, oral study product should be held, the PSRT notified, and the test repeated within one week. If a level of <60mL/min is confirmed, study product will be permanently discontinued. If either retesting cannot occur within one week or if retesting yields a result of ≥60 mL/min, the IoR/designee must consult the PSRT for further guidance on resuming product use.

- Study VR or tablet need not be held in the event of an STI/RTI requiring treatment, 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.

** 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 currently using the VR will be in accordance with the following:

  Superficial epithelial disruption (abrasion/peeling)
  - Continue study VR use.
  - Perform naked eye evaluation.
  - Re-evaluate by speculum examination in 3-5 days.
  - If condition worsens, temporarily hold study VR use and consult the PSRT; otherwise continue study VR use.

  Deep epithelial disruption (ulceration)
  - Temporarily hold study VR for deep epithelial disruption confirmed by site investigator.
  - Re-evaluate in 3-5 days and resume study VR use if resolved.
  - If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time, may resume study VR 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 VR 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 VR use and consult the PSRT; otherwise continue study VR 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 VR.
  - Perform naked eye evaluation.
  - Re-evaluate in 3-5 days and resume study VR use if resolved.
  - If unresolved at 3-5 days, re-evaluate within 2-3 days. If resolved at that time may resume 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 VR 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 VR use.

Cervicitis (including findings on exam such as inflammation and/or friability)
- Temporarily hold study VR.
- 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 VR use.

Genital petechia(e)
- Continue study VR use .
- Perform naked eye evaluation.
- Further evaluation or treatment per clinician discretion.

Genital ecchymosis
- Continue study VR use.
- Perform naked eye evaluation.
- Further evaluation or treatment per clinician discretion.

9.6 HIV Infection

A participant who has a positive test for HIV must have study product held, but will not be withdrawn from the study. If the participant is subsequently determined to be HIV-uninfected according to the algorithm in Appendix 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.

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 adolescent females 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 Pregnancy

Pregnancy testing will be performed at designated study visits and participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who tests positive for pregnancy regarding possible risks to the fetus according to site SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

A participant who tests positive for pregnancy during the course of the study will have study product discontinued and will be offered the option to continue follow-up visits with a modified study visit/procedure schedule, as per Section 7.5.2. A participant who is pregnant at study termination will continue to be followed until the pregnancy outcome is ascertained (or if in consultation with the PSRT it is determined that the pregnancy outcome cannot be ascertained). Pregnancy and infant outcomes will be reported on relevant CRFs, and outcomes meeting criteria for EAE reporting also will be reported on EAE forms.

The study site will make every reasonable effort to contact participants and collect infant outcomes up to one year after delivery for those pregnancies that result in live birth to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy.

Participants who become both pregnant and HIV-infected will have expedited HIV-1 resistance testing performed at the MTN LC to provide information about possible resistance that might impact the efficacy of ART regimens to reduce mother-to-child HIV-1 transmission. The participant will be referred to local providers for antenatal care, and prevention of mother-to-child transmission services. HIV testing for infants is provided by the study if not otherwise accessible by the participant.

FTC/TDF is classified as an FDA pregnancy Category B drug. Additional general information about FTC/TDF can be found in the most recent Truvada® package

insert.[23] In the Partners PrEP study, in which women discontinued oral PrEP upon confirmation of pregnancy, their babies did not appear to display negative health outcomes.[42] Data from PrEP trials has demonstrated that periconception use is safe in terms of pregnancy incidence, pregnancy outcomes, and infant outcomes.[47]

9.8 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 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 STATISTICAL CONSIDERATIONS

10.1 Overview and Summary of Design

The MTN-034 trial is a multi-site, randomized, two-sequence, three-period, open-label, crossover Phase 2a trial. Young adult (18-21 years old) and adolescent (16-17 years old) female participants are expected to be enrolled in a 2:1 ratio. All the enrolled participants will use both treatment regimens in sequence. All participants will be randomly assigned to one of two treatment regimen sequences to use for the first two study product use periods, and will be able to choose between treatment regimens during the third study product use period. The total length of follow-up is approximately one and a half years which includes up to 72 weeks of product use (two 24-week periods on randomized treatment regimen and one 24-week period on freely chosen treatment regimen) plus an additional four weeks beyond the Period 3 end visit to collect data on any new or worsening AEs. Due to ethical reasons delineated in Section 2.10 of the protocol, there is no washout period between the three study product use periods.

10.2 Study Endpoints

10.2.1 Primary Endpoints

- **Safety**
  - Grade 2 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])

- **Adherence**
  - Detectable drug levels in blood
  - Residual drug levels in returned VRs

10.2.2 Secondary Endpoints

- **Acceptability**
  - Participant report of acceptability

- **Adherence**
  - Detectable drug levels in blood
  - Residual drug levels in returned VRs

- **Study product preference**
  - Participant product selection during third product use period
  - Participant report of product preference

10.3 Primary Study Hypotheses

The study hypotheses for the primary objectives are:

- **Safety:** Daily FTC/TDF tablet (oral) and dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks will be generally safe and well-tolerated.

- **Adherence:** Adherence to daily FTC/TDF tablet (oral) and to the dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks will be high in this adolescent and young adult female population.

10.4 Sample Size and Power Calculations

Sample size/power formulas for a parallel design (i.e., independent groups of participants on each treatment regimen) can be used to compute sample size/power. Sample size/power calculations assume the primary comparisons will be between the first and second periods of the study (randomized periods). The sample size resulting from the assumption of independent groups can then be adjusted to reflect

that there will be intra-participant correlation in the crossover study design. This sample size adjustment is obtained using the formula:

$N' = N(1-\rho)/2$

where N' is the sample size for the crossover study, N is the total number of participants necessary for a parallel design with two arms (N/2 in each arm) and ρ is the correlation between responses within a single participant during different study product use periods (intra-participant correlation).

To our knowledge, there are no data available to estimate the intra-participant correlation in this population of participants for any of the outcomes. However, for all outcomes it is highly likely that this correlation will be positive and large.

10.4.1 Primary Endpoints

Safety

Based on previous studies we expect to observe rates of the primary safety endpoints between 2% to 10%. Table 13 shows the minimum detectable difference in rates of safety events assuming 80% power, α=0.05, a two-sided test based on Fisher's Exact Test, varying rates of safety events in the treatment regimen with the lower rate, varying values of ρ (the intra-participant correlation), a sample size of 300 participants and 10% loss to follow-up (a working sample size of 270). The 10% loss to follow-up is based on previously completed studies.

Table 13: Minimum Detectable Difference in Rates of Safety Outcomes Assuming 80% Power

	ρ			
	0.0	0.3	0.5	0.7
Rate of Safety Event in Treatment Regimen with Lower Rate	Minimum Detectable Difference Between Treatment Regimens			
2%	9.1%	7.6%	6.4%	5.0%
5%	11.2%	9.4%	7.9%	6.1%
10%	13.4%	11.2%	9.5%	7.3%

If there is no intra-participant correlation for safety outcomes, the study will have 80% power to detect a minimum difference of 9.1% to 13.4% depending on the rate of the safety event in the treatment regimen with the lower rate. If the intra-participant correlation is moderately high (0.5), this minimum detectable difference ranges from 6.4% to 9.5%.

Adherence

Based on previous studies we expect to observe a high rate of participants with at least 80% of their visits with detectable drug levels in plasma (for the oral regimen) and detectable drug levels in plasma and residual ring drug levels consistent with

high adherence (for the DPV ring regimen). Table 14 shows the minimum detectable difference in rates of ≥80% adherence assuming 80% power, α=0.05, a two-sided test based on the Normal approximation of the Binomial distribution, varying rates of ≥80% adherence in the treatment regimen with the lower rate, varying values of ρ (the intra-participant correlation), a sample size of 300, and 10% loss to follow-up (a working sample size of 270).

Table 14: Minimum Detectable Difference in Rates of ≥80% Adherence Assuming 80% Power

	ρ			
	0.0	0.3	0.5	0.7
≥80% Adherence Rate in Treatment Regimen with Lower Rate	Minimum Detectable Difference Between Treatment Regimens			
60%	16.5%	13.8%	11.7%	9.0%
70%	14.9%	11.5%	9.8%	7.5%
80%	12.4%	9.8%	8.3%	6.4%
90%	8.6%	7.6%	6.4%	4.9%

10.4.2 Secondary Endpoints

Acceptability

Based on previous studies we expect to observe a high rate of acceptability. Table 15 below shows the minimum detectable difference in rates of acceptability of the two regimens assuming 80% power, α=0.05, a two-sided test based on the Normal approximation of the Binomial distribution, varying rates of ρ (intra-participant correlation), a sample size of 300, and 10% loss to follow-up (a working sample size of 270).

Table 15: Minimum Detectable Difference in Rates of Acceptability Assuming 80% Power

	ρ			
	0.0	0.3	0.5	0.7
Acceptability Rate in Treatment Regimen with Lower Rate	Minimum Detectable Difference Between Treatment Regimens			
60%	16.5%	13.8%	11.7%	9.0%
70%	14.9%	11.5%	9.8%	7.5%
80%	12.4%	9.8%	8.3%	6.4%
90%	8.6%	7.6%	6.4%	4.9%

Adherence

Adherence to product will be measured by detectable drug levels in blood (for both FTC/TDF oral tablets and dapivirine ring), and residual dapivirine levels in returned VRs. These adherence measures will be compared between the third product use period (when the product is chosen) and the prior period when the same product was randomly assigned. Table 16 shows the minimum detectable difference in rates of ≥80% adherence assuming 80% power, α=0.05, a two-sided test based on the Normal approximation of the Binomial distribution, varying rates of ≥80% adherence

in the treatment period with the lower rate, varying sample sizes (depending on the rate at which a product is chosen in the third period) and ρ (the intra-participant correlation) of 0 (conservative).

Table 16: Minimum Detectable Difference in Rates of ≥80% Adherence Assuming 80% Power and ρ =0

	Sample size			
	30	90	150	225
≥80% Adherence Rate in Treatment Period with Lower Rate	Minimum Detectable Difference Between Treatment Periods			
60%	30.6%	19.1%	15.1%	12.5%
70%	26.5%	17.0%	13.6%	11.3%
80%	20.0%	14.0%	11.3%	9.5%
90%	8.6%	7.6%	6.4%	4.9%

Study product preference

Study product preference will be assessed by the rate at which each product is first chosen for the third period of the study and by reported product preference at the PUEV. Table 17 shows the precision around an estimate of preference (exact 95% CI) for varying preference rates and varying sample sizes (varying numbers of participants choosing any product in the third period). The final column of Table 17 (n=270) shows the precision around an estimate of reported product preference at PUEV for varying rates.

Table 17: Precision of Estimate of Preference Rate

	Sample Size			
	150	200	250	270
Preference rate	95% CI of preference rate			
20%	(13.9%, 27.3%)	(14.7%, 26.2%)	(15.2%, 25.5%)	(15.4%, 25.3%)
50%	(41.7%, 58.3%)	(42.9%, 57.1%)	(43.6%, 56.4%)	(43.9%, 56.1%)
70%	(62.0%, 77.2%)	(63.1%, 76.3%)	(63.9%, 75.6%)	(64.2%, 75.4%)

10.5 Participant Accrual, Follow-up and Retention

The accrual period will be approximately 12 months at each site. Approximately 300 participants will be enrolled.

Each participant will be followed for approximately 76 weeks (two periods of 24 weeks on randomized treatment regimen and one period of 24 weeks on freely chosen treatment regimen plus an additional four weeks beyond the Period 3 end visit to collect any new or worsening AEs). Study termination is defined as the 28th day after the Period 3 Final Clinic Visit date. For participants who terminate early from the study, their termination date is considered the date the Early Termination Visit is completed, or the date the participant is considered no longer in the study. In a crossover study, it is important to have completeness of the data such that the target retention should be set at 100%. Therefore, once a participant has enrolled in the study, the study site will make every reasonable effort to retain the participant for

the entire study. While an average retention rate of 95% is targeted across sites, all sample size and power calculations assume a "worst-case scenario" (i.e., conservative estimates) of 10% loss to follow-up.

Note: Replacement participants will be considered in consultation with the SMC if loss to follow-up is higher than expected.

10.6 Randomization

Randomization to product sequence will be stratified by site. Within each site, participants will be randomly assigned to one of the two study sequences outlined in Table 18 below. In an unblinded trial, special care needs to be taken to ensure that the study staff cannot control or guess assignment. The MTN SDMC will coordinate the randomization procedures.

Table 18: Study Regimen

Sequence	**Period 1** (24 weeks)	**Period 2** (24 weeks)	**Period 3** (24 weeks)
1	Oral (Daily FTC/TDF)	Vaginal (dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks)	Free choice: Vaginal (dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks) **OR** Oral (Daily FTC/TDF) **OR** neither
2	Vaginal (dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks)	Oral (Daily FTC/TDF)	Free choice: Vaginal (dapivirine vaginal matrix ring (25 mg) inserted once every 4 weeks) **OR** Oral (Daily FTC/TDF) **OR** neither

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.

10.8 Analyses

Baseline data will be reported by sequence to assess the balance achieved through randomization. Baseline values between participants lost to follow-up and those not lost to follow-up will be described and used to interpret the generalizability of the results. Additional sensitivity analyses will analyze endpoints among all participants in only the first period of follow-up to describe the sensitivity of the results to loss to follow-up of participants.

10.8.1 Primary Safety Analysis

Generalized estimating equation models with a Poisson (log) link, an offset of the number of visits per study product use period, an exchangeable correlation structure and robust errors (controlling for study product use period) will be used to compare the two treatment regimens for the safety endpoints during the first two study product use periods (randomized periods). Due to there being no washout period between the two study product use periods it will be difficult to assign AEs that occur or worsen during the first week of the second period to one treatment regimen or the other. The study team will assess each of these AEs individually to determine whether each one is attributable to one of the treatment regimens or potentially both.

10.8.2 Primary Adherence Analysis

A Generalized Estimating Equation model with a Poisson (log) link, an offset of the number of visits with drug levels measured per study product use period, an exchangeable correlation structure and robust errors will be used to compare adherence to the two regimens (controlling for study product use period) during the first two study product use periods. These comparisons will be done using: 1) plasma data for participants during the oral regimen, and 2) both plasma and residual ring data for participants during the VR regimen.

10.8.3 Analysis of Secondary Endpoints

A Generalized Estimating Equation model with a logit link, exchangeable correlation structure and robust errors controlling for period will be used to compare the two treatment regimens for the acceptability endpoint during the first two study product use periods. Generalized Estimating Equation models with a Poisson (log) link, an offset of the number of visits with drug levels measured per study product use period, and exchangeable correlation structure and robust errors will be used to compare adherence to the study products during the third period (choice period) and the previous period when the same product was randomized. These comparisons will be done using: 1) plasma data for participants choosing the oral regimen, and 2) both plasma and residual ring data for participants choosing the VR regimen. Rates and 95% CIs for measures of study product preference will be computed.

10.8.4 Missing Data

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

univariate binary and quantitative outcome, respectively, a generalized linear model with a binomial or Normal error distribution will be used for estimation and testing. Sensitivity analyses will be conducted comparing the regimens using only the first study product use period data for all of the outcomes.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents. Study data is entered into the electronic CRFs in the MTN-034 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 assent/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

Site investigators will make every effort to minimize risks to participants. Participants and study staff members will take part in a thorough informed assent/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-034 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. Parents/guardians will be required to come to the clinic for signing of the consent only. 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

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-034 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 adolescent and young adult women. Participants may also appreciate the opportunity to contribute to the field of HIV prevention research.

Participants will be offered the HBV and HPV vaccine series which can help prevent Hepatitis B and infection by specific types of HPV as well as prevent cervical cancer, respectively. Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, pelvic examination, and routine laboratory testing. 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.

13.5 Informed Consent/Assent Process

Written informed consent will be obtained from adults and from minors who are legally able to consent as per US regulations and local authorities. Written informed assent and parental permission will be obtained from all other minors. Informed consent for adults and parental permission from a parent and/or legal guardian for minors is required prior to initiation of MTN-034 procedures as per US regulations, except in situations meeting the requirements for waiver of consent under either 21 CFR 50.23 (a)-(c) or 21 CFR 50.24, i.e., for individual emergency use or for emergency research without consent, respectively. A written informed adult consent will be obtained from all enrolled participants who turn the age of 18 during the course of this study. Written informed assent and 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 assent/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 assent/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 assent/consent process to be implemented at all study sites, which will be detailed in the MTN-034 SSP manual.

The informed assent/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-034 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, parents/guardians would have no reason to come to the clinic except to sign the consent, and 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-034 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 Females

Females who test positive for pregnancy at Screening or Enrollment Visits will not be eligible to participate in this study. Participants will be referred to local health care services, as needed. Should a woman test positive for pregnancy after Enrollment, a product discontinuation will be implemented. Follow-up will be completed and data collected per Section 7.5.2. A urine pregnancy test will be performed at scheduled study visits, and additionally at interim visits as indicated; the IoR/designee will temporarily discontinue study product for participants who test positive for pregnancy. During the informed assent/consent process, participants will be informed that the VR and tablets are not methods of contraception and the effects of the VR and tablet on a developing human fetus are unknown.

Animal studies of both study products have failed to demonstrate risk to the fetus, but there are no adequate and well-controlled studies in pregnant women completed to support their inclusion to date.

13.7.2 Children

The NIH has mandated that children be included in research trials when appropriate. This study will provide knowledge about a female adolescent population, including critical safety data. It is recognized that the planned study population are a vulnerable population and will be treated as such given the sensitive nature of the proposed research and the potential for social harms if their participation in the trial was discovered. The risk involved in this research is considered greater than minimal risk but presents the prospect of direct benefit to the individual participants. Both products being used in this study have been shown to be safe and effective in adults. However, as of December 2016, dapivirine was not approved in the countries

where the implementation of this trial is planned, and though FTC/TDF for oral PrEP was approved in two of the trial countries, South Africa and Kenya, it has not yet been made widely accessible in either country. Therefore, this research holds out the prospect of direct benefit to the health and well-being of adolescent females. The solicitation of participants' assent and the permission of their parents or guardians will be sought, pursuant to regulations set forth by the 45 CFR 46 and 21 CFR 50, and will not be coerced or subjected to undue influence.

13.8 Compensation

Pending IRB/EC approval, participants will be compensated for time and effort in this study, and/or will be reimbursed for travel to study visits and time away from work or school. Site-specific reimbursement amounts will be specified in the study ICFs. Each study site will determine appropriate compensation with their overseeing IRBs/ECs.

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 assent/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 product 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 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, National Institute of Mental Health (NIMH), and IPM, and Gilead for review prior to submission.

15 APPENDICES

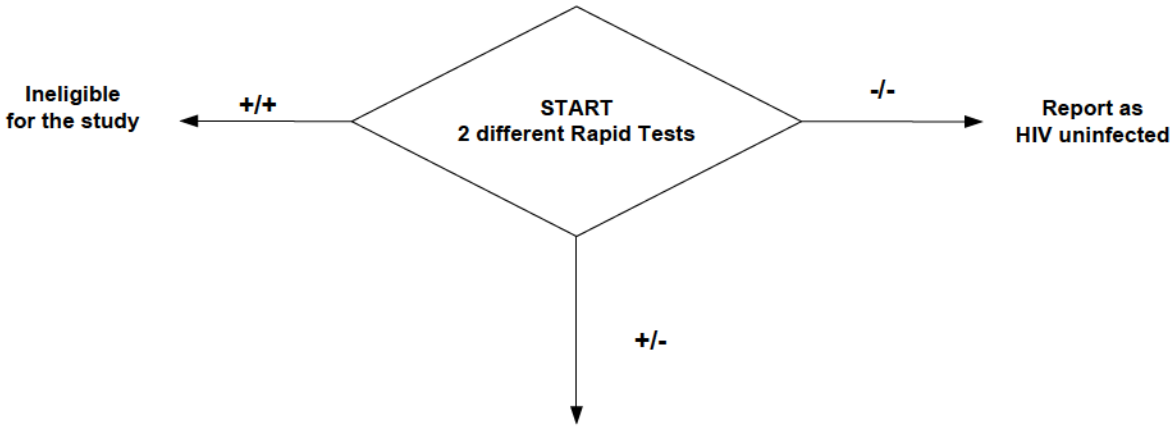
APPENDIX I: TABLE OF VISITS AND STUDY PROCEDURES

	SCR: Visit 1	ENR: Visit 2	Visits/Phone Contacts 3, 10, 17	Visits 4-9, 11-16, 18-22	PUEV: Visit 23	SEV: Visit 24
ADMINISTRATIVE AND REGULATORY						
Obtain Informed assent/consent(s) and, as needed, parental or guardian consent	X					
Assign a unique Participant Identification (PTID) number	X					
Assess and/or confirm eligibility	X	X				
Demographic information	X					
Collect/review/update locator information	X	X	X	X	X	X
Randomization		X				
Provide Reimbursement	X	X	X	X	X	X
Schedule next visit/contact	*	*	X	X	*	*
BEHAVIORAL						
HIV pre- and post-test counseling	X	X		X	X	
HIV/STI risk reduction counseling	X	X	*	▲	▲	*
Contraceptive counseling	X	X	*	*	*	*
Protocol adherence counseling		X	X	▲		
Product adherence disclosure counseling				□		
Behavioral assessment	X (Targeted)	X		∞	X	
Adherence assessment				∞	X	
Product preference / acceptability assessment		X		∞	X	
Social harms/benefits assessment				∞*	X	
Qualitative activities (In-depth interview [IDI] or focus group discussion [FGD]) (subset of participants only)				X♦		
FGD (subset of participants only)					X∇	
CLINICAL						
Medical/menstrual history	X	X	X	X	X	X
Concomitant medications	X	X		X	X	
Physical exam	X	*		X (Targeted)	X	
Pelvic exam	X	X		∞*	X	
Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI)/sexually transmitted infection (STI)	*	*	*	*	*	*
Disclosure of available test results	X	X	X	X	X	X
Offer and, if accepted, provide HBV and HPV vaccine series		*	*	*	*	
Collect AEs			X	X	X	X
LABORATORY						
URINE hCG	X	X		X	X	

	Dipstick urinalysis (UA) and/or urine culture	*	*		*	*	
BLOOD	HIV-1 testing	X	X		X	X	
	HSV-2 antibody		X		∞*	X	
	HBsAG	X					
	Plasma archive/storage		X		∞	X	
	Blood creatinine and creatinine clearance	X	*		ϕ*	X	
	CBC with platelets	X	*		ϕ*	X	
	Syphilis serology	X	*		∞*	X	
	Dried blood spot (DBS) for PK				X	X	
PELVIC	Rapid test for Trichomonas test	X	*		∞*	X	
	NAAT for GC/CT	X	*		∞*	X	
	Wet prep/KOH wet mount for candidiasis and/or BV	*	*		*	*	
	Vaginal pH	*	X		∞*	*	
	Vaginal swabs for microbiota		X		∞ (except Visit 20)		
	Vaginal Gram stain		X		∞	X	
	Vaginal swab for biomarkers (self-collected at visits when no pelvic exam is performed)		X		X	X	
	CVL for biomarkers		X		∞	X	
	Cervical swab for biomarkers		X		∞	X	
	Cervical cytobrush for flow cytometry (designated site(s) only)		X		∞	X	
STUDY PRODUCT	Adherence assessment(s): Returned Study VR(s)				X	X	
STUDY PRODUCT / SUPPLIES							
Provision of study VR(s) or study tablets			X		X		
Provision of product use instructions			X		X		
Insertion of one study VR (clinician to check VR placement if problem with insertion) or directly observed dosing (DOD) of first study tablet			X		X		
Retrieval and collection of study VR(s) or study tablets					X	X	
Offer male condoms		X	X		X	X	*

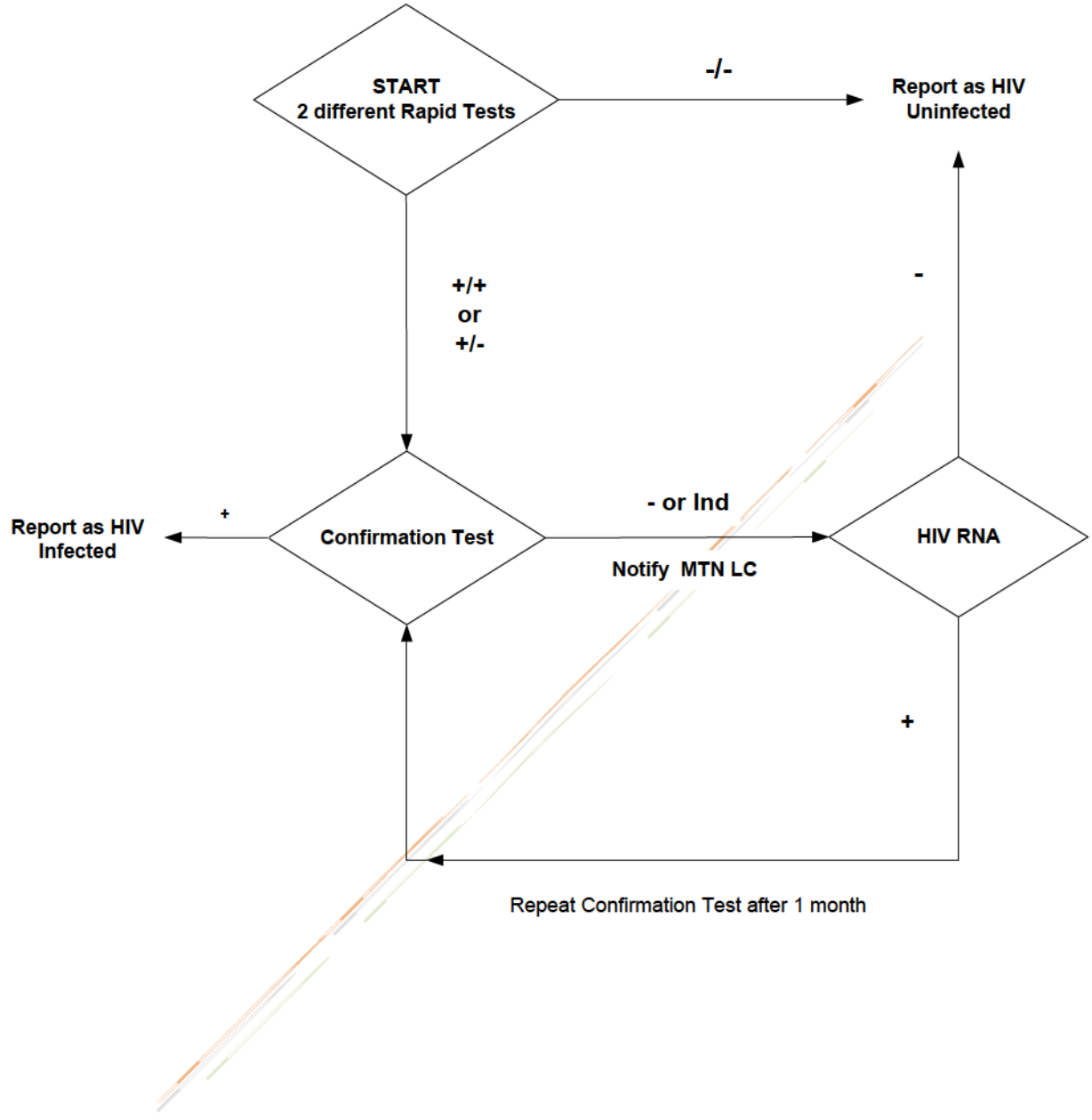
X = required, * = if indicated and/or per local standard of care, ♦ = Conducted once per product use period, and may be scheduled any time between the second and last monthly clinic visit of each period, ∇ = May be scheduled any time between Visit 20 and study exit to accommodate participant availability, ▲ = modified if necessary, ϕ= Required at Visits 9 and 16, ∞ = Required at Visits 6, 9, 13, 16, and 20, □ = Required at Visits 5, 8, 12, 15, 19, and 22, pending lab results availability

APPENDIX II: ALGORITHM FOR HIV TESTING-SCREENING/ENROLLMENT



Notify the MTN Laboratory Center for follow-up.

APPENDIX III: ALGORITHM FOR HIV TESTING- FOLLOW-UP



Ind: Indeterminate test results
LC: Laboratory Center

APPENDIX IV: SAMPLE INFORMED ASSENT

MTN-034
A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population

DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

Version 2.0
December 7, 2017

PRINCIPAL INVESTIGATOR: ***[Sites to insert]***
PHONE: ***[Sites to insert]***
Short Title for the Study: Reversing the Epidemic in Africa with Choices in HIV Prevention (REACH)

INTRODUCTION

You are being asked to join this research study because you are a young woman under 18 years old. Before you decide if you want to join, we want you to know about the study.

This form gives you information about this study. The decision to join is up to you. You are free to say "yes" or "no", or to drop out at any time after joining. Take your time to read through this form and to ask study staff as many questions about the study as you would like. If there are any words or information that you do not understand, study staff will explain them to you. If you agree to join this study, we will ask you to sign or make your mark on this form. We will offer you a copy of this form to keep.

WHY IS THIS STUDY BEING DONE?

A vaginal ring (which contains a drug called dapivirine) and an oral tablet (which is called Truvada) have been proven to be safe for use by adolescents and adults, and to protect against HIV infection when used consistently by people 18 years and older. HIV is the virus that causes AIDS. This study is trying to find out if those two products are safe and acceptable to young women, and to understand how young women use both products while in the study. Three hundred healthy young women who are 16 to 21 years old will be enrolled in the study across South Africa, Kenya, Uganda and Zimbabwe.

WHAT HAPPENS IF I DECIDE TO BE IN THIS STUDY?

There are three parts to this study, each lasting six months. You will use a vaginal ring for six months, getting a new ring every month. You will take a tablet once a day for another six months. Which product you will use first is decided by chance. *[SITES TO INSERT PREFERRED DESCRIPTION OF 'RANDOMIZATION']* After you take the tablets daily for 6 months and use the ring monthly for another 6 months, you will choose what you want to use for the final 6 months of the study, or you can choose not to use anything.

You will come to the clinic monthly, and check in one week after you first start using each new product, for a total of 24 study visits including the visit today. You will be in the study for about 19 months. You may also come to the clinic at other times if you have a medical problem related to use of the study products or would like to talk with the clinic staff about anything that is bothering you. Each visit will take about *[SITES TO INSERT THE APPROXIMATE LENGTH OF TIME]*.

Because we want to study these two products in women who are not pregnant, you must use a family planning method (e.g., birth control pills, implant, injection, intrauterine device [IUD]) even if you are not currently sexually active. If you are not currently using a family planning method, the study staff can assist you in selecting a family planning method that is right for you.

WHAT WILL BE DONE AT MY VISITS?

The following things may happen during your study visits:

- We will ask questions about your health and any medications you may be taking. We will also ask questions about your living situation to see if it affects your use of the study products, and about your reasons for wanting to join this study and how worried you are about getting HIV.
- At some visits, you will complete a questionnaire using a computer. You will answer questions about using the study product and other behaviors, including sexual activity, if you are sexually active. Some of the questions may be sensitive. If you ever feel uncomfortable, you can choose not to answer questions at any time. You will also answer questions about what you liked and did not like about this study and about the study products. When you finish the questionnaire, the computer "locks in" your information. No one in the clinic can see your answers.
- We may also ask you to do one or more interviews with staff alone or with other young women who are in the study. We may audio-record the interview(s). It is your choice if you want to do the interview(s).
- At some visits, we will draw blood to make sure you are healthy and to test you for HIV. We will also test your blood to see if you are using the study products.
- We will collect a urine sample for a pregnancy test.
- At some visits, we will give you a physical exam and pelvic exam to check for infections and to make sure you are healthy. The study doctor or nurse will use a speculum to do the pelvic exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine your vagina and cervix and take some fluids. The study doctor or nurse may do a vaginal wash during the pelvic exam. This means they will rinse your vagina and cervix with a small amount of sterile fluid, and then will collect the fluid in a tube for research purposes only.
- There are some instructions that we will ask you to follow in this study. We will talk with you about what you need to do to be in this study, how to use the study products, how to protect yourself from getting an infection, including HIV, and how to keep from getting pregnant. If you want, we can send you texts or call you if you need help remembering to use the products or have other difficulties using the products. You can also choose to be in a support group with other young women to

talk about ways to use the products successfully. We may also audio-record these conversations to see how our study staff counsel you. The recordings will not be used to collect information about what you say specifically.

- When you come in for each of your visits, we will give you either another ring to use, or another month of tablets to take. If the ring ever falls out and you can't put it back in, or if you need more tablets, or if you have any difficulty with the ring or the tablets at any time, you should come back to the clinic and we will assist you.
- We will give you the results of any blood or urine tests when available. We will also give you the results of other tests done to see if you are using the study products.
- We will give you treatment for sexually transmitted and other kinds of infections if you need them.
- We will give you referrals for other services, if you need them.
- These visits will take about *[sites to insert average visit duration]* to complete.

We are also asking your parent(s)/guardian(s) to let you join this study. But, the information you give during your visits will not be shared with them, unless you want it to be shared. If we learn something that may put you or others in danger, we will share this information with the hospital, police, social services, or other groups. *[SITES TO INSERT DETAILS REGARDING THE CONFIDENTIALITY OF PROTECTED HEALTH INFORMATION AND CONDITIONS UNDER WHICH THE CLINICIAN MAY SHARE PROTECTED HEALTH INFORMATION WITH THE PARTICIPANT'S PARENT/GUARDIAN]*

After you sign this form, we will check to see if you can join this study. If it seems like you can join, we will ask you to come back for an Enrollment visit.

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

WHAT ARE THE RISKS OF THE STUDY?

- You may feel a slight needle prick when we draw your blood. Some people may have a slight bruise that will go away in a day or two. Sometimes, people feel light headed or faint. It may also cause you to get an infection where the needle goes in your arm or hand.
- Some of the questions you are asked may seem personal or make you feel uncomfortable. You are free to skip any questions for any reason. You may also become embarrassed and/or worried; study staff will help you with any feelings or questions you have.
- You may feel discomfort or pressure during the pelvic exam. You may also have some vaginal bleeding or spotting after the exam.
- We will make every effort to protect your privacy, but it is possible that others may learn that you are in this study.
- The tablet and the ring can protect you from getting HIV, but based on what we know, the level of protection may be different between the two products. This

difference may have an effect on your risk of getting HIV. Trained study counselors will help you with any feelings or questions.

Some women who used the vaginal rings in other studies have had:

- Discharge from the vagina, some pain, burning or itchiness in the vagina, or vaginal bleeding in between usual periods.

Some people (about 1 out of 10) who used Truvada tablets have had:

- Upset stomach, stomach pain, vomiting, soft or liquid stools, passing gas, headache, dizziness, tiredness, or inability to sleep. Many of these side effects only last for the first month of taking the pills and get better with time or go away completely.

Rarely, people who used Truvada tablets have had:

- Rash, bone pain and bone changes, allergic reaction, problems with their kidneys (which helps to get waste out of the blood and make urine), and problems getting rid of acid from the body (which can cause shortness of breath, nausea and liver failure). Also, symptoms may worsen for people who have hepatitis B that suddenly stop taking Truvada. Participants will be closely monitored for any side effects.

You should call or come to the study clinic if you have any problems urinating, experience any sudden weight loss, cramps or muscle pain, have trouble breathing, or if you feel dizzy, extremely tired, get an upset stomach or feel like throwing up.

HOW WILL BEING IN THIS STUDY HELP ME?

Information from this study will help us learn ways to prevent young women from getting HIV in the future. Both the tablet and the vaginal ring may prevent you from getting HIV when used consistently. You will get health exams and you will be tested for HIV and other diseases, including sexually transmitted infections. You will also get counseling according to your needs. You will be offered the hepatitis B and HPV vaccines if you have not already had them. These vaccines help prevent viral infections which can lead to cancer of the liver and the cervix, respectively. We will give you some medical care as part of this study, but for any medical care not related to the study, study staff will refer you to another medical provider. Finally, you will get condoms, if you want them, and be put on a family planning method, if you are not already on one.

NEW INFORMATION

You will be told any new information learned during this study. For example, if we learn that the study products work in young females or cause bad side effects.

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

You do *not* have to be in this study. If you join today, you can change your mind later. You will be treated the same no matter what you decide. You can still join other studies. You will still be able to get your health care if you do not join the study.

COST AND REIMBURSEMENT:

You will not have to pay to be in this study. You will receive *[SITES TO INSERT AMOUNT $xx]* for being in this study and for travel to and from the clinic for each study

visit. You may also receive *[SITES TO INSERT AMOUNT $xx]* for any extra study visits during which you need to see a study doctor. You may receive *[Sites to insert amount $xx]* for responding to text messages. If you are chosen to take part in the discussion(s) with staff alone or in a group, you will receive *[Sites to insert amount $xx].*

CONFIDENTIALITY

Your records may be reviewed by representatives of the US Federal Government, including the US FDA, US OHRP, NIH and/or NIH contractors, and other US, local, and international regulatory entities. Your records may also be reviewed by the companies supplying the study products, study monitors, institutional review boards and ethics committees, and study staff. The study staff will do everything they can to protect your privacy.

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

LEFTOVER SAMPLES and RELATED HEALTH INFORMATION

There may be a small amount of urine, blood, and other body fluids left over at the end of the study. We would like to use them and some of your health information in future work that could include drug testing and testing for HIV risk. They will be stored safely and securely. Only approved study staff will be able to use them. You can change your mind about this at any time.

I agree _____ I do NOT agree _____

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

You can ask any questions at any time to the people listed below:

- [Name of the investigator or other study staff]
- [Telephone number of above]

For questions about your rights as a research participant, contact:

- [Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [Telephone number of above]

SIGNATURE PAGE

If you have read this assent form (or had it explained to you), all your questions have been answered and you agree to join this study, please sign your name or make your mark below.

_____
Minor Participant's Name (Print)

_____ _____
Minor Participant's Signature Date

_____
Study Staff's Name Conducting
Assent Discussion (Print)

_____ _____
Study Staff Conducting Date
Assent Discussion (Signature)

_____
Witness Name (Print)

_____ _____
Witness Name (Signature) Date

APPENDIX V: SAMPLE PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE)

SAMPLE PARENT/GUARDIAN PERMISSION

MTN-034
A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population

DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

Version 2.0
December 7, 2017

PRINCIPAL INVESTIGATOR: ***[Sites to insert]***
PHONE: ***[Sites to insert]***
Short Title for the Study: Reversing the Epidemic in Africa with Choices in HIV Prevention (REACH)

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

Before you decide if you want your child to join this study, we want you to know about it. This form gives you information about this study. The study staff will talk with you and your child about it and answer your questions. For your child to be in the study, both you and she must agree. You may choose to stop your child from being in the study at any time. Once you read, discuss, and understand the study, and if your child agrees, we will ask you to sign this form. We will offer you a copy of this form to keep.

Why is this research being done?
This research study is known as MTN-034, or REACH. One main purpose is to find out if the two study products, the ring and the tablet, are safe and acceptable to adolescent and young women. The study is also trying to learn how adolescent and young women use these products while in the study.

The ring contains a drug called dapivirine. Dapivirine works by stopping HIV from making copies of itself. The dapivirine ring was tested and found to be safe for use by adolescent (15-17 years old) and adult (18 years and older) women. It was also found to be effective in preventing HIV in women ages 22-45 when used consistently. Researchers believe that younger women were not protected from getting HIV because

they did not use the rings consistently. Another reason to conduct this study is to learn if inconsistent use or something else was the reason why the ring was not effective in young women.

The tablet, known as Truvada®, contains two drugs called emtricitabine and tenofovir disoproxil fumarate. The tablet is an HIV prevention method approved for adults. Truvada® works by stopping HIV from making copies of itself. Truvada® is also approved to treat HIV infection in people older than 12 years when combined with other drugs.

All of these drugs are used to prevent HIV, the virus that causes AIDS.

Who will be in this research study?
Three hundred healthy adolescent and young women who are 16 to 21 years old will be enrolled in the study across various sites in South Africa, Kenya, Uganda and Zimbabwe.

What will my child be asked to do if she joins this research study?
There are three parts to this study, each lasting six months. Your child will use a vaginal ring for 6 months, replacing it every month. She will take a Truvada® tablet once a day for another 6 months. Which of the two products she will use first will be decided by chance *[SITES TO INSERT PREFERRED DESCRIPTION OF 'RANDOMIZATION']*. Neither she nor the study staff can decide which of the two products she will use first. After using the ring and the tablet for 6 months each, she will choose between using the ring or taking the tablet for the final 6 months of the study, or she can choose not to use anything.

Your child will come to the clinic monthly, and check in one week after she first starts using each new product, for a total of 24 study visits including the visit today. She will be in the study for about 19 months. Each visit will take about *[SITES TO INSERT THE APPROXIMATE LENGTH OF TIME]*.

Does your child have to be in this study?
Your child does *not* have to be in this study. She can still get the care she needs even if she does not join the study. If she joins today, you or your child can change your minds later.

What procedures will be done for this study?
Your child's first visit will happen today after you and her read, discuss, understand and sign the permission and assent forms. The procedures done at this visit will let us know if she can join this study, and will take about *[SITES TO INSERT THE APPROXIMATE LENGTH OF TIME]*.

If it seems like she can join, she will be asked to come back for an Enrollment visit no later than 70 days from today. During the Enrollment Visit, she will begin using the vaginal ring or begin taking the Truvada® tablet, depending on which study group she has been assigned to.

The following things may happen during her study visits:

- We will ask questions about your child's health and any medications she may be taking. We will also ask questions about her living situation to see if it affects her use of the study products, and about her reasons for wanting to join this study and how worried she is about getting HIV.
- At some visits, she will complete a questionnaire using a computer. She will answer questions about using the study products and other behaviors, including sexual activity, if she is sexually active. She will also answer questions about what she liked and did not like about this study and about the study products. When she finishes the questionnaire, the computer "locks in" the information. No one in the clinic can see her answers.
- We may also ask your child to do one or more interviews with staff alone or with other young women who are in the study. She may choose not to do either. During the interview(s) or group discussion(s), we may ask her to discuss her use of the study products, her feelings about the study products and about being in the study, and other questions that can help researchers to better understand participants' experiences while in the study. We may audio-record the interview(s) or group discussion(s). We will keep the audio recording and related materials confidential and no one other than the study team will have access to her responses.
- At some visits, we will draw blood to make sure your child is healthy and to test her for HIV. We will also test her blood to see if she is using the study products.
- We will collect a urine sample for a pregnancy test.
- At some visits, we will give your child a physical exam and pelvic exam to check for infections and to make sure she is healthy.
- We will discuss with your child the rules of the study, how to use the study products, how to protect herself from getting an infection, including HIV, and how to keep from getting pregnant. We may also audio-record these discussions to see how our study staff counsel her. The recordings will not be used to collect information about what your child says. We will keep the audio recording and related materials confidential.
- When your child comes in for each of her visits, we will give her either another ring to use, or another month of tablets to take.
- We will give your child the results of any blood or urine tests when available. We will also give her the results of other tests done to see if she is using the study products.
- We will give your child treatment for sexually transmitted and other kinds of infections, if she needs them.
- We will give your child referrals for other services, if she needs them.
- These visits will take about *[sites to insert average visit duration]* to complete.

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

Your child may be asked to make additional visits so we can do more laboratory tests or have study procedures repeated. We will do this if there are abnormal test results or a mistake during the collection or the processing of samples. We will also do this if she

experiences any changes in her physical condition, including symptoms of urine or sexually transmitted infections (STIs).

What if she becomes infected with HIV?
Being in this study will not cause HIV infection. But, there is always a chance that your child can get HIV through sex or other activities. If she becomes HIV-positive, she will stop using the study products. But, we will ask her to continue to come for her study visits and for some of the study procedures. The study staff will refer her for medical care and other available services. If she gets HIV, it is possible that the virus is resistant to some drugs. This means that some drugs may not work well to treat her HIV. We will do a blood test to find out if she has drug resistance. These results can help us know which drugs would be best to treat her HIV.

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

What if she becomes pregnant?
The vaginal ring and the tablet are not family planning methods and will not prevent pregnancy. We do not know what effect the study products have on pregnancy, including any effect on the unborn babies. Because of this, pregnant women may not join this study. Also, your child must use an effective family planning method (e.g., birth control pills, hormonal-based methods, intrauterine device [IUD], the patch) other than a vaginal ring, even if she is not currently sexually active.

If your child becomes pregnant during the study, study staff will refer her to available medical care and other services. The study does not pay for this care. She will stop using study products. But, we will ask her to continue to come for her study visits. We will change the study procedures as needed to protect her health while she is pregnant. We may also contact her to find out about the health of her pregnancy and baby.

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws
Your child may feel discomfort or pain when her blood is drawn. She may feel dizzy or faint. She may have a bruise, swelling, small clot, or infection where the needle goes into her hand or arm.

Risks of Genital Exams
Your child may feel discomfort or pressure during the pelvic exam. She may have a small amount of vaginal bleeding or spotting which should stop shortly after the exam.

Risks of the Vaginal Ring
The vaginal ring can cause some side effects, such as an allergic reaction. Signs of an allergic reaction include, but are not limited to: rash or other skin irritation, itching, joint pain, or difficulty in breathing.

We do not yet know all the side effects of the vaginal rings. Some women who used the vaginal rings in other studies have had:

- Discharge from the vagina
- Pain, burning, or itchiness in the vagina
- Vaginal bleeding in between their usual periods

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

Risks of the Truvada® tablet
Most people who take Truvada® do not have any side effects. The side effects that some people taking Truvada® may have are well known because the drugs have been used by many people.

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

Other side effects are more serious, but less than one in a hundred people who take Truvada® may have them. These rare side effects include: rash; liver problems; serious kidney damage; and allergic reaction. People taking Truvada® may also have small changes in the thickness of their bones, but these changes have not caused problems for the people who had them. Some people with HIV who take Truvada® in combination with other drugs may get lactic acidosis. This is a serious side effect of some drugs used to treat HIV that can cause shortness of breath, nausea, and liver failure. Your child should call or come to the clinic if she has unexplained changes in urination, weight loss, cramps, muscle pain, dizziness, tiredness, nausea, vomiting, or shortness of breath. If she has these symptoms, or any other symptoms that concern her, the study staff will check her and see if she should stop taking Truvada®.

A small number of people in this study may have these side effects or other side effects that we do not know about. But, we will screen your child's kidneys and overall health

before she joins the study and during the study. This will reduce her chances of having any side-effects.

Risks of HIV and Sexually Transmitted Infection (STI) Testing
HIV and STI testing may make your child feel anxious regardless of the test results. Finding out her HIV status may also cause problems with her family, friends, or partner.

Other Possible Risks
Your child may feel embarrassed and/or worried when talking about sexual activities (if she is currently sexually active), her living situation, ways to protect against HIV and STIs, and her test results. She can choose not to answer questions at any time. Trained study counselors will help her with any feelings or questions.

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

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

BENEFITS
Your child will be using two study products that may prevent her from getting HIV if she uses them consistently. Information learned from this study may help us learn how to prevent young women like her from getting HIV. She will receive medical exams and counseling and testing for HIV and STIs. She will be offered the Hepatitis B virus vaccine series and the HPV vaccine, if she has not had them yet. She will also have tests to check her overall health.

This study cannot give your child general medical care, but study staff will refer her to another medical provider for care, if needed. She will get free condoms, if she needs them. She will be put on a family planning method, if she is not on one already. If she has an STI diagnosed, she will receive medicine or a referral, if she needs it.

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

A description of this clinical trial is available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify your child. At

most, the website will include a summary of the results. You can search this website at any time.

WHY YOUR CHILD MAY STOP TAKING THE STUDY DRUG EARLY OR BE ASKED TO LEAVE THE STUDY

Your child may need to leave the study early without her/your permission if:

- The study is cancelled by the US FDA, US NIH, IPM, Gilead Sciences, Inc., the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants.
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. A SMC reviews the progress of the study and the kinds of effects that people report while they are in the study.
- She is not able to keep appointments.
- Other reasons that may prevent her from completing the study successfully.

The study doctor will ask your child to stop using the study products if she:

- Gets HIV.
- Becomes pregnant.
- Starts breastfeeding.
- Uses drugs for HIV prevention beyond what the study gives her.
- Uses drugs to prevent infection after being exposed to HIV.
- Uses injectable drugs for fun.
- Has a bad reaction to study product, or a study doctor decides that using study product would be bad for her.
- Is unable or unwilling to follow the study rules.

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

If your child is removed from the study or chooses to leave, we will ask her to return the study product and to come back for one final clinic visit. If she does not have the study product with her when she comes to the clinic, staff members will make every effort to assist her in returning it as soon as possible. *[SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES.]*

ALTERNATIVES TO BEING IN THE STUDY

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

COSTS TO YOU

[SITE TO COMPLETE ACCORDING TO SITE CAPACITY] There is no cost to you or your child for study visits, study products, physical exams, laboratory tests or other

procedures. We can give her treatments for STIs other than HIV free of charge while she is in the study, or we can refer her for available treatment.

REIMBURSEMENT

[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:] Your child will receive *[SITES TO INSERT AMOUNT* $xx*]* for her time, effort, and travel to and from the clinic for each study visit. She may receive *[SITES TO INSERT AMOUNT* $xx*]* for any extra study visits. She may receive [*Sites to insert amount* $xx] for responding to text messages. If she is chosen to take part in the discussion(s) with staff alone or in a group, she will receive [*Sites to insert amount* $xx].

CONFIDENTIALITY

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

Study visits will take place in private. We will keep the information about your child's study visits in a secure place that only certain people can access for the purposes of this study. We will only enter her information into computers protected by passwords and will not include information that could identify her. We will only record her study number. If she is selected to do the interview(s) or group discussion(s), she can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. During group discussions, we will not reveal your child's full name to the others, and we will ask everyone not to tell anyone outside of the group what was said during the discussion.

[SITES TO INSERT DETAILS REGARDING THE CONFIDENTIALITY OF PROTECTED HEALTH INFORMATION AND CONDITIONS UNDER WHICH THE CLINICIAN MAY SHARE PROTECTED HEALTH INFORMATION WITH THE PARTICIPANT'S PARENT/GUARDIAN].

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

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

Your child's records may be reviewed by:

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

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

RESEARCH-RELATED INJURY

[SITES TO SPECIFY INSTITUTIONAL POLICY:] It is unlikely that your child will be injured by being in this study. This US federally funded study cannot offer compensation for research-related injury. If she is injured or gets sick from being in this study, please tell study staff immediately. We may be able to give her emergency treatment but you or your insurance company may be charged for this treatment. You are not giving up any legal rights by signing this form.

YOUR CHILD'S RIGHTS AS A RESEARCH PARTICIPANT

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

PROBLEMS OR QUESTIONS

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

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

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

PERMISSION FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION

There may be a small amount of urine, blood, vaginal and cervical fluids left over after we have done all of the study related testing. We would like to store your child's leftover body fluids for future work that could include drug testing and testing for HIV risk. If you agree, her samples and related health information will be stored safely and securely.

Only approved researchers will be able to use these samples and health information. Some employees will need to have access to these samples to store them and keep track of where they are, but these people will not have information that directly identifies your child.

There is no time limit on how long her samples will be stored. Her samples may be shipped and/or stored outside of the country. We do not yet know the specific type of testing that will be done with these samples. But, they may be used to check that certain laboratory tests perform correctly. Any other testing beyond that will have to be approved by an IRB/EC. We do not plan to do genetic testing of any kind.

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

PARENT/GUARDIAN INITIALS	
_____ Initials _____ Date	I DO agree to allow my child's biological specimens and health data to be stored and used in future research studies.
_____ Initials _____ Date	I DO NOT agree to allow my child's biological specimens and health data to be stored and used in future research studies.

SIGNATURE PAGE

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB/EC:]
All of the above has been explained to me and all of my current questions have been answered. I understand that I can ask questions about any aspect of this research study during the course of this study, and that future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my child's rights as a research participant will be answered by *[INSERT LOCAL IRB INFORMATION].*

I understand that, as a minor (age less than 18 years), my daughter is not allowed to participate in this research study without my permission. I voluntarily agree to allow my daughter to whom I am the legal guardian to be in this research study. A copy of this permission form will be given to me.

Parent's or Guardian's Name (Print)	Relationship to Participant/Child
Parent's or Guardian's Signature	Date
Study Staff's Name Conducting Parent/Guardian Permission Discussion (Print)	
Study Staff Conducting Parent/Guardian Permission Discussion (Signature)	Date
Witness Name (Print)	
Witness Signature	Date

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

SAMPLE INFORMED CONSENT

MTN-034
A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population

DIVISION OF AIDS, NIAID, NICHD, NIMH, NIH

Version 2.0
December 7, 2017

PRINCIPAL INVESTIGATOR: ***[Sites to insert]***
PHONE: ***[Sites to insert]***
Short Title for the Study: Reversing the Epidemic in Africa with Choices in HIV Prevention (REACH)

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

Before you decide if you want to join this study, we want you to know about it. This form gives you information about this study. The study staff will talk with you about it and answer your questions. You may choose to stop being in the study at any time. Once you read, discuss, and understand the study, and if you agree, we will ask you to sign this form. We will offer you a copy of this form to keep.

Why is this research being done?
This research study is known as MTN-034, or REACH. One main purpose is to find out if the two study products, the ring and the tablet, are safe and acceptable to adolescent and young women. The study is also trying to learn how adolescent and young women use these products while in the study.

The ring contains a drug called dapivirine. Dapivirine works by stopping HIV from making copies of itself. The dapivirine ring was tested and found to be safe for use by adolescent (15-17 years old) and adult (18 years and older) women. It was also found to be effective in preventing HIV in women ages 22-45 when used consistently. Researchers believe that younger women were not protected from getting HIV because they did not use the rings consistently. Another reason to conduct this study is to learn if

inconsistent use or something else was the reason why the ring was not effective in young women.

The tablet, called Truvada®, has two drugs called emtricitabine and tenofovir disoproxil fumarate. The tablet is an HIV prevention method approved for adults. Truvada® works by stopping HIV from making copies of itself. Truvada® is also approved to treat HIV infection in people older than 12 years when combined with other drugs.

Who will be in this research study?
Three hundred healthy adolescent and young women who are 16 to 21 years old will be enrolled in the study across various sites in South Africa, Kenya, Uganda and Zimbabwe.

What will I be asked to do if I join this research study?
There are three parts to this study, each lasting six months. You will use a vaginal ring for 6 months, replacing it every month. You will take a Truvada® tablet once a day for another 6 months. Which of the two products you will use first will be decided by chance *[SITES TO INSERT PREFERRED DESCRIPTION OF 'RANDOMIZATION'].* Neither you nor the study staff can decide which of the two products you will use first. After using the ring and the tablet for 6 months each, you will choose between using the ring or taking the tablet for the final 6 months of the study, or you can choose not to use anything.

You will come to the clinic monthly, and check in one week after you first start using each new product, for a total of 24 study visits including the visit today. You will be in the study for about 19 months. Each visit will take about *[SITES TO INSERT THE APPROXIMATE LENGTH OF TIME].*

Do I have to be in this study?
You do *not* have to be in this study. You can still get the care you need even if you do not join the study. If you join today, you can change your mind later.

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

If it seems like you can join, you will be asked to come back for an Enrollment visit no later than 70 days from today. During the Enrollment Visit, you will begin using the vaginal ring or begin taking the Truvada® tablet, depending on which study group you have been assigned to.

The following things may happen during your study visits:

- We will ask questions about your health and any medications you may be taking. We will also ask questions about your living situation to see if it affects your use of the

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

- At some visits, you will complete a questionnaire using a computer. You will answer questions about using the study products and other behaviors, including sexual activity, if you are sexually active. Some of the questions may be sensitive. If you ever feel uncomfortable, you can choose not to answer questions at any time. You will also answer questions about what you liked and did not like about this study and about the study products. When you finish the questionnaire, the computer "locks in" the information. No one in the clinic can see your answers.
- We may also ask you to do one or more interviews with staff alone or with other young women who are in the study. You may choose not to do either. During the interview(s) or group discussion(s), we may ask you to discuss your use of the study products, your feelings about the study products and about being in the study, and other questions that can help researchers to better understand participants' experiences while in the study. We may audio-record the interview(s) or group discussion(s). We will keep the audio recording and related materials confidential and no one other than the study team will have access to your responses.
- At some visits, we will draw blood to make sure you are healthy and to test you for HIV. We will also test your blood to see if you are using the study products.
- We will collect a urine sample for a pregnancy test.
- At some visits, we will give you a physical exam and pelvic exam to check for infections and to make sure you are healthy. The study doctor or nurse will use a speculum to do the pelvic exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine your vagina and cervix and take some fluids. The study doctor or nurse may do a vaginal wash during the pelvic exam. This means they will rinse your vagina and cervix with a small amount of sterile fluid, and then will collect the fluid in a tube for research purposes only.
- We will talk with you about what you need to do to be in the study, how to use the study products, how to protect yourself from getting an infection, including HIV, and how to keep from getting pregnant. If you want, we can send you texts or call you if you need help remembering to use the products or have other difficulties using the products. You can also choose to be in a support group with other young women to talk about ways to use the products successfully. We may also audio-record these conversations to see how our study staff counsel you. The recordings will not be used to collect information about what you say. We will keep the audio recording and related materials confidential.
- When you come in for each of your visits, we will give you either another ring to use, or another month of tablets to take.
- We will give you the results of any blood or urine tests when available. We will also give you the results of other tests done to see if you are using the study products.
- We will give you treatment for sexually transmitted and other kinds of infections, if you need them.
- We will give you referrals for other services, if you need them.
- These visits will take about *[sites to insert average visit duration]* to complete.

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

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

What if I become infected with HIV?

Being in this study will not cause HIV infection. But, there is always a chance that you can get HIV through sex or other activities. If you become HIV-positive, you will stop using the study products. But, we will ask you to continue to come for your study visits and for some of the study procedures. The study staff will refer you for medical care and other available services. If you get HIV, it is possible that the virus is resistant to some drugs. This means that some drugs may not work well to treat your HIV. We will do a blood test to find out if you have drug resistance. These results can help us know which drugs would be best to treat your HIV. *[SITES TO INCLUDE/AMMEND THE FOLLOWING:* If you are interested, study staff will inform you of other research studies you may be eligible for.]

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

What if I become pregnant?

The vaginal ring and the tablet are not family planning methods and will not prevent pregnancy. We do not know what effect the study products have on pregnancy, including any effect on the unborn babies. Because of this, pregnant women may not join this study. Also, you must use an effective family planning method (e.g., birth control pills, hormonal-based methods, intrauterine device [IUD], the patch) other than a vaginal ring, even if you are not currently sexually active.

If you become pregnant during the study, study staff will refer you to available medical care and other services. The study does not pay for this care. You will stop using study products. But, we will ask you to continue to come for your study visits. We will change the study procedures as needed to protect your health while you are pregnant. We may also contact you to find out about the health of your pregnancy and baby. *[SITES TO INCLUDE/AMMEND THE FOLLOWING:* We may also contact you about a study that collects information about pregnancy and children up to one year old.]

RISKS AND/OR DISCOMFORTS

Risks of Blood Draws

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

Risks of Genital Exams

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

Risks of the Vaginal Ring

The vaginal ring can cause some side effects, such as an allergic reaction. Signs of an allergic reaction include, but are not limited to: rash or other skin irritation, itching, joint pain, or difficulty in breathing.

We do not yet know all the side effects of the vaginal rings. Some women who used the vaginal rings in other studies have had:

- Discharge from the vagina
- Pain, burning, or itchiness in the vagina
- Vaginal bleeding in between their usual periods

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

Risks of the Truvada® tablet

Most people who take Truvada® do not have any side effects. The side effects that some people taking Truvada® may have are well known because the drugs have been used by many people.

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

Other side effects are more serious, but less than one in a hundred people who take Truvada® may have them. These rare side effects include: rash; liver problems; serious kidney damage; and allergic reaction. People taking Truvada® may also have small changes in the thickness of their bones, but these changes have not caused problems for the people who had them. Some people with HIV who take Truvada® in combination with other drugs may get lactic acidosis. This is a serious side effect of some drugs

used to treat HIV that can cause shortness of breath, nausea, and liver failure. You should call or come to the clinic if you have unexplained changes in urination, weight loss, cramps, muscle pain, dizziness, tiredness, nausea, vomiting, or shortness of breath. If you have these symptoms, or any other symptoms that concern you, the study staff will check you and see if you should stop taking Truvada®.

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

Risks of HIV and Sexually Transmitted Infection (STI) Testing
HIV and STI testing may make you feel anxious regardless of the test results. Finding out your HIV status may also cause problems with your family, friends, or partner.

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

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

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

BENEFITS
You will be using two study products that may prevent you from getting HIV if you use them consistently. Information learned from this study may help us learn how to prevent young women like you from getting HIV. You will receive medical exams and counseling and testing for HIV and STIs. You will be offered the Hepatitis B virus vaccine series and the HPV vaccine, if you have not had them yet. You will also have tests to check your overall health.

This study cannot give you general medical care, but study staff will refer you to another medical provider for care, if needed. You will get free condoms, if you need them. You will be put on a family planning method, if you are not on one already. If you have an STI diagnosed, you will receive medicine or a referral, if you need it.

NEW INFORMATION
You will be told any new information learned during this study that may affect your willingness to stay in the study. For example, we will let you know if we learn that the

study products may be causing bad side effects. We will tell you any new information about preventing HIV, regardless of the product, if we learn that it works in young women. We will also tell you when study results may be available, and how to learn about them.

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

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

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

- The study is cancelled by the US FDA, US NIH, IPM, Gilead Sciences, Inc., the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional Review Board (IRB)/Ethics Committee (EC). An IRB/EC is a committee that watches over the safety and rights of study participants.
- The Study Monitoring Committee (SMC) recommends that the study be stopped early. A SMC reviews the progress of the study and the kinds of effects that people report while they are in the study.
- You are not able to keep appointments.
- Other reasons that may prevent you from completing the study successfully.

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

- Get HIV.
- Become pregnant.
- Start breastfeeding.
- Use drugs for HIV prevention beyond what the study gives you.
- Use drugs to prevent infection after being exposed to HIV.
- Use injectable drugs for fun.
- Have a bad reaction to study product, or a study doctor decides that using study product would be bad for you.
- Are unable or unwilling to follow the study rules.

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

If you are removed from the study or choose to leave, we will ask you to return the study product and to come back for one final clinic visit. If you do not have the study product with you when you come to the clinic, staff members will make every effort to assist you in returning it as soon as possible. *[SITES TO SPECIFY ALLOWANCES FOR SPECIAL CIRCUMSTANCES.]*

ALTERNATIVES TO BEING IN THE STUDY

[SITES TO INCLUDE/AMEND THE FOLLOWING, IF APPLICABLE: You may be able to join other studies here or in the community. There may be other places where you can

go for HIV counseling and testing and family planning. We will tell you about those studies and those places if you wish.]

COSTS TO YOU

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

REIMBURSEMENT

[SITES TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:] You will receive *[SITES TO INSERT AMOUNT* $xx*]* for your time, effort, and travel to and from the clinic for each study visit. You may receive *[SITES TO INSERT AMOUNT* $xx*]* for any extra study visits. You may receive [*Sites to insert amount* $xx] for responding to text messages. If you are chosen to take part in the discussion(s) with staff alone or in a group, you will receive [*Sites to insert amount* $xx].

CONFIDENTIALITY

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

Study visits will take place in private. We will keep the information about your study visits in a secure place that only certain people can access for the purposes of this study. We will only enter your information into computers protected by passwords and will not include information that could identify you. We will only record your study ID number. If you are selected to do the interview(s) or group discussion(s), you can choose not to answer questions at any time. We will keep the audio recordings and materials from all interviews and discussions confidential and will only use study numbers or fake names. During group discussions, we will not reveal your full name to the others, and we will ask everyone not to tell anyone outside of the group what was said during the discussion.

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

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

Your records may be reviewed by:

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

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

RESEARCH-RELATED INJURY

[SITES TO SPECIFY INSTITUTIONAL POLICY:] It is unlikely that you will be injured by being in this study. This US federally funded study cannot offer compensation for research-related injury. If you are injured or get sick from being in this study, please tell study staff immediately. We may be able to give you emergency treatment but you or your insurance company may be charged for this treatment. You are not giving up any legal rights by signing this form.

YOUR RIGHTS AS A RESEARCH PARTICIPANT

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

PROBLEMS OR QUESTIONS

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

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

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

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

There may be a small amount of urine, blood, vaginal and cervical fluids left over after we have done all of the study related testing. We would like to store your leftover body fluids for future work that could include drug testing and testing for HIV risk. If you agree, your samples and related health information will be stored safely and securely.

Only approved researchers will be able to use these samples and health information. Some employees will need to have access to these samples to store them and keep track of where they are, but these people will not have information that directly identifies you.

There is no time limit on how long your samples will be stored. Your samples may be shipped and/or stored outside of the country. We do not yet know the specific type of testing that will be done with these samples. But, they may be used to check that certain laboratory tests perform correctly. Any other testing beyond that will have to be approved by an IRB/EC. We do not plan to do genetic testing of any kind.

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

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

SIGNATURE PAGE

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

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

Any questions I have about my rights as a research participant will be answered by *[INSERT LOCAL IRB INFORMATION].*

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

_____
Participant's Name (Print)

_____ _____
Participant's Signature Date

_____
Study Staff's Name Conducting
Consent Discussion (Print)

_____ _____
Study Staff Conducting Date
Consent Discussion (Signature)

_____
Witness Name (Print)

_____ _____
Witness Signature Date

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