MTN-033

An Open Label Randomized Phase 1 Pharmacokinetic Study of Dapivirine Gel Administered Rectally to HIV-1 Seronegative Adults

Microbicide Trials Network

Funding Agencies:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
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LIST OF ABBREVIATIONS AND ACRONYMS

AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine transaminase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the curve
BAT	Dosing Before and After Sex </= Two doses in 24h
BRWG	Behavioral Research Working Group
BV	bacterial vaginosis
CASI	computer assisted self-interview
CBC	complete blood count
CD4	cluster of differentiation 4
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	maximum concentration
CNS	central nervous system
CRF	case report form
CRMS	Clinical Research Management System
CRS	Clinical Research Site
CT	*Chlamydia trachomatis,* Chlamydia
CTA	Clinical Trial Agreement
CV	coefficient of variation
CVL	cervicovaginal lavage
CWG	Community Working Group
CYP3A	cytochrome P450, family 3, subfamily A genetic locus
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DAIDS PRO	DAIDS Protocol Registration Office
DAPY	di-amino-pyrimidine
DLV	delavirdine
DNA	deoxyribonucleic acid
DOD	directly observed dosing
DPV	dapivirine
EAE	expedited adverse event
EC	ethics committees
EC_{50}	50% effective concentration
EFV	efavirenz
ENR	enrollment
FDA	(US) Food and Drug Administration

FHCRC	Fred Hutchinson Cancer Research Center
g	grams
GC	*Neisseria gonorrhoeae,* gonorrhea
GCP	Good Clinical Practices
GEE	generalized estimating equations
GMP	Good Manufacturing Practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HEC	hydroxyethylcellulose
HEENT	Head, Eye, Ear, Nose and Throat Examination
HHS	(U.S.) Department of Health and Human Services
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus type 1
HIV-1 IIIB	Human Immunodeficiency Virus type 1, IIIB strain
HPTN	HIV Prevention Trials Network
HPV	human papillomavirus
HSV	herpes simplex virus
HSV-1/2	herpes simplex virus type 1/2
hu-PBL	human peripheral blood lymphocytes
hu-SCID	humanized severe combined immunodeficient
IATA	International Air Transport Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDI	In-Depth Interview
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IoR	Investigator of Record
IPM	International Partnership for Microbicides
IRB	Institutional Review Board
IUD	intrauterine device
kg	kilogram
LC	Laboratory Center
LDMS	Laboratory Data Management System
LOC	Leadership and Operations Center
µg	microgram
MDP	Microbicides Development Programme
mg	milligram
mL	milliliter
mM	millimolar
MO	Medical Officer
mOsm	milliosmole
MPA	medroxyprogesterone acetate
mRNA	mitochondrial ribonucleic acid
MT-2	human melatonin receptor 2
MTN	Microbicide Trials Network

MTT	3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, a tetrazole
n	number
N-9	nonoxynol-9
NAAT	nucleic acid amplification test
NF	National Formulary
ng	nanogram
nM	nanomolar
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
NL	network laboratory
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleotide analogue reverse transcriptase inhibitor
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSAIDS	non-steroidal anti-inflammatory drugs
NVP	nevirapine
OHRP	Office for Human Research Protections
P24	protein 24
PBL	peripheral blood lymphocytes
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PD	pharmacodynamics
PEP	post-exposure prophylaxis
pH	potential of hydrogen
PK	pharmacokinetics
PMPA	9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate
PoR	Pharmacist of Record
PPD	Pharmaceutical Product Development, Inc.
PrEP	pre-exposure prophylaxis
PRO	Protocol Registration Office
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PSS	polystyrene sulfonate
PT	prothrombin time
PTID	participant identification
PVC	polyvinyl chloride
PVI	penile-vaginal intercourse
RAI	receptive anal intercourse
RE	Regulatory Entity
RG	reduced-glycerin
RNA	ribonucleic acid
RSC	Regulatory Support Center
RT	reverse transcriptase
RTI	reproductive tract infection
RT-PCR	real-time polymerase chain reaction
Rx	treatment
SAE	serious adverse event

SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SCID	severe combined immunodeficient
SCR	screening
SDMC	Statistical Data Management Center
SHIV	simian human immunodeficiency virus
SMC	Study Monitoring Committee
SOP	standard operating procedure
SMS	short message service
SSP	study specific procedures
STI	sexually transmitted infection
SUSAR	suspected, unexpected serious adverse reaction
TCID	tissue culture infective dose
TEAE	treatment-emergent adverse events
T_{max}	Time at which C_{max} is observed
TPGS	tocopheryl polyethylene glycol succinate
UA	urinalysis
ULN	upper limit of normal
UPMC	University of Pittsburgh Medical Center
USA	United States of America
USP	United States Pharmacopoeia
UTI	urinary tract infection
VR	vaginal ring
WHO	World Health Organization
w/w	weight/weight
wt	wild type

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INVESTIGATOR SIGNATURE FORM

Version 2.0; December 8, 2017
A Study of the Microbicide Trials Network

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

IND Sponsor:
DAIDS (DAIDS Protocol ID: 12065)

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

_____ _____
Signature of Investigator of Record Date

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An Open Label Randomized Phase 1 Pharmacokinetic Study of Dapivirine Gel Administered Rectally to HIV-1 Seronegative Adults

PROTOCOL SUMMARY

Short Title: Rectal PK Study of Dapivirine (DPV) Gel

Clinical Phase: Phase 1

IND Sponsor: DAIDS

Protocol Chair: Ken Ho, MD

Sample Size: MTN-033 will enroll approximately 16 evaluable participants.

Study Population: HIV-uninfected men who have sex with men (MSM) and transgender women who have sex with men, 18 years or older

Study site: Site selected by MTN Executive Committee

Study Design: Phase 1, single-site, randomized (1:1), open label trial

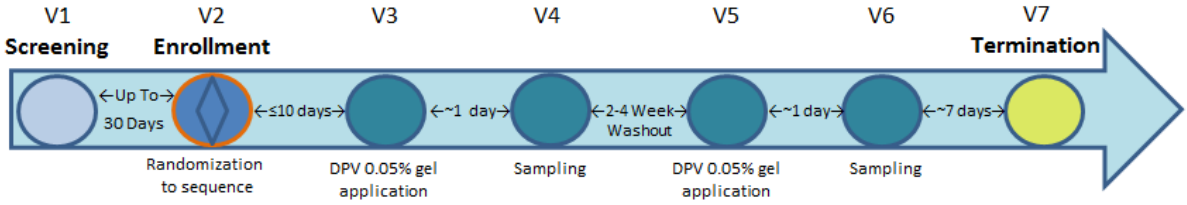
Study Duration: Approximately 1 month of follow-up per participant is planned with a projected accrual period of 6-8 months. The total duration of the study will be approximately 8-10 months.

Study Products: Dapivirine (DPV) gel 0.05%, 2.5 g (applicator-only phase); up to 10 g (coital simulation device phase)

Study Regimen:

	N	Period 1	Washout ~2-4 weeks	Period 2
Sequence A	8	One dapivirine gel applicator (2.5 g) administered into rectum		Up to 10 g administered into rectum via coital simulation device
Sequence B	8	Up to 10 g administered into rectum via coital simulation device		One dapivirine gel applicator (2.5 g) administered into rectum

Figure 1: MTN-033 Study Visit Schedule



Primary Objective:

Pharmacokinetics

- To characterize the systemic and compartmental pharmacokinetics of dapivirine 0.05% gel applied rectally by two different methods

Primary Endpoint:

Pharmacokinetics

- Dapivirine concentrations
  - Rectal fluid
  - Plasma
  - Rectal mucosal tissue homogenates

Secondary Objectives:

Safety

- To assess the safety profile of dapivirine gel administered rectally via HTI vaginal applicator, and with a coital simulation device

Acceptability

- To identify product attributes considered likely to challenge and/or facilitate future sustained use of dapivirine 0.05% gel when applied rectally by participants

Secondary Endpoints:

Safety

- Grade 2 or higher AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 2 and 3 (Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).

Acceptability

- Product attributes considered likely to challenge and/or facilitate future sustained use by participants

Exploratory Objectives:

***Ex Vivo* Efficacy**

- To assess the preliminary (*ex vivo)* efficacy of dapivirine 0.05% gel formulation

Biomarkers of Mucosal Safety

- To evaluate the mucosal immunotoxicity of dapivirine 0.05% gel formulation when applied rectally

Exploratory Endpoints:

***Ex Vivo* Efficacy**

- Changes in laboratory-applied HIV-1 replication as measured by p24 levels in colorectal explant supernatant obtained from biopsies collected after dapivirine 0.05% gel application

Biomarkers of Mucosal Safety

- Rectal microbiome
- Rectal histology
- Rectal proteome
- Rectal transcriptome

1 KEY ROLES

1.1 Protocol Identification

Protocol Title:	An Open Label Randomized Phase 1 Pharmacokinetic Study of Dapivirine Gel Administered Rectally to HIV-1 Seronegative Adults
Protocol Number:	MTN-033
Short Title:	Rectal PK Study of Dapivirine (DPV) Gel
Date:	December 8, 2017

1.2 Funding Agencies, Sponsor and Monitor Identification

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2 INTRODUCTION

2.1 Background of Rectal Microbicide Research and Study Rationale

Microbicides are products that are designed to be applied to the vaginal or rectal mucosa with the intent of preventing the acquisition of sexually transmitted infections (STIs) including the human immunodeficiency virus (HIV).[1] While the original impetus for vaginal microbicide development was to provide women with options for HIV prevention in settings where their partners were unwilling to use condoms for penile-vaginal intercourse, there is recognition that rectal microbicides are needed for men and women who practice receptive anal intercourse (RAI).

RAI is associated with the highest probability for sexual acquisition of HIV infection. Unprotected RAI is the sexual behavior with the highest per act risk of HIV acquisition conferring approximately 10 to 20 times more risk than unprotected receptive vaginal intercourse.[2, 3] Globally, transgender women and men who have sex with men (MSM) are 19 times more likely to be living with HIV compared with the general population.[4, 5]

The preclinical safety studies and clinical trials performed to date support the favorable safety profile and tolerability of microbicide dapivirine dosage forms.[6] The highest daily dose of dapivirine delivered from a vaginal gel to date (approximately 1250 µg/day) is 280 times lower than the maximum tolerated single dose for oral dapivirine (350 mg) and 480 times lower than the maximum tolerated multiple dose for oral dapivirine (300 mg twice a day for 14 days).[6] The same dose of dapivirine gel (2.5 g of dapivirine 0.05% gel = 1250 µg) is proposed for rectal administration.

Multiple gel formulations of dapivirine have been developed for vaginal use. Dapivirine Gel 4759 (Gel 4759) is the gel formulation planned for this trial. The Gel 4759 is highly viscous and opaque. Dapivirine 0.05% gel has an osmolality of approximately 870 mOsm/kg, similar to the safe and acceptable reduced glycerin 1% tenofovir formulation that was used in MTN-007, which had an osmolality of approximately 850 mOsmol/kg (additional information regarding the MTN-007 study is available at www.mtnstopshiv.org/studies). Please refer to Section 2.4.1 for further evidence of safety and acceptability of dapivirine gel.

MTN-033 will evaluate the pharmacokinetics (PK) of dapivirine administered rectally using an applicator and with a coital simulation device.

2.2 Dapivirine Gel

2.2.1 Description

NNRTIs bind to the HIV reverse transcriptase (RT) enzyme preventing viral replication and consequently production of infectious virus. The primary ingredient of dapivirine gel is water, with hydroxyethylcellulose (HEC) and polycarbophil used as thickening agents. Other ingredients of the gel include methyl- and propylparaben, as preservatives,

propylene glycol as solvent, and sodium hydroxide for pH adjustment. The excipients contained in the drug product formula are United States Pharmacopoeia (USP) grade components (e.g., propylene glycol) with a history of use in currently approved vaginal products.[6]

Table 1: Dapivirine Gel 4759, 0.05%, 2.5 g Formulation[6]

Name	Quality Standard	Function	% Composition/Dose (dose = 2.5 g gel [2.5 mL])
Dapivirine	Manufacturer's Certificate of Analysis	Active pharmaceutical ingredient (API)	0.05
Purified water	USP	Solvent	90.99
HEC	National Formulary (NF)	Thickening/binding agent	3.50
Polycarbophil	USP	Thickening agent	0.20
Propylene Glycol	NF	Solvent	5.00
Methylparaben	NF	Preservative	0.20
Propylparaben	NF	Preservative	0.05
Sodium hydroxide	NF	pH adjustment	0.01

2.2.2 Strength of Study Product

The dapivirine gel strength proposed for use in MTN-033 is 0.05%.

2.3 Non-Clinical Studies of Dapivirine Gel

2.3.1 Virology and Pharmacology

Anti-HIV-1 Activity

The activity of dapivirine against wild-type (wt) 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, with 50% effective concentration (EC_{50}) values ranging from 0.3 ng/mL (0.9 nM) against laboratory isolates to <33 ng/mL (<100 nM) for 80% of HIV-1 isolates encoding one or more known NNRTI resistance mutations. The anti-HIV activity was also confirmed in an *ex vivo* model of human cervical explant cultures and a humanized severe combined immunodeficient (hu-SCID) mouse model.[7,8] Further, studies have been performed with both ectocervical and colonic explant tissues.[9] Dapivirine proved effective at blocking HIV infection in both tissue types.

Resistance

A panel of recombinant viruses was constructed from clinical isolates derived from different geographical origins, representing strains from HIV-1 group M subtypes A, B, C, D, F and H as well as circulating recombinant forms: CRF01_AE, CRF02_AG, CRF05_DF and HIV-1 group O. All group M viruses tested were sensitive to dapivirine with EC_{50} values below 1.0 ng/mL and fold change in EC_{50} values below 4. Eight of the group M viruses carried mutations in the RT coding region at positions associated with NNRTI resistance (positions 98, 101, 106, and 179). The group O virus tested

(V029524) naturally harbored amino acids at positions 98 (G), 179 (E) and 181 (C), which are associated with NNRTI resistance in HIV-1 strains from group M. This virus displayed significantly reduced sensitivity to nevirapine (NVP) (89-fold change), delavirdine (140-fold change), efavirenz (EFV) (42-fold change), and dapivirine (150-fold change, which is typical of Type O strains treated with NNRTI).[6]

Cross-resistance

In comparison with NVP, delavirdine (DLV), emivirine and EFV, 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 as compared to 56% of the strains for efavirenz.

When tested against 433 clinical isolates with phenotypic resistance to at least one of the NNRTIs NVP, delavirdine, EFV or emivirine, 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.[6]

Spermatozoa Motility

Assays using human semen samples from normal, healthy, male donors showed that dapivirine did not affect the motility of spermatozoa at a concentration of up to 2 mM (659 µg/mL), which exceeded the limit of solubility.[6]

Safety Pharmacology

In a series of preclinical safety pharmacology studies, dapivirine was generally devoid of adverse effects on overt behavior, reflexes and other body functions. Although these studies revealed no cardiovascular effects, there was evidence of an increase in QT interval during the 1- and 6-month oral toxicity studies in dogs. However, this was only seen at ≥30 mg/kg/day at which C_{max} and area under the curve (AUC) values were more than 1600 and 850 times greater, respectively, than the values achieved in women following daily use of dapivirine gels 4750 and 4789.[6]

2.3.2 Pharmacokinetics

Dapivirine

Systemic exposure to dapivirine was low following vaginal administration of dapivirine gels to rabbits.[6] Much higher systemic exposures were obtained in single-dose oral and subcutaneous toxicity studies in mice and rats, and in repeat dose oral toxicity studies in rats, dogs and monkeys. The free fraction of dapivirine in plasma was 0.19-0.34% in the male rat, 0.18-0.39% in the female rat, 0.21-0.22% in the dog and 0.15% in humans. In rats, tissue to plasma AUC_{0-24} ratios following a single oral dose were 11 in liver, 7-8 in lung, kidney and adrenals, about 4 in spleen and lymph nodes, and 2-3 in brain, heart and muscle. Plasma/tissue equilibrium was rapid, and there was no undue retention of dapivirine in tissues. Following a single oral or vaginal dose of ^{14}C-dapivirine, absorption and distribution of drug-related material to the tissues was moderate in non-pregnant and slow in pregnant female rats. Vaginal dosing did not result in greater

distribution to the reproductive tissues (except the vaginal wall) than oral dosing. For virtually all tissues, maximal concentrations after vaginal dosing were <1% of those after oral dosing. Drug-related material was shown to freely cross the placenta to the fetus. In dogs, dapivirine concentrations following oral administration for 14 days were about 9 times higher in liver and muscle, and about 5 times higher in lymph nodes and brain than in plasma. Preliminary metabolism studies demonstrated the presence of free and conjugated metabolites in rats, dogs, monkeys and humans, but the molecular structures have not been elucidated. There was evidence of extensive cytochrome P450 (particularly CYP3A4) mediated metabolism.[6]

2.3.3 Toxicology

General Toxicity

The gel formulation to be used in this trial was evaluated in a study in rabbits in which dapivirine concentrations of 0.05%, 0.2%, and 0.5% (w/w) were administered rectally once daily for 14 days using a dose volume of 1 mL. Three animals died or were killed prematurely during the study but none of the deaths were attributed to treatment. The no observable adverse effect level (NOAEL) was considered to be 0.5% (w/w). In addition, this formulation was evaluated in two intravaginal studies in female rats. In a 13-week study in which gels containing 0.2% and 0.5% (w/w) dapivirine were administered intravaginally using a daily dose volume of 0.2 mL, no evidence of local or systemic toxicity was observed. The carcinogenic potential of dapivirine was also evaluated when administered intravaginally at concentrations of 0.05, 0.2 and 0.5% (w/w) using a dose volume of 0.2 mL for 104 weeks. There were no neoplastic or non-neoplastic findings that were attributable to treatment with dapivirine. It was concluded that the NOEL was 0.5%. Furthermore, in other intravaginal studies in rabbits using various formulations of dapivirine gel, there were no significant local or systemic findings following repeat administration at up to 20 mg/mL for 14 days, up to 5 mg/mL for 13 weeks or up to 2 mg/mL for 39 weeks. In studies conducted via the oral route of administration, a “no observed effect level” (NOEL) was not established in the rat. However, the main findings (effects on liver, thyroid, and pituitary) were considered adaptive rather than adverse responses, and therefore the “no observed adverse effect” (NOAEL) was considered to be 20 mg/kg/day. This dosage was also the NOAEL in the dog. At higher dose levels, hepatotoxicity was observed in dogs and slight hematological and clinical chemistry changes were observed in rats. In the guinea pig, dapivirine (2 mg/mL) did not demonstrate any potential to cause contact sensitization when evaluated using a maximization test.[6]

Mutagenicity

Dapivirine was considered to be non-genotoxic based on the results from a range of *in vitro* and *in vivo* mutagenicity assays, including the Ames Test, L5178Y Mouse Lymphoma Test, Human Peripheral Lymphocyte Test, Mouse Micronucleus Test, and Unscheduled DNA Synthesis Test.[6]

Reproductive Toxicity

In rats, some effects on the developing fetus were observed following oral administration at maternally toxic doses (80 and 320 mg/kg) of dapivirine. However,

there were no effects in rats at the maternally non-toxic dose of 20 mg/kg/day, or in rabbits at up to 90 mg/kg. No toxicity to maternal animals or the developing embryo/fetus was seen in embryo-fetal development studies performed via the vaginal route in rats (up to 3.3 mg/mL using a dose volume of 0.2 mL/kg) and rabbits (up to 2 mg/mL using a dose volume of 1.0 mL).[6]

2.4 Clinical Studies of Dapivirine Gel

To date, 30 Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted: nine trials in which 501 participants used dapivirine gel, ten trials in which 442 participants used dapivirine rings, and 11 trials in which 211 participants used oral dapirivine.[6] In addition, one Phase 1 clinical trial has been conducted in 48 male participants to evaluate the safety and tolerability of dapivirine vaginal gel (Gel 4759) following multiple topical penile exposures.[6] Three Phase 1 clinical trials that evaluated the vaginal film formulation of dapivirine in 81 women have been conducted.[10-12] Additionally, two Phase III trials (IPM 027 [The Ring Study] and MTN-020 [ASPIRE]) evaluating the safety and efficacy of the 25 mg DPV VR Ring-004 (IND 108,743) were recently completed, having enrolled a total of 4588 participants.

In MTN-020 (ASPIRE)[13] there was no significant difference detected between the dapivirine and placebo treatment groups in frequency of the primary safety endpoint, defined as the incidence of any SAE, any Grade 3 or 4 AE, and any Grade 2 AE that was assessed by the investigator as being related to the investigational product (IP). The primary safety endpoint was observed in 180/1313 (14%) of the dapivirine VR arm compared to 186/1316 (14%) in the placebo arm (P=0.80 for the overall comparison by chi-square test). The DPV VR resulted in a 27% (95% CI: 1-46%, p=0.05) relative reduction in HIV-1 incidence overall, 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, and a 56% (95% CI: 31-71%, p<0.001) reduction in a post-hoc analysis among women older than 21 years of age. In IPM 027 (The Ring Study)[14] no clinically significant differences in the frequency of treatment emergent adverse events between the DPV and placebo groups were detected. 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.

2.4.1 Safety

<u>Dapivirine Gel 4759</u>
Three trials have evaluated the safety of the planned gel for this trial, Gel 4759. IPM 020 evaluated the safety and PK of Gel 4789 and Gel 4759 in healthy, HIV-negative women who used the gel for a period of 12 weeks. The safety of Gel 4759 was further assessed in IPM 014A in healthy, HIV-negative, sexually active women who used the gel for a period of 6 weeks. Maximum exposure (days) to the gels ranged from 7 days to 84 days during these trials.

Across the two completed Dapivirine Gel 4759 trials (IPM 014A and IPM 020), of the 184 participants who were assigned to Dapivirine Gel 4759, 73% (133/184) reported a treatment-emergent adverse event (TEAE). In the placebo arms, 77% (139/181) of the participants reported a TEAE. The cumulative incidence of TEAEs (which occurred in ≥ 5% of participants in any group of the respective trials) were similar across dapivirine gel and placebo treatment groups apart from vulvovaginal pruritus which occurred at a frequency of 7.6% across dapivirine vaginal gel groups and 4.4% across placebo groups.[6]

IPM 020 was a double-blind, randomized, placebo-controlled Phase 1/2 expanded safety study conducted in the USA. The trial enrolled 128 healthy, sexually active, HIV-negative women to assess the safety of Dapivirine Gel 4759, 0.05% 2.5g and Dapivirine Gel 4789, 0.05% 2.5g as compared to the HEC-based Universal Placebo gel. Three serious adverse events (SAEs) were reported during the trial, one by a participant in the Dapivirine Gel 4759 group and two by participants in the Universal placebo gel group. In the Gel 4759 group, one woman was reported with Grade 3 (severe) breast cellulitis. In the Universal placebo gel arm, one woman was reported with Grade 3 abdominal pain of unclear origin and one woman with Grade 3 asthma. None of these events were assessed by the Investigator as related to product use. Two TEAEs resulted in early trial discontinuation of two participants, both from the Dapivirine Gel 4759 group: worsening of a cervicovaginal human papillomavirus (HPV) infection that was reported by the Investigator as Grade 1 (mild), and Grade 1 (mild) hypersensitivity (reported as an allergic response; symptoms reported included vaginal burning, itching and erythema); both events were regarded by the Investigator as probably related to IP. In the placebo gel group, one woman experienced a mild (Grade 1) ulcer on the clitoral hood and discontinued gel use permanently; however, she completed all trial visits. The event was regarded by the Investigator as possibly related to the placebo gel.[6]

In addition to IPM 020, the safety of Gel 4759 was also tested in IPM 014A, conducted in 280 healthy, sexually active, HIV-negative women in South Africa, Rwanda, Malawi and Kenya.[15] IPM 014A was a double-blind, randomized, placebo-controlled Phase 1/2 study to evaluate the safety and acceptability of Dapivirine Gel 4759, 0.05%, 2.5g, administered daily over a 6-week period. The trial was conducted using daily monitored adherence. No SAEs were reported and no participants were discontinued from the trial. Additionally, there were no permanent discontinuations from dapivirine or placebo gel use due to TEAEs during the trial.

In addition to the safety trials performed in women for Gel 4759, one trial (MTN-012/IPM 010) was conducted in male participants to assess the safety and tolerability of the gel.[16] The study was conducted in 48 healthy, HIV-uninfected, adult males, 24 of whom were circumcised and 24 were uncircumcised. Participants self-applied the gel to the penis once daily over a 7-day period. Topical seven-day penile application of dapivirine 0.05% gel was locally and systemically safe, was acceptable to male participants, and resulted in systemic exposure to the drug. There were no Grade 2 genitourinary adverse events (AEs) in 47 participants completing the final clinic visit. There were 13 AEs reported; all were Grade 1 except one Grade 2 corneal laceration unrelated to

study product. No deaths, SAEs or discontinuations due to TEAEs were reported during the study.

MTN-026 is a planned trial evaluating Gel 4759 and is anticipated to begin enrollment in Q3 2017. MTN-026 will be the first clinical trial to collect safety and PK data on the rectal application of dapivirine gel (0.05%) in a cohort of HIV-uninfected adults. MTN-026 is a Phase 1, randomized, double-blind, multi-site, placebo-controlled trial designed to evaluate the safety and PK of dapivirine gel (0.05%) when administered rectally to healthy men and women. MTN-026 will enroll a total of approximately 27 evaluable participants between the ages of 18 and 45 years (inclusive). Participants will be randomized to receive either a single dose of dapivirine gel (0.05%) or universal HEC placebo gel rectally, followed by 7 daily doses of the same product to be administered under direct observation in the clinic. Specimens will be collected at multiple time points to assess drug concentrations, HIV explant infection and mucosal safety. Complete safety data from MTN-026 will not be available prior to implementation of MTN-033, however preliminary blinded safety data will be reviewed in an ongoing basis by the MTN-026 PSRT and any concerning findings would trigger a MTN-026 Study Monitoring Committee review prior to initiation of MTN-033.

Other Dapivirine Gels

Dapivirine Gel 001 and 002

Vaginal application of Gel 001 and 002 were found to be well-tolerated by healthy participants. Details regarding TEAEs are summarized along with other safety data in Table 2. Additional information can be found in the IB.[6]

Dapivirine Gels 4750 and 4789

A similar formulation (Gel 4750) was studied in IPM 012. Gel 4750 contained dapivirine drug substance, purified water, HEC, Vitamin E TPGS, polycarbophil, propylene glycol, methyl paraben, and sodium hydroxide. Gel 4750 and the gel being tested in this study, Gel 4759 are essentially the same except 4750 included the Vitamin E TPGS (dispersing agent, 0.50).[6] In IPM 012, the safety and PK of two formulations of dapivirine vaginal gel were compared with the HEC-based Universal Placebo gel in 36 healthy, HIV-negative, sexually abstinent women 18 to 40 years of age.[17] This Phase 1, randomized, double-blind, placebo-controlled trial was conducted at one research center in Belgium. Women were randomized in a 1:1:1 ratio to once daily applications of Gel 4750 (0.05%, 2.5 g), Gel 4789 (0.05%, 2.5 g), or placebo gel for 11 days (Day 1 followed by a 3-day washout period and then for 10 consecutive days, Days 5-14). There were no SAEs or discontinuations due to TEAEs in the trial. Most subjects (83-100%) in each group had at least one TEAE during the trial. Headache was the event that occurred most often; 42-67% of subjects in the dapivirine gel groups and 42% of subjects in the placebo gel group reported at least one headache. For most subjects with headaches (13/18; 72%), the event was assessed as possibly related to the investigational product.

All but two TEAEs were assessed as Grade 1 (mild). One subject in the Gel 4789 group had a Grade 2 (moderate) headache assessed as possibly related to the investigational product, and a different subject in the same group had Grade 2 pyrexia assessed as not

related to the investigational product. Thirty-four percent (36/105) of TEAEs were assessed as possibly related to the investigational product, and one subject in the Gel 4789 group had two episodes of vulvovaginal pruritus that were assessed as probably related. Among participants using Gel 4750 (the gel formulation most similar to the one planned for this trial), the other TEAEs deemed related to the gel included malaise (1/12) and cervix erythema (1/12).[17]

Gel 4789 was also tested in IPM 020 as described above. In that study, two TEAEs led to the permanent discontinuation of gel use in participants assigned to the Gel 4789, who in return withdrew their consent due to these TEAEs. One participant was reported with vulvovaginal pruritus (Grade 2) which was assessed by the Investigator as probably not related to IP. Another participant was reported with vulvovaginal discomfort (Grade 2) and vulvovaginal pruritus (Grade 2) which were both assessed by the Investigator as probably related to IP.[6]

Summary of Dapivirine Gel Clinical Data

TEAEs with incidence in all of the completed dapivirine trials involving HIV-negative participants are summarized in Table 2 below:

Table 2: Treatment-Emergent AEs from Dapivirine Gels Across Vaginal Gel Trials* (Regardless of Causality)[6]

MedDRA SOC/Preferred Term	Gel-001**, Gel-002, Gel 4750, Gel 4789 N=295	Gel 4759*** N=184
	N (%)	N(%)
Metrorrhagia	28 (9.5)	41 (22.3)
Headache	45 (15.3)	13 (7.1)
Vaginitis Bacterial	38 (12.9)	13 (7.1)
Vaginal Candidiasis	18 (6.1)	10 (5.4)
Abdominal Pain Lower	17 (5.8)	5 (2.7)
Vulvovaginal Pruritus	7 (2.4)	14 (7.6)
Upper Respiratory Tract Infection	2 (0.7)	13 (7.1)
Blood Urine Present	14 (4.7)	0 (0.0)
Gynaecological Chlamydia Infection	6 (2.0)	7 (3.8)
Nasopharyngitis	10 (3.4)	3 (1.6)
Neutropenia	12 (4.1)	1 (0.5)
Oligomenorrhoea	8 (2.7)	5 (2.7)
Influenza	11 (3.7)	1 (0.5)
Urinary Tract Infection	6 (2.0)	6 (3.3)
Vaginal Discharge	9 (3.1)	3 (1.6)

* For comparisons across gel trials it should be noted that these trials were conducted in different populations in Africa, Europe and the USA, and with different gel formulations.
** To compare results with those obtained for trials using Gel 002, Gel 4750, Gel 4789, and Gel 4759, only data for HIV-1 negative participants (Part A and Part B Group 1) are included here.
***Gel planned for MTN-033

Oral Dapivirine

There have been 11 oral administration trials in which a total of 211 participants have been dosed with dapivirine. The maximum tolerated dose established was 350 mg for a single dose, and for multiple doses, 300 mg twice a day for 14 days. There were no

deaths during clinical trials of oral dapivirine, and no trials were stopped for safety reasons. A total of 10 participants stopped dapivirine treatment prior to trial completion for safety reasons, six of whom stopped due to a clear dose dependent increase in central nervous system (CNS) and gastrointestinal TEAEs, thereby establishing the maximum tolerated dose at 300 mg twice a day. These TEAEs resolved within 1-2 days after discontinuation of use of oral dapivirine. One of the discontinuations was classified as an SAE, with hospitalization due to elevated liver function tests. This participant was also infected with hepatitis C virus. The only other SAE noted in these trials was a hospitalization due to a bicycle accident.[6]

2.4.2 Pharmacokinetics

MTN-012/IPM 010 (Gel 4759)
Plasma was collected for PK by blood draw at the final clinic visit. Dapivirine was detectable in all 23 dapivirine arm study participants (one participant failed to present to the clinic for the final study visit). On average, the circumcised participants' dapivirine concentrations were 54% of those in uncircumcised participants ($p = 0.07$).[16]

IPM 012 (Gels 4750 & 4789)
Dapivirine concentrations were measured in cervicovaginal fluids and plasma on Days 1, 2, 5, 9, 11, 14-17, 19, 21, and 24. Systemic absorption of dapivirine was low. C_{max} and $AUC_{0\text{-}24h}$ values for dapivirine in plasma were slightly higher for Gel 4750 than Gel 4789 on Days 1 and 14; however, the differences did not achieve statistical significance. For both gels, Day 14 values were 2- to 4-fold higher than values on Day 1. T_{max} was variable; on Day 1 the mean was 23.5 hours for both gels, whereas by Day 14 means were 10-12 hours. Terminal half-life was much longer in plasma (73-90 hours) than in cervicovaginal fluids (15-17 hours).[17]

FAME-02B (Gel 4759)
FAME-02B was a Phase 1, two-arm, randomized crossover study conducted in Baltimore, MD that compared the multi-compartment PK and *ex vivo* PD characteristics between the Gel 4579 and vaginal film formulations of dapivirine.[12] Ten healthy, HIV-uninfected women ages 18-45 years old were randomized (1:1) to receive either a single dose of dapivirine Gel 4579 followed by a single dose of dapivirine vaginal film one week later, or to receive a single dose of vaginal film followed by a single dose of Gel 4579 a week later. PK was assessed in blood, cervical tissue and CVF, while PD was assessed via HIV tissue explant challenge. No SAEs were recorded, and 75% (18 of 24) of AEs were Grade 1. No AEs were determined to be related to study product, and the AEs that occurred during the dosing intervals were evenly distributed between the two study products (10 with film and 11 with gel). There were no statistically significant PK or PD differences between the film and gel study products for plasma, CVF or tissue, except for a greater dapivirine concentration in mid-vaginal CVF for film as compared to gel. CVF DPV concentrations 5 hr after dosing were greater than tissue concentrations, and both were greater than plasma concentrations. Plasma half-life was significantly greater than estimated maximum half-life for both CVF and cervical tissue, which were similar to each other.

2.5 Other Clinical Studies of Dapivirine

Several other studies of the safety and/or effectiveness of dapivirine for HIV prevention have been completed, are ongoing or are in development. These studies are included in Table 3 below.

Table 3: Clinical Studies of Dapivirine

Trial Number	Description	Country	Gel-4759 (2.5 g)	Gel-4789 (2.5 g)	Gel-4759 & Gel-4789 (2.5 g)	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25mg)	Ring-004 matrix** (25mg)	Ring-004 matrix*** (25mg)	Ring-102 matrix** (200mg DPV/ 320 mg LNG)	Ring-104 matrix** (200 mg)	Placebo Ring or Gel
IPM 001	Safety and PK in women; 7 days	Belgium	--	--	--	12	--	--	--	--	--	--	12 (cross-over)
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 014A	Safety and acceptability in women; 42 days	Kenya, Rwanda, South Africa, Malawi	141	--	141	--	--	--	--	--	--	--	139
IPM 014B[15]	Safety and acceptability in women; 42 days	South Africa	--	50	50	--	--	--	--	--	--	--	50
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 020	Safety; 84 days	United States	43	43	86	--	--	--	--	--	--	--	42
IPM 024	Safety and PK in women; 28 days	Belgium	--	--	--	--	--	--	8	--	--	--	8

Trial Number	Description	Country	Gel-4759 (2.5 g)	Gel-4789 (2.5 g)	Gel-4759 & Gel-4789 (2.5 g)	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25mg)	Ring-004 matrix** (25mg)	Ring-004 matrix*** (25mg)	Ring-102 matrix** (200mg DPV/ 320 mg LNG)	Ring-104 matrix** (200 mg)	Placebo Ring or Gel
IPM 027	Safety and efficacy; 2 years	South Africa, Uganda	--	--	--	--	--	--	1307	--	--	--	652
IPM 028	Safety and PK in women, Drug-drug interaction; 112 days	Belgium	--	--	--	--	--	--	36	--	--	--	--
IPM 032	Open label; continued safety and adherence; 1 year	South Africa, Uganda	--	--	--	--	--	--	1400	--	--	--	--
IPM 034	Safety and PK in women; 7 to 84 days	Belgium	--	--	--	--	--	--	40	--	--	--	--
IPM 035	Menses and tampon use; 28 days	Belgium							32				
IPM 036	Drug-drug interaction with clotrimazole; 28 days	Belgium							36				
MTN-012/IPM 010	Male tolerance; 7 days	United States	24	--	24	--	--	--	--	--	--	--	--
MTN-013/IPM 026[18]	Safety and PK in women; 52 days	United States	--	--	--	--	--	--	--	12	--	--	12
MTN-020	Safety and efficacy in women; median 1.6 years	Malawi, South Africa, Uganda, Zimbabwe	--	--	--	--	--	--	1313	--	--	--	1316

Trial Number	Description	Country	Gel-4759 (2.5 g)	Gel-4789 (2.5 g)	Gel-4759 & Gel-4789 (2.5 g)	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25mg)	Ring-004 matrix** (25mg)	Ring-004 matrix*** (25mg)	Ring-102 matrix** (200mg DPV/ 320 mg LNG)	Ring-104 matrix** (200 mg)	Placebo Ring or Gel
MTN-023/IPM 030	Safety in adolescent females; 24 weeks	United States	--	--	--	--	--	--	73	--	--	--	23
MTN-024/IPM 031	Safety in post-menopausal women; 12 weeks	United States	--	--	--	--	--	--	72	--	--	--	24
MTN-025	Safety and adherence in women; 1 year	Malawi, South Africa, Uganda, Zimbabwe	--	--	--	--	--	--	(Former MTN-020 participants)	--	--	--	--
MTN-026	Safety and PK of rectally applied gel in men and women	United States, Thailand	27	--	--	--	--	--	--	--	--	--	--
MTN-029/IPM 039	PK in lactating women; 14 days	United States	--	--	--	--	--	--	16	--	--	--	--
MTN-030/IPM 041	Safety and PK in women; 14 days	United States	--	--	--	--	--	--	--	--	12	12	--
MTN-034/IPM 045 (Not yet enrolling)	Safety and adherence in adolescent & young adult females; 24-48 weeks	Kenya, South Africa, Zimbabwe	--	--	--	--	--	--	300	--	--	--	--
TOTAL participants			**235**	**93**	**301**	**12**	**18**	**8**	**3341**	**12**	**12**	**12**	**2441**

*Tin-catalyzed matrix ring
**Platinum-catalyzed matrix ring
***Platinum-catalyzed matrix ring Ring-004, but did not contain the silicone oil MED360 - only silicone elastomer and the API(s).

More information regarding safety and PK can be found in the IB.[6]

2.6 Study Hypothesis and Rationale for Study Design

2.6.1 Study Primary Hypothesis

It is hypothesized that when up to 10 g of dapivirine gel is applied using a rectal coital simulation device, the rectal and systemic dapivirine PK levels will be lower than when applied using the standard microbicide delivery HTI applicator which holds 2.5 g of gel.

2.6.2 Rationale for Study Design

Rectal microbicides are needed for individuals at risk of acquiring HIV infection through receptive anal intercourse (RAI). It is important to expand the rectal microbicide pipeline though the addition of products from different classes such as dapivirine (a non-nucleoside reverse transcriptase inhibitor [NNRTI]). As most RAI is facilitated by the use of a lubricant (such as digital application to the perianal area, penis, and/or the rectal area prior to intercourse, or the use of pre-lubricated condoms), the use of a rectal gel microbicide has the potential advantage of both familiarity and context. There is considerable community desire to use rectal microbicides as lubricants, but there are no PK data to support this practice.[6, 19, 20]

Rationale for the Dosing and Pharmacokinetic Sampling Schedule

Intermittent dosing of rectal gel associated with sexual activity may be a more feasible strategy for long-term use. Data are needed on the safety, acceptability, and PK of this dosing schedule in at-risk men and transgender women.

MTN-033 participants will administer 2.5 g of DPV 0.05% using an applicator and up to 10 g of DPV 0.05% using a coital simulation device. (Note: 10 g of DPV 0.05% represents 5000 µg DPV, which is 70 times lower than the maximum tolerated single dose for oral dapivirine (350 mg) and 120 times lower than the maximum tolerated multiple dose for oral dapivirine (300 mg b.i.d. for 14 days)). Participants will be randomized to sequence. This crossover design allows for the comparison of PK data within individuals who have been exposed to both a single dose (2.5 g) of dapivirine gel applied rectally using an applicator and up to 10 g of product while using a coital simulation device which may be representative of episodic or coital dosing.

The ideal coital-dosing regimen for dapivirine gel applied rectally is not yet known. The selection of the proposed dose for use during the coital simulation device insertion phase (up to 10 g) is consistent with a growing literature regarding lubricant use practices among MSM in the US and elsewhere, findings that contribute toward a profile of 'typical' lubricant use in RAI. A study[21] conducted from 2007-2010 recruited 168 HIV seronegative, racially/ethnically diverse, low-income MSM (mean age 35.5 years; range not provided) residing in Los Angeles, California, USA who practice RAI and among whom substance abuse was common. At baseline and follow-up visits, participants who reported using lubricant were queried via computer assisted self-interview (CASI) about their last sexual event with up to 3 recent partners, including the amount of commercial lubricant used and number of re-applications. Nearly two-thirds (62.8%) reported using 10 mL (2 teaspoons) or less in their most recent RAI encounter (see Table 4).

Table 4: Lubricant Practices

Los Angeles, CA, USA N=289 Sexual Events	
How much lubricant was used?	
5 mL or less (1 teaspoon)	26%
About 10 mL (2 tsp)	36.8%
About 15 mL (3 tsp)	21.7%
About 30 mL (6 tsp)	10.4%
About 50 mL (10 tsp)	5.2%
How many times was lubricant reapplied?	
Never	26%
Once	27.3%
Twice	29.4%
Three or more times	17.3%

Another study[22] assessed rectal lubricant use in 1995-1996 among 307 HIV seropositive and -negative Latino MSM residing in New York City (mean age 31; range 18-55). Of those reporting lubricant use (N=273) who provided responses, 94% used at least 5 mL (1 tsp) per encounter, about a third (35%) used ≤10 mL, and nearly two thirds (60%) used ≤15 mL.

Additionally, a 2008 study[23] that recruited 843 HIV seropositive and –negative Peruvian MSM aged 18 and older (61% aged 18-29) assessed lubricant use via CASI. While not queried about the amount of lubricant used, 85% of participants who reported having used lubricant during RAI with their most recent partner reported applying it 1-2 times (82% applied it prior to sexual contact).

Rationale for the Selection of the Proposed Coital Simulation Device

The artificial phallus proposed for use as a coital simulation device in this protocol is similar in size and approximate shape to an erect penis. Since all participants will have a history of engaging in RAI, the use of the device itself does not pose any risk beyond what the participants experience as part of their activities of daily life. Researchers at Johns Hopkins University have used this device extensively in prior clinical studies, including in several studies under IND, with only one AE attributable to the device, a brief episode of mild rectal bleeding attributed to the IV catheter in the urethral position which will not be used in the MTN-033 study. Safety of the device in over 100 separate uses has been reported in 6 peer-reviewed papers.[24-29] It is important to note that this specific device was selected by former participants who used a previous coital simulation device that they had found to be unacceptable. Participants will be counseled to stop insertion of the device if they experience unusual discomfort or pain. Additional details about the coital simulation device may be found in the MTN-033 SSP Manual.

3 OBJECTIVES

3.1 Primary Objective

Pharmacokinetics

- To characterize the systemic and compartmental pharmacokinetics of dapivirine 0.05% gel applied rectally by two different methods

3.2 Secondary Objectives

Safety

- To assess the safety profile of dapivirine gel administered rectally via HTI vaginal applicator, and with a coital simulation device

Acceptability

- To identify product attributes considered likely to challenge and/or facilitate future sustained use of dapivirine 0.05% gel when applied rectally by participants

3.3 Exploratory Objectives

***Ex Vivo* Efficacy**

- To assess the preliminary (*ex vivo*) efficacy of dapivirine 0.05% gel formulation

Biomarkers of Mucosal Safety

- To evaluate the mucosal immunotoxicity of dapivirine 0.05% gel formulation when applied rectally

4 STUDY DESIGN

4.1 Identification of Study Design

MTN-033 is a Phase 1, single-site, randomized (1:1), open label trial.

4.2 Summary of Major Endpoints

Primary Endpoint:

Pharmacokinetics

- Dapivirine concentrations
  - Rectal fluid
  - Plasma
  - Rectal mucosal tissue homogenates

Secondary Endpoints:

Safety

- Grade 2 or higher AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 2 and 3 (Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).

Acceptability

- Product attributes considered likely to challenge and/or facilitate future sustained use by participants

Exploratory Endpoints:

***Ex Vivo* Efficacy**

- Changes in laboratory-applied HIV-1 replication as measured by p24 levels in colorectal explant supernatant obtained from biopsies collected after dapivirine 0.05% gel application

Biomarkers of Mucosal Safety

- Rectal microbiome
- Rectal histology
- Rectal proteome
- Rectal transcriptome

4.3 Description of Study Population

The study population will consist of HIV-uninfected men who have sex with men (MSM) and transgender women who have sex with men who are 18 years or older and meet the criteria outlined in Sections 5.2 and 5.3.

4.4 Time to Complete Accrual

The time to complete accrual is anticipated to be approximately 6-8 months.

4.5 Study Groups

MTN-033 will enroll approximately 16 evaluable participants randomized (1:1) to sequence of dapivirine gel (0.05%) application.

4.6 Expected Duration of Participation

Each participant will be on study for approximately one month. The total duration of the study will be approximately 8-10 months.

4.7 Site

Site selected by the MTN Executive Committee.

5 STUDY POPULATION

5.1 Selection of the Study Population

The inclusion and exclusion criteria in Sections 5.2 and 5.3 will be used to ensure the appropriate selection of study participants.

5.1.1 Recruitment

Participants will be recruited from a variety of sources, including outpatient clinics, universities and community-based locations. Recruitment materials will be approved by site Institutional Review Boards (IRBs) prior to use.

5.1.2 Retention

Once a participant is enrolled and randomized in MTN-033, the study site will make every effort to retain the participant in follow-up to minimize possible bias associated with loss-to-follow-up. A retention rate of 95% will be targeted. The site will be responsible for developing and implementing local Standard Operating Procedures (SOPs) to target and ensure high rates of retention.

5.2 Inclusion Criteria

Individuals who meet the following criteria are eligible for study inclusion:

1. Men and transgender women who are 18 years or older at Screening, verified per site SOP
2. Able and willing to provide written informed consent
3. HIV-1/2 uninfected at Screening and Enrollment, per applicable algorithm in Appendix II and willing to receive HIV test results
4. Able and willing to provide adequate locator information, as defined in site SOP
5. Available to return for all study visits and willing to comply with study participation requirements
6. In general good health at Screening and Enrollment, as determined by the site IoR or designee
7. At Screening, history of consensual RAI at least once in the past year per participant report

8. Willing not to take part in other research studies involving drugs, medical devices, genital or rectal products, or vaccines for the duration of study participation (including the time between Screening and Enrollment)

9. Willing to abstain from receptive anal intercourse (RAI), receptive oral anal stimulation (i.e., rimming), rectal stimulation via fingers, as well as the insertion of any non-study products into the rectum for 72 hours before and after each study visit

5.3 Exclusion Criteria

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

1. At Screening:
    a) Hemoglobin Grade 1 or higher*
    b) Platelet count Grade 1 or higher*
    c) White blood count Grade 2 or higher*
    d) Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher*
    e) Serum creatinine >1.3× the site laboratory upper limit of normal (ULN)
    f) International normalized ratio (INR) >1.5× the site laboratory ULN
    g) Positive for hepatitis C antibody
    h) Positive for hepatitis B surface antigen
    i) History of inflammatory bowel disease by participant report

    **As per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Corrected Version 2.1, July 2017*

    Note: Otherwise eligible participants with an exclusionary test result (other than HIV, HBV or HCV) can be re-tested during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 30 days of providing informed consent for screening, the participant may be enrolled.

2. Known adverse reaction to latex or polyurethane (ever)

3. Anticipated use of and/or unwillingness to abstain from the following medications during study participation:
    a) Anticoagulant medications
    b) Aspirin (greater than 81 mg/day)
    c) Non-steroidal anti-inflammatory drugs (NSAIDS)
    d) Any other drugs that are associated with increased likelihood of bleeding
    e) Rectally-administered medications or products containing N-9 or corticosteroids
    f) CYP3A inducer(s) and/or inhibitor(s) as specified in the MTN-033 Study Specific Procedures (SSP) Manual
    g) Hormone-replacement therapy in tablet, injectable or gel form

4. Known adverse reaction to any of the components of the study product, applicator or coital simulation device

5. Use of pre-exposure prophylaxis (PrEP) for HIV prevention within 1 month prior to Enrollment, and/or anticipated use and/or unwillingness to abstain from PrEP during trial participation

6. Use of post-exposure prophylaxis (PEP) for potential HIV exposure within the 6 months prior to Enrollment

7. Use of systemic immunomodulatory medications within the 6 months prior to Enrollment, and/or anticipated use during trial participation

8. RAI without a condom and/or penile-vaginal intercourse with a partner who is known to be HIV-positive in the 6 months prior to Enrollment

9. Non-therapeutic injection drug use in the 12 months prior to Enrollment

10. Participation in research studies involving drugs, medical devices, genital or rectal products, or vaccines within 30 days of the Enrollment Visit

11. Per participant report at Screening, treatment of an anogenital STI (after diagnosis) within the past 3 months

12. At Screening, participant-reported symptoms, and/or clinical or laboratory diagnosis of active anorectal or reproductive tract infection (RTI) requiring treatment per current CDC guidelines (http://www.cdc.gov/std/treatment) or symptomatic urinary tract infection (UTI). Infections requiring treatment include symptomatic Neisseria gonorrhea (GC), Chlamydia trachomatis (CT) infection, syphilis, active herpes simplex virus (HSV) lesions, anogenital sores or ulcers, or symptomatic genital warts, chancroid, trichomoniasis.

    Note: Otherwise eligible participants with an exclusionary UTI may be re-tested during the screening process.

13. At Enrollment, active anorectal infection or RTI requiring treatment per current CDC guidelines (http://www.cdc.gov/std/treatment) or symptomatic UTI. Infections requiring treatment include symptomatic GC, CT, syphilis, active HSV lesions, anogenital sores or ulcers, symptomatic genital warts, trichomoniasis, chancroid.

    Note: HSV-1 or HSV-2 seropositive diagnosis with no active lesions is permitted since treatment is not required.

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

5.4 Co-enrollment Guidelines

As indicated in Sections 5.2 and 5.3, participants must not take part in other research studies involving drugs, medical devices, genital or rectal products, or vaccines after the Screening Visit and while taking part in MTN-033 unless approved by the Protocol Safety Review Team (PSRT). Participation in the following types of studies may be allowed at the discretion of the IoR/designee:

- Participants may take part in ancillary studies if approved by MTN-033 PSRT
- Participants who become infected with HIV may take part in observational and/or interventional studies for HIV-positive persons

Should any participant report concurrent participation in contraindicated studies after enrolling in MTN-033, 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

Sixteen participants will receive dapivirine gel 0.05%, 2.5 g (applicator-only phase) and up to 10 g (coital simulation device phase). The sequence of the method of administration will be randomized to a single dose of dapivirine gel administered via an applicator followed by a single dose of the gel administered via a coital simulation device (Sequence A) or the reverse sequence of methods (Sequence B). There will be a two- to four-week washout period between the methods of administration.

Table 5: Study Product Regimen

	N	Period 1	Washout ~2-4 weeks	Period 2
Sequence A	8	One dapivirine gel applicator (2.5 g) administered into rectum		Up to 10 g administered into rectum via coital simulation device
Sequence B	8	Up to 10 g administered into rectum via coital simulation device		One dapivirine gel applicator (2.5 g) administered into rectum

6.2 Administration

At Visit 3 or 5, based on randomization, participants will insert into the rectum the entire contents of one pre-filled applicator of dapivirine gel in the clinic or participants will apply up to 10 g (the contents of four pre-filled 2.5 g applicators of dapivirine gel) to a coital simulation device and/or to the anus for administration. In the clinic, when the coital

simulation device is used, the dapivirine gel from four applicators (2.5 g each) will be expelled into a weighing cup for an initial weight measurement. When the participant is finished with the device, the unused gel remaining in the weighing cup will be measured to calculate the quantity of gel that the participant chose to use. The coital simulation device will be used for approximately 5 minutes.

Additional details on administration, participant education, and measurement of gel use will be provided in the MTN-033 SSP Manual.

6.3 Study Product Formulation

Dapivirine gel 0.05%, 2.5 g is formulated as an aqueous semi-solid (gel). The primary ingredient is water, with hydroxyethylcellulose and polycarbophil as thickening agents. Other ingredients of the gel include methylparaben and propylparaben as preservatives, propylene glycol as solvent, and sodium hydroxide for pH adjustment. The excipients in the drug product formula are pharmacopoeia grade components that have a history of use in currently approved vaginal products. Dapivirine gel has a pH of 4.7. Each pre-filled applicator will deliver approximately 2.5 g (2.5 mL) of 0.05% dapivirine gel.

Dapivirine gel should be stored at room temperature 25°C (77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F).

6.4 Study Applicator and Coital Simulation Device

MTN-033 will use the HTI pre-filled applicator, the same applicator that has been utilized in other rectal studies, including RMP02/MTN-006, MTN-007, Project GEL, CHARM 01, CHARM 03, and MTN-017 and is planned for use in MTN-026. The applicator is manufactured by HTI Plastics, Lincoln NE, USA, in accordance with HTI's quality assurance procedures and the Good Manufacturing Practices as established by the Food and Drug Administration.

The coital simulation device is made of polyvinyl chloride (PVC) and is phthalate-free. The dimensions of the coital simulation device are 5.8 x 1.7 inches.

6.5 Study Product Supply and Accountability

6.5.1 Study Product Supply

MTN (Pittsburgh, PA) will supply the dapivirine gel prefilled applicators. MTN will ensure the manufacture of dapivirine gel and analyze/release the gel under Good Manufacturing Practices (GMP). Study product will ship directly to the Pharmacist of Record (PoR).

6.5.2 Study Product Accountability

The Clinical Research Site (CRS) Pharmacist of Record (PoR) is required to maintain complete records of the study product received and subsequently dispensed.

6.6 Study Product Dispensing

Following receipt of a written prescription from an authorized prescriber, one pre-filled applicator (2.5 g) or 4 pre-filled applicators (4 x 2.5 g) of study product will be dispensed to study staff on behalf of the participant at each study product administration visit. An authorized prescriber includes the IoR or a licensed clinician directly responsible to the IoR as noted on the United States (US) Food and Drug Administration (FDA) 1572 Form.

6.7 Ancillary Study Supplies

Clinic staff will offer all participants study-provided lubricant to facilitate the insertion of the single rectal applicator only. Each participant will receive a coital simulation device at the beginning of the period when the device will be used.

Study-provided condoms will be offered to participants at all clinic visits.

6.8 Concomitant Medications

Enrolled study participants may use concomitant medications during study participation with the exception of medications and products not permitted per the inclusion and exclusion criteria and listed in Section 6.8.1 below. All concomitant medications reported throughout the course of the study will be recorded in the study database. Concomitant medications include all prescription medications, over-the-counter preparations, vitamins, nutritional supplements, and herbal preparations.

6.8.1 Prohibited and Discouraged Medications and Practices

Use of anticoagulants, aspirin (greater than 81 mg/day), non-steroidal anti-inflammatory drugs (NSAIDS), other drugs that are associated with increased likelihood of bleeding other drugs that are associated with increased likelihood of bleeding, CYP3A inducer(s) and/or inhibitor(s), immunomodulatory medications, and hormone-replacement therapy in tablet, injectable or gel form are prohibited. Use of perianally applied topical steroids and other rectally-administered medications, including products containing N-9, are also prohibited.

Should a participant report taking any of the medications noted above (i.e., medications which may increase risk of bleeding, periannaly applied topical steroids, or rectal products containing N-9) within 72 hours prior to a PK sample collection, if possible the visit should be rescheduled within the visit window. If it is determined that rescheduling the visit within the window is not possible, the visit may proceed at IoR discretion after proper participant counseling has occurred. If desired, the IoR may request rapid PSRT consultation to assist in making the determination as to whether or not to proceed with the visit at that time or to reschedule as an interim visit. If the decision is made to reschedule as an interim visit, any missed procedures (including biopsy collection) should be performed during the interim visit.

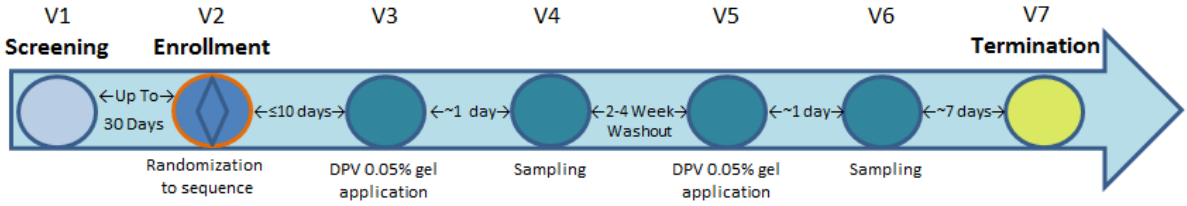
Participants are to abstain from inserting any non-study products into the rectum for 72 hours prior to and following clinic visits. Participants are to abstain from the following for 72 hours before and after biopsy collection and PK sample collection: receptive anal intercourse (RAI), receptive oral anal stimulation (i.e., rimming), rectal stimulation via fingers, as well as the insertion of any non-study products into the rectum. Should a participant report such practices within 72 hours prior to dispensation of product and PK sample collection, dispensation of product and biopsy collection will be performed at IoR discretion.

Finally, use of PrEP for HIV prevention within 1 month prior to Enrollment and during study participation, and use of PEP within 6 months prior to Enrollment and during study participation, is prohibited.

7 STUDY PROCEDURES

An overview of the study visit and evaluations schedule is presented in Appendix I. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures as well as information regarding the study visit windows are provided in the MTN-033 SSP Manual available at http://www.mtnstopshiv.org/studies.

Figure 2: MTN-033 Study Visit Schedule



7.1 Pre-screening

As part of participant outreach and recruitment strategies, study staff can pre-screen potential study participants at either on-site or off-site locations. During these interactions, study staff may explain the study to potential participants and ascertain elements of presumptive eligibility (e.g., willingness to use the study product, willingness to use a coital simulation device, willingness to adhere to the study rules, etc.), to be confirmed at an on-site screening visit. Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants, provided the information is collected in such a manner that it cannot be linked to participant identifiers, unless a waiver is granted from the local IRB. Procedures and documentation will comply with local IRB requirements.

7.2 Screening

A Screening Visit will take place up to 30 days prior to the Enrollment Visit (Day 0). Multiple visits may be conducted to complete all required screening procedures, if necessary. Written informed consent for Screening/Enrollment will be obtained before any screening procedures are initiated. For participants who do not meet the eligibility criteria, Screening will be discontinued once ineligibility is determined.

Note: In the event that a participant is ineligible based upon a behavioral criterion, the behavioral eligibility assessment may be completed in its entirety, so as to avoid socially desirable reporting.

Table 6: Visit 1- Screening Visit

Visit 1-Screening Visit		
Component		**Procedures**
Administrative and Regulatory		• Obtain written informed consent • Assess consent form comprehension • Assign a unique Participant Identification (PTID) number • Assess eligibility • Collect demographic information • Collect locator information • Provide reimbursement • Schedule next visit/contact*
Behavioral/Counseling		• HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol counseling
Clinical		• Collect medical history • Perform physical examination • Perform genital examination • Perform rectal examination • Collect concomitant medications • Treat or prescribe treatment for RTI/UTI, or STIs* • Disclosure of available test results
Laboratory	**Throat**	• Pharyngeal swab for GC/CT
	Urine	• NAAT for GC/CT • Urine dipstick/culture*
	Blood	• CBC with differential and platelets • Chemistries (AST/ALT/Creatinine) • Syphilis serology • HIV-1/2 test • HBsAg • HCV serology • Coagulation (PT/INR)

Visit 1-Screening Visit		
Component		**Procedures**
	Anorectal	• NAAT for GC/CT • HSV 1/2 detection*
Study Product/Supplies		• Offer condoms

* If indicated

7.3 Enrollment (Day 0)

The Enrollment Visit occurs up to 30 days after the Screening Visit.

Table 7: Visit 2- Enrollment Visit

Visit 2- Enrollment Visit		
Component		**Procedures**
Administrative and Regulatory		• Review informed consent/ confirm participant's willingness to participate in study • Assess and confirm eligibility • Review/update locator information • Provide reimbursement • Schedule next visit/contact* • Randomization
Behavioral/Counseling		• HIV pre- and post-test counseling • HIV/STI risk reduction counseling • Protocol counseling • Behavioral assessment
Clinical		• Review/update medical history • Perform physical examination • Perform genital examination • Perform rectal examination • Review/update concomitant medications • Treat or prescribe treatment for RTI/UTI, or STIs* • Disclosure of available test results
Laboratory	**Throat**	• Pharyngeal swab for GC/CT*
	Urine	• Urine dipstick/culture* • NAAT for GC/CT*
	Blood	• HIV-1/2 test • Plasma for archive • Syphilis serology* • CBC with differential and platelets* • Chemistries (AST/ALT/Creatinine)*

Visit 2- Enrollment Visit		
Component		**Procedures**
	Anorectal	• Rectal fluid for microbiome • Rectal enema effluent for PD baseline prior to biopsy collection • Rectal tissue for *ex vivo* challenge • Rectal tissue for histology, transcriptomics, proteomics • HSV 1/2 detection* • NAAT for GC/CT*
Study Product/Supplies		• Offer condoms

* If indicated

7.4 Follow-up Visits

7.4.1 Visit 3- Period 1 Dosing Visit and Visit 5- Period 2 Dosing Visit

Visit 3 - Period 1 Dosing Visit ideally should occur within approximately 10 days of the Enrollment Visit. Visit 5 -Period 2 Dosing Visit ideally occurs 2-4 weeks after Visit 4 - Sampling Visit. The PSRT must be consulted prior to progression into the second dosing period for any participant who has unresolved abdominal, genital, or anorectal AEs of any Grade or unresolved Grade 3 or 4 AEs, regardless of organ system.

Table 8: Visit 3- Period 1 Dosing Visit and Visit 5- Period 2 Dosing Visit

Visit 3- Period 1 Dosing Visit and Visit 5- Period 2 Dosing Visit		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact
Behavioral/Counseling		• Protocol counseling • Behavioral assessment • In-depth interview (IDI)
Clinical		• Review/update medical history • Review/update concomitant medications • Perform rectal examination • Disclosure of available test results • Record/update AEs • Perform targeted physical examination* • Perform genital examination* • Treat or prescribe treatment for RTI/UTI, or STIs*
Laboratory	**Throat**	• Pharyngeal swab for GC/CT*
	Urine	• Urine dipstick/culture* • NAAT for GC/CT*

Visit 3- Period 1 Dosing Visit and Visit 5- Period 2 Dosing Visit		
Component		**Procedures**
	Blood	• Plasma for PK♦ • Chemistries (AST/ALT/Creatinine)* • CBC with differential and platelets* • Syphilis serology*
	Anorectal	• Rectal enema effluent for PK and PD prior to biopsy collection⌂ • Rectal tissue for *ex vivo* challenge⌂ • Rectal tissue for PK⌂ • Rectal fluid for PK⌂ • NAAT for GC/CT* • HSV 1/2 detection*
Study Product/Supplies		• Provision of study product and study product use counseling • Offer condoms • Provision of coital stimulation device* • Provision of study lubricant*

* If indicated. ⌂= Participants will be randomized to provide samples either 1 hour or 4 hours after dose administration
♦= Participants will provide samples at Baseline, 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after dose administration

7.4.2 Visit 4 - Sampling Visit and Visit 6 - Sampling Visit/Early Termination

Visit 4 - Sampling Visit and Visit 6 - Sampling Visit ideally should occur approximately 24 hours after the DPV 0.05% gel application.

Table 9: Visit 4 - Sampling Visit and Visit 6 - Sampling Visit/Early Termination

Visit 4 - Sampling Visit and Visit 6 - Sampling Visit/Early Termination		
Component		**Procedures**
Administrative and Regulatory		• Review/update locator information • Provide reimbursement • Schedule next visit/contact ᴨ
Behavioral/Counseling		• Protocol counseling • HIV pre- and post-test counseling (Required at Visit 6 only) • HIV/STI risk reduction counseling (Required at Visit 6 only)
Clinical		• Review/update medical history • Review/update concomitant medications • Perform rectal examination • Perform targeted physical examination* • Perform genital examination* • Disclosure of available test results • Treat or prescribe treatment for RTI/UTI, or STIs* • Record/update AEs
Laboratory	**Throat**	• Pharyngeal swab for GC/CT*
	Urine	• Urine dipstick/culture* • NAAT for GC/CT*

Visit 4 - Sampling Visit and Visit 6 - Sampling Visit/Early Termination		
Component		**Procedures**
	Blood	• Plasma for PK π • Chemistries (AST/ALT/Creatinine)* (Required at Visit 6) • HIV-1/2 test (Required at Visit 6 only) • CBC with differential and platelets* • Syphilis serology*
	Anorectal	• Rectal enema effluent for PK and PD prior to biopsy collectionπ • Rectal fluid for microbiome π • Rectal fluid for PK π • Rectal tissue for histology, transcriptomics, proteomics π • Rectal tissue for PK π • NAAT for GC/CT* • HSV 1/2 detection*
Study Product/Supplies		• Offer condoms

* If indicated π Please reference the MTN-033 SSP Manual for additional details (www.mtnstopshiv.org) regarding the appropriate procedures to complete for an Early Termination Visit.
NOTE: Participants will be instructed to call in to the clinic to report any issues related to the collection of samples via the flexible sigmoidoscopy for up to 72 hours following Visits 4 and 6. See SSP Manual for additional details.

7.4.3 Visit 7- Termination Visit/Contact

Approximately 7 days following Visit 6, study staff will contact participants (clinic visit or via phone) to inquire about AEs that they might have experienced as a result of the study product(s) or procedures performed. This contact will also serve as the participant's study termination.

Table 10: Visit 7- Termination Visit/Contact

Visit 7- Termination Visit/Contact	
Component	**Procedures**
Administrative and Regulatory	• Review/update locator information • Provide reimbursement ~ • Schedule next visit/contact*
Clinical	• Disclosure of available test results • Record/Update AEs • Treat or prescribe treatment for RTI/UTI, or STIs*
Study Product/Supplies	• Offer condoms*

* If indicated ~ Site to reference SOPs regarding participant reimbursement

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

7.5.1 Participants Who Become Infected with HIV-1/2

If a participant tests positive for HIV-1/2 after the Enrollment Visit, s/he will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed. Continued study participation would be of no added benefit, thus follow-up visits will be discontinued and the participant will be considered terminated from the study. An Early Termination Visit will be conducted, if the participant is willing. Participants who seroconvert after randomization may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated, per discussions between the site IoR and LC. Please reference the MTN-033 SSP Manual for additional details (www.mtnstopshiv.org).

7.5.2 Participants Who Permanently Discontinue Study Product for Other Reasons

Participants who permanently discontinue study product use for any reason (clinician-initiated or self-initiated) will be considered terminated from the study and the PSRT should be notified. Continued study participation would be of no added benefit, thus follow-up visits will be discontinued. An Early Termination Visit will be conducted, if the participant is willing. Participants who permanently discontinue study product use due to an AE must continue to be followed off-study until resolution or stabilization of the AE is documented.

7.5.3 Interim Visits

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

- For administrative reasons, e.g., a participant may have questions for study staff, or may need to re-schedule a follow-up visit or to perform missed procedures.
- 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 also Section 9).
- For interim STI counseling and testing in response to STI symptoms.
- For interim HIV counseling and testing in response to participant report of symptoms consistent with acute infection or presumed exposure to HIV
- To provide participants with the results of confirmatory HIV test results, per the algorithm in Appendix II.
- For other reasons at participant request, e.g., social harm.

All interim contacts and visits will be documented in participants' study records.

7.6 Protocol Counseling: Adherence and Study Product Use Counseling

At Dosing Visits, participants will receive study product and study product use counseling appropriate to the visit. Study staff will document dispensation of study product and that the counseling was provided. Protocol adherence counseling will be provided to study participants upon enrollment into the study. Counseling will be provided in accordance with standard study methods. Counseling also will include reminders regarding concomitant medication and behavioral restrictions prior to and following collection of biopsies.

7.7 Clinical Evaluations and Procedures

Physical Examination

The physical examination will include the following assessments:

- General appearance
- Weight*
- Vital signs
  - Temperature
  - Pulse
  - Blood pressure
  - Respirations
- Height*
- Abdomen*
- Head, Eye, Ear, Nose and Throat (HEENT) Examination*
- Oral mucosa*
- Lymph nodes*
- Neck*
- Heart*
- Lungs*
- Extremities*
- Skin*
- Neurological*
- Other components as indicated by participant symptoms

* = May be omitted after Enrollment Visit

Anorectal Examination

The anorectal examination may include the following:

- Visual exam
- Digital exam
- Anoscopy
- Flexible sigmoidoscopy

Genital Examination

- General inspection via naked eye and hand-held magnifying glass of the following:
    - Entire penile surface
        - Glans
        - Urethral meatus
        - Internal and external foreskin (if present)
        - Shaft
    - Scrotum
    - Inguinal lymph nodes

Note: Detailed information regarding the rectal and genital examination, as well as the associated procedures required for collecting rectal specimens at each visit, can be found in the MTN-033 SSP Manual.

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.

7.8 Behavioral Assessments

Participants will respond to CASI at the Enrollment Visit (Visit 2) and at the two dosing visits, Visit 3 and Visit 5. The assessment done at enrollment will include, among other topics, questions on participants' prior experience and comfort using rectal products, as well as douching or other rectal hygiene practices. The follow-up assessments will explore reactions to product, applicator, and administration method. These assessments will allow the identification of product attributes likely to challenge and/or facilitate future sustained use when applied rectally by participants (secondary objective: acceptability). Suggestions for product improvement will also be collected.

An IDI is planned after the application of each single dose (Visit 3 and Visit 5). The IDIs will include, among other topics, questions on user acceptability of the product, user-centered suggestions for product design and delivery, and experiences with the direct application method.

Major components of both CASI and IDI assessments have been used successfully and validated in prior rectal microbicide trials (e.g., MTN-006, MTN-007, MTN-017) and are planned as part of MTN-026.

7.9 Pharmacokinetics, Pharmacodynamics and Biomarkers of Mucosal Safety

Table 11: Specimens to be Collected to Assess PK, *Ex Vivo* Challenge, PD, Histology, Transcriptomics, Proteomics, Microbiome

Visit	Specimens Collected to Assess Drug Concentrations (PK)	Specimens Collected for *Ex Vivo* Challenge and PD	Specimens Collected to Assess Biomarkers of Mucosal Safety
Visit 2: Enrollment (Baseline Samples)		• Rectal enema effluent for PD prior to biopsy collection • Rectal tissue for *Ex Vivo* Challenge (~3 samples)	• Rectal tissue for histology, transcriptomics, proteomics (~4 samples) • Rectal fluid for microbiome
Visit 3: Period 1 Dosing Visit	• Blood♦ • Rectal tissue (~6 samples) ⌂ • Rectal fluid ⌂ • Rectal enema effluent for PK prior to biopsy collection ⌂	• Rectal enema effluent for PD prior to biopsy collection ⌂ • Rectal tissue for *Ex Vivo* Challenge (~3 samples) ⌂	
Visit 4: Sampling Visit (24 hours after dose administration)	• Blood • Rectal tissue (~6 samples) • Rectal fluid • Rectal enema effluent for PK prior to biopsy collection	• Rectal enema effluent for PD prior to biopsy collection	• Rectal tissue for histology, transcriptomics, proteomics (~4 samples) • Rectal fluid for microbiome
Visit 5: Period 2 Dosing Visit	• Blood♦ • Rectal tissue (~6 samples) ⌂ • Rectal fluid ⌂ • Rectal enema effluent for PK prior to biopsy collection ⌂	• Rectal enema effluent for PD prior to biopsy collection ⌂ • Rectal tissue for *Ex Vivo* Challenge (~3 samples) ⌂	
Visit 6: Sampling Visit (24 hours after dose administration)	• Blood π • Rectal tissue (~6 samples) π • Rectal fluid π • Rectal enema effluent for PK prior to biopsy collection π	• Rectal enema effluent for PD prior to biopsy collection π	• Rectal tissue for histology, transcriptomics, proteomics (~4 samples) π • Rectal fluid for microbiomeπ

♦= Participants will provide samples at Baseline (Pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after dose administration
⌂= Participants will be randomized to provide samples either 1 hour or 4 hours after dose administration
π= Please reference the MTN-033 SSP Manual for additional details (http://www.mtnstopshiv.org/) regarding the appropriate procedures to complete for an Early Termination Visit

7.10 Laboratory Evaluations

Local Laboratory

The local laboratory will run the following, as indicated:

- Urine specimens
  - Urine GC/CT by NAAT
  - Dipstick/culture
- Throat specimens
  - Pharyngeal swab for GC/CT
- Anorectal specimens
  - Rectal fluids for:

        - Rectal GC/CT by NAAT
        - HSV 1/2 viral detection
    - Rectal tissue for:
        - *Ex vivo* challenge
- Blood specimens
    - HIV-1/2 testing, with confirmatory testing as needed
    - CBC with differential and platelets
    - Syphilis serology
    - Creatinine, AST, ALT
    - Hepatitis B surface antigen
    - HCV serology
    - Coagulation (PT/INR)

Laboratory Center (LC)

- Blood specimens
    - PK (Pharmacology Core)
    - Plasma archive
- Anorectal specimens
    - Rectal fluids and/or lavage for:
        - PK (Pharmacology Core)
        - PD (Protocol Support Core)
        - Microbiome
    - Rectal tissue for:
        - PK (Pharmacology Core)
        - Histology
        - Transcriptomics
        - Proteomics

7.11 Specimen Management

The study site will adhere to the standards of good clinical laboratory practice (https://www.niaid.nih.gov/sites/default/files/gclp.pdf), in accordance with current DAIDS Laboratory Requirements, MTN-033 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, the site is permitted to re-draw specimens. Further, as part of quality control, researchers may need to look at short pieces of non-coding repetitive 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/research/daids-clinical-research-policies-us-labs)

7.13 Biohazard Containment

As the acquisition 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 CDC and National Institutes of Health (NIH). All biological specimens will be transported using packaging mandated by 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. Biohazardous waste will be contained according to institutional, transportation/carrier, and all other applicable regulations.

8 ASSESSMENT OF SAFETY

8.1 Safety Monitoring

The site IoR is responsible for continuous close safety monitoring of all study participants and for alerting the Protocol Team if unexpected concerns arise. A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, and Protocol Safety Physicians will serve as the PSRT. The MTN Statistical Data 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 and Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators 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, the PSRT and study sponsors. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

MTN SDMC staff will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer and designated SDMC staff for review.

The PSRT will meet approximately every month via conference call to review clinical data reports generated by the MTN SDMC. The content, format and frequency of the clinical data reports will be agreed upon by the PSRT and the SDMC in advance of study implementation. In addition to the 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 representing expertise in the fields of microbicides, biostatistics, HIV acquisition and medical ethics may be invited to join the PSRT safety review. A recommendation to pause or stop the trial may be made by the PSRT at this time or at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

The Study Monitoring Committee (SMC) will review participant safety data as part of their regular reviews (see Section 10.6.1), since no Data and Safety Monitoring Board oversight is planned for MTN-033. The SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued. Members of the SMC will be independent investigators with no interest (financial or otherwise) in the outcomes of this study. If at any time a decision is made to discontinue enrollment and/or study product use in all participants, DAIDS will notify the FDA and the Site IoR will notify the responsible IRB expeditiously.

In addition to the safety monitoring, the MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, and study or lab issues. These reviews will take place approximately every 4-6 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.

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 groups, and is applied to all groups beginning at the time of enrollment (i.e., once a participant is

randomized) through the termination visit. The term “investigational product” for this study refers to all study products.

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 captured in the study database. 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 will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 2 and 3 (Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).

Bleeding at the time of coital simulation device use, applicator use, anoscope, flexible sigmoidoscope insertion/removal, and/or biopsy collection that is judged by the clinician to be within the range of what is normally anticipated will not be reportable as an AE. Bleeding of greater quantity or longer duration than what is typical, per clinician assessment, will be reportable as an AE. Fecal urgency, bloating and flatulence associated with rectal procedures deemed to be within the range of what is normally expected will not be reportable as AEs.

8.3.2 Serious Adverse Events

An SAE will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), as an AE that:

- Results in death
- Is life-threatening
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization
  Note: Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event. Thus, hospitalization in the absence of an AE is not regarded as an AE, and is not subject to expedited reporting. The following are examples of hospitalization that are not considered to be AEs:
    - Protocol-specified admission (e.g., for procedure required by study protocol)

- Admission for treatment of target disease of the study, or for pre-existing condition (unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator)
- Diagnostic admission (e.g., for a work-up of an existing condition such as persistent pretreatment lab abnormality)
- Administrative admission (e.g., for annual physical)
- Social admission (e.g., placement for lack of place to sleep)
- Elective admission (e.g., for elective surgery)

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed 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(s)
- *Not Related:* There is not a reasonable possibility that the AE is related to the study agent(s)

8.4 Adverse Event Reporting Requirements

8.4.1 Expedited 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 DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited adverse event (EAE) reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted using the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at (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 agent for which expedited reporting is required is: 0.05% dapivirine gel.

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 Division of AIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 2 and 3 (Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies), will be used and are 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 at enrollment (i.e., randomization) and continues through the participant's termination from the study.

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 Regulatory Requirements

Information on all reported AEs will be included in reports to the FDA and other applicable government and regulatory authorities. Site IoRs/designees will submit AE and any relevant safety information in accordance with local regulatory requirements.

8.6 Social Harms Reporting

Although the study site 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. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the PSRT and responsible site IRBs according to their individual requirements.

9 CLINICAL MANAGEMENT

Guidelines for clinical management and permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to permanently discontinue study product use at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. The IoR/designee will document all permanent discontinuations on applicable CRFs.

9.1 Grading System

AE severity grading is described in Section 8.4.3.

9.2 Dose Modification Instructions

No dose modifications will be undertaken in this study.

9.3 General Criteria for Permanent Discontinuation of Study Product

Permanent Discontinuation

A participant will be permanently discontinued from product use by the IoR/designee for any of the following reasons:

- Acquisition of HIV infection; for those who acquire HIV, study product should be held beginning immediately upon recognition of the first positive/reactive HIV test
- Anorectal STIs
- 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.
- Reported use of CYP3A inducers and inhibitors
- Reported use of hormone-replacement therapy in tablet, injectable or gel form

At the discretion of the IoR/designee, a participant may be permanently discontinued for reported use of the following prohibited medications*

- Anticoagulant medications, aspirin (greater than 81 mg/day), other non-steroidal anti-inflammatory drugs (NSAIDS) and other drugs that are associated with increased risk of bleeding

*Should a participant report taking any of the medications noted above, which may increase risk of bleeding, periannaly applied topical steroids or using rectal products containing N-9 within 72 hours prior to a PK sample collection, if possible the visit should be rescheduled within the visit window. If it is determined that rescheduling the visit within the window is not possible, the visit may proceed at IoR discretion after proper participant counseling has occurred. If desired, the IoR may request rapid PSRT consultation to assist in making the determination as to whether or not to proceed with the visit at that time or to reschedule as an interim visit. If the decision is made to

reschedule as an interim visit, any missed procedures (including biopsy collection) should be performed during the interim visit.

9.4 Follow-up in Response to Observed Adverse Events

Grade 1 or 2

In general, a participant who develops a Grade 1 or 2 AE as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 or Addenda 2 and 3 (Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies), regardless of relationship to study product, may continue product use. If the IoR/designee opts to discontinue study product, the PSRT must be notified.

Grade 3 Unrelated

For participants who develop a Grade 3 unrelated AE as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 or Addenda 2 and 3 (Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies), the IoR must consult with PSRT regarding continued study product use.

Grade 3 Related or Grade 4

For participants who develop a Grade 3 related or any Grade 4 AE as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 or Addenda 2 and 3 (Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies), study product must be permanently discontinued and the PSRT notified.

9.5 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee 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, after consultation with the PSRT. Participants also may be withdrawn if NIAID, MTN, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs terminate the study prior to its planned end date. Every reasonable effort is made to complete a final evaluation of participants who withdraw or are withdrawn from the study prior to completing follow-up (see details regarding the Early Termination Visit in Section 7.4.2). Study staff members will record the reason(s) for all withdrawals in participants' study records.

10 STATISTICAL CONSIDERATIONS

10.1 Overview and General Design

This is a phase 1, single-site, randomized (1:1), open label trial designed to characterize the PK and safety profiles of dapivirine gel administered rectally via HTI vaginal applicator, and via a coital simulation device. Sixteen HIV-uninfected men who have sex with men (MSM) or transgender women who have sex with men will be randomized to receive two sequences (AB or BA) of the two application methods for dapivirine gel. In the one study phase, a single dose of study product will be administered via applicator. In the other study phase, the study product will be applied via a coital simulation device to be inserted and withdrawn rectally for a period of 5 minutes to simulate receptive anal intercourse.

10.2 Study Endpoints

10.2.1 Primary Study Endpoints

Consistent with the primary study objective to characterize the systemic and compartmental PK of dapivirine 0.05% gel applied rectally by two different methods, the following endpoints will be assessed:

- Dapivirine concentrations
  - Rectal fluid
  - Plasma
  - Rectal mucosal tissue homogenates

The endpoint will be limited to dapivirine concentrations; other measures will not be considered.

10.2.2 Secondary Study Endpoints

Consistent with the secondary study objectives assessing the safety of dapivirine gel administered rectally via HTI vaginal applicator and with a coital simulation device and the product attributes likely to challenge and/or facilitate future sustained use, the following endpoints will be assessed:

- Grade 2 or higher AEs as defined by the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 2 and 3 (Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies).

- Product attributes considered likely to challenge and/or facilitate future sustained use by participants

10.3 Sample Size and Power

The sample size and power calculation for a cross-over design can start from two-arm, equal size comparison assuming the independence, then adjust this resulted sample size by intro-individual correlation in the cross-over design. The sample size adjustment can be obtained by this formula:

N'=N(1-rho)/2

Where N' is the sample size for a cross-over design, N is total number required for a two independent arm design, and rho is the correlation between drug concentrations after two routes of gel use within the same individual.

There is no PK data to date on the rectal use of dapivirine gel. The sample size and power calculation are based on the coefficient of variation (CV) data from the rectal use of TFV gel in the completed MTN-006 trial, assuming the CV for the two products will be similar. Based on the MTN-006 data, the TFV concentrations in rectal fluid and rectal tissue biopsy are quite variable. The CV for concentration in rectal tissue homogenates after a single dose of TFV gel is around 1.5. The plasma concentration is relatively more stable, with a CV around 0.75 ~1.0.

It is hypothesized that when up to 10 g of dapivirine gel is applied using a rectal coital simulation device, the rectal and systemic dapivirine PK levels will be lower than when applied using the standard microbicide delivery HTI applicator which holds 2.5 g of gel. It is expected that coital simulation insertion of gel will result in 10-fold lower concentration systemically and rectally.

To compute the power for comparing the concentrations of one compartment under the two routes of gel use, we assume the coefficients of variation vary at 1, 1.5 or 2, and we assume the within-individual correlation ranges from 0.2 to 0.8. For an effective sample size of 16 participants who have completed data for both methods of application, we list the power to detect significant difference between the concentrations under two methods in Table 12, when the fold change of concentration is 10. The coefficients of variation remain the same for the concentrations under two routes of use. Because it is expected that the applicator use will result in a higher concentration than coital simulation use, we use one-sided type I error in the power computation. The test statistic is one sample paired-test of mean being different from 0, accounting for within-subject correlation.

Table 12: Power Calculations

The power to detect significant difference for cross-over design for an effective sample size of 12 or 24, the coefficient variation 1.0 or 1.5, within subject correlation 0.2, 0.5, or 0.8, and the actual fold difference is 10. The one-sided type I error is set to 0.05.			
CV		Rho	Total sample size
			16
Concentration in plasma	1.0	0.2	0.98
	1.0	0.5	0.98
	1.0	0.8	0.99
Concentration in rectal tissue	1.5	0.2	0.79
	1.5	0.5	0.81
	1.5	0.8	0.83

Table 12 shows that for the PK parameters that have a CV <=1.5 such as concentrations in plasma and rectal tissue, our sample size provides adequate power to detect the ten-fold difference. For more variable measures our sample size provides good power to detect the ten-fold difference.

Participants may fail to complete both periods of cross-over. The recently completed MTN-014 trial conducted by MTN, which also used the same crossover design and two-week use of TFV gel in each period, has achieved high adherence to the two-period administration of gel: only 1 out of 14 participants did not complete the study crossover periods. The sample size calculation in Table 12 is based upon participants who successfully completed the study. If there are a few participants who fail to come back to the second period of rectal application, we will recruit additional replacement participants to cover the loss of power.

10.4 Randomization Procedures

Participants will be randomly assigned with the ratio 1:1 to one of two sequences of study product application method. Participants will also be randomly assigned with the ratio 1:1 to provide tissue and rectal enema effluent samples either 1 hour or 4 hours after each dose administration. The randomized assignments will be in blocks to keep the balance of equal allocation. The randomization scheme, including enrollment of replacement participants, will be generated and maintained by the MTN SDMC.

10.5 Participant Accrual and Retention

The accrual period is expected to require approximately 6-8 months. The study will enroll approximately 16 MSM and transgender women.

The target retention rate for each study visit is 95%. Therefore, once a participant is enrolled in the study, the study site will make every reasonable effort to retain the participant for the entire study duration so that the participant is evaluable.

10.6 Data and Safety Monitoring Procedures

10.6.1 Study Monitoring Committee

No Data and Safety Monitoring Board oversight is planned for this study. The MTN SMC will conduct interim reviews of study progress, including rates of participant accrual, retention, completion of primary and main secondary endpoint assessments, study or lab issues, and, in a closed report, safety data by arm of the study. These reviews will take place approximately every 4-6 months, or as needed. Reviews may also be conducted on an as needed basis. At the time of this review, or at any other time, the SMC may recommend that the study proceed as designed, proceed with design modifications, or be discontinued.

Note: Data available from ongoing dapivirine gel safety studies will be considered by the SMC.

10.7 Data Analyses

10.7.1 Primary Data Analyses on PK Measures

All participants who have PK data collected will be used in the analysis. The comparison is primarily based on the concentrations after two methods of gel applications. For each method of application, mean and standard deviation will be computed for each period separately, and for two periods of the same method combined. The skewness of drug concentration values will be assessed and log transformation will be considered if this is the case. A linear mixed model will be used to account for the cross-over design, paired data structure and controlling for period effect. In addition, a signed rank Wilcoxon test will be also conducted to remove the concern of skewed PK concentration and outliers. Although no carry-over effect would be expected after a 2-4-week washout period, if that is detected, we will resort to analyzing only the data from the Period 1 as a simple two arm parallel design using statistical methods for independent data.

10.7.2 Secondary Data Analyses on Safety and Acceptability

A list of AEs as defined as secondary endpoints will be tabulated by the method of gel application and the treatment period. The difference of AE rates between different routes of delivery will be assessed by a generalized linear mixed model accounting for the period effect.

Product attributes considered likely to challenge and/or facilitate future sustained use by participants will be summarized for each method of use. The comparison of the acceptability measures between methods of use will be assessed by a generalized linear mixed model accounting for the period effect.

10.8 Missing Data

A retention rate of 95% is targeted. Based on previous MTN trials, minimal missing data is expected. If missing data rates are higher than anticipated (over 10%), sensitivity analyses will be conducted to assess the impact of missing data on trial inference. Assuming missing data are ignorable, we will use multiple imputation based on all available baseline predictors and available trial outcomes.

11 DATA HANDLING AND RECORDKEEPING

11.1 Data Management Responsibilities

Data collection tools will be developed by the MTN SDMC in conjunction with the protocol team. Quality control queries routinely will be generated for study site verification and resolution. As part of the study activation process, the study site must identify all CRFs to be used as source documents. Study CRF data will be entered and cleaned using the Medidata Rave EDC tool, a data management system compliant with the International Council on Harmonization (ICH) Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture.

11.2 Source Documents and Access to Source Data/Documents

The study site will maintain source data/documents in accordance with current DAIDS policies. (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.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

The study site will conduct quality control and quality assurance procedures in accordance with current DAIDS policies. (https://www.niaid.nih.gov/sites/default/files/qmppolicy.pdf)

12 CLINICAL SITE MONITORING

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

- Review informed consent forms, procedures, and documentation
- Assess compliance with the study protocol, Good Clinical Practices (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

The IoR/designee will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, LC, NIAID, FDA, OHRP, IRBs and other local, US, and international regulatory authorities. A site visit log will be maintained at the study site to document all visits.

13 HUMAN SUBJECTS PROTECTIONS

Site investigators will make efforts to minimize risks to participants. Participants and study staff members will take part in a thorough informed consent process. Before beginning the study, the IoR/designee will have obtained IRB approval and the protocol will have been submitted to the FDA. The IoR/designee will permit audits by the NIH, the FDA, OHRP, MTN LOC, IRBs, SDMC, and other local, US, and international regulatory authorities or any of their appointed agents.

13.1 Institutional Review Boards/Ethics Committees

The participating institution is responsible for assuring that this protocol, the associated site-specific informed consent forms (ICFs), and study-related documents (such as participant education and recruitment materials) are reviewed by an IRB responsible for

oversight of research conducted at the study site. Any amendments to the protocol must be approved by the responsible IRBs prior to implementation.

Subsequent to the initial review and approval, the responsible IRBs must review the study at least annually. Each IoR/designee will make safety and progress reports to the IRBs at least annually and within three months after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. In addition, the results of all SMC reviews of the study will be provided to the IRBs. The study site will submit documentation of continuing review to the DAIDS Protocol Registration Office (PRO) in accordance with the DAIDS Protocol Registration Policy and Procedures Manual.

13.2 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, the site must have the protocol and the protocol consent forms approved, as appropriate, by its local IRB and any other applicable regulatory entity (RE). Upon receiving final approval, the site will submit all required protocol registration documents to the DAIDS 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 the site 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 and any other applicable RE approval(s) for an amendment, the site should implement the amendment immediately. The site is 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 of the required documents have been received. Site-specific ICF(s) *will not* be reviewed and approved by the DAIDS PRO and the site 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.

Study implementation will be directed by this protocol, which may not be amended without prior written approval from the Protocol Chair and DAIDS Medical Officer. Study implementation will also be guided by a common Study-Specific Procedures (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 products and documenting product accountability; and other study operations. Standardized study-specific training will be provided to the site 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 and documentation. 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

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

Phlebotomy
Phlebotomy may lead to excessive bleeding, discomfort, feelings of dizziness or faintness, bruising, swelling, venous thrombosis and/or infection.

Pharyngeal Swab
Pharyngeal (throat) swab collection often causes a momentary gagging reflex.

Rectal Enema
An enema will be standard procedure that may be used prior to insertion of a flexible sigmoidoscope since fecal matter can obscure the test. The main risk from having an enema is temporary discomfort. A hollow tube about the thickness of a pencil will be used to put approximately 120 mL of normal saline 0.9% into the rectum and flush it out again (a larger volume may be required if the initial volume does not produce results), along with any stool that is there. There is a risk of a bloated/cramping feeling. The tube is small, but it might cause some anal or rectal discomfort if the subject has any hemorrhoids or other painful conditions.

Anoscopy
Insertion of a lubricated anoscope will likely cause some discomfort.

Flexible Sigmoidoscopy and Rectal Biopsy Collection
Flexible sigmoidoscopy is a commonly practiced endoscopic medical procedure and will not involve any increased risk over usual sigmoidoscopy performed for clinical indications. There is a low risk of infection, mild rectal irritation, low blood pressure, and

feeling a sudden urge to defecate during or after the flexible sigmoidoscopy procedure. There is a very low risk of intestinal tear during the flexible sigmoidoscopy procedure.

There is a risk of limited rectal bleeding 1-2 days after flexible sigmoidoscopy, associated with collection of biopsy samples. The rate of perforation of a hollow viscus following endoscopic biopsy occurs less than 88 out of every 100,000 times.[30] A recent retrospective analysis of approximately 1,000 research flexible sigmoidoscopies (including collection of rectal biopsies) conducted at the University of Pittsburgh demonstrated an overall adverse event rate of 1.6%. The majority of AEs were gastrointestinal in nature and of mild/moderate severity.[31]

Participants will be instructed to refrain from sexual intercourse and counseled not to use NSAIDs, aspirin (over 81 mg per day) and/or other drugs that are associated with the increased likelihood of bleeding for 72 hours before and after the flexible sigmoidoscopy. If participants engage in sexual intercourse before the biopsy has healed they may experience some temporary discomfort. If participants are sexually active they may also be at increased risk for STIs and HIV acquisition, if exposed. There is a small risk of infection and heavier bleeding. Participants will be instructed to contact the clinic if symptoms are bothersome, if heavy bleeding is noted or if the participant develops any abnormal odor or discharge from the rectum.

Rectal Fluid Collection
There is the risk of mild discomfort in addition to a slight risk of bleeding with the insertion of rectal swabs and sponges for collection of rectal fluid.

Rectal Applicator (for Administration of Study Product)
Use of an applicator to deliver a microbicide into the rectal compartment may be associated with minor anorectal trauma including lacerations and bruising in the anorectal area. Side effects observed with rectal application of microbicides in previous research studies include: mild rectal fullness; incontinence or diarrhea; flatulence; mild abdominal pain; and proctalgia.

Rectal Coital Simulation Device (for Administration of Study Product)
Use of a coital simulation device to deliver a microbicide into the rectal compartment may be associated with minor discomfort, minor anorectal trauma including lacerations and bruising in the anorectal area, and (rarely) minor bleeding. Side effects observed with rectal application of microbicides in previous research studies include: mild rectal fullness; incontinence or diarrhea; flatulence; mild abdominal pain; and proctalgia.

Other Risks
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.

Sexual partner notification in response to diagnosed STI or HIV infection could cause problems in participants' relationships. Participants also could have problems in their partner relationships associated with maintenance of study-required abstinence.

Site staff will make every effort to protect participant privacy while in the study. Although the study site 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 (i.e., because participants could become known as HIV-positive or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Risks Associated With DPV Gel

AEs among female participants who dosed vaginally with DPV gel included:

- Headache
- Upper respiratory tract infection
- Abdominal pain
- Hypophosphataemia
- Neutropenia

These side effects may or may not be associated with rectal use of DPV gel.

In previously completed studies involving rectally-applied products, the following gastrointestinal AEs were common and/or occurred at a Grade 3 or higher:

- Abdominal distension
- Abdominal bloating
- Abdominal pain/cramps
- Defecation urgency
- Diarrhea
- Flatulence
- Tenesmus

These side effects may or may not be associated with the use of DPV gel.

13.4.2 Benefits

Participants in this study may experience no direct benefit. Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of safe and effective interventions to prevent HIV acquisition and transmission. Participants also may appreciate the opportunity to contribute to the field of HIV prevention research.

Participants will receive HIV/STI risk reduction counseling, HIV and STI testing, physical examination, and routine laboratory testing related to blood, liver, and kidney function. Participants may be provided or referred for STI treatment free of charge, and STI

testing and treatment may be offered and/or referrals may be provided (for their partners). For other medical conditions identified as part of the study screening and/or follow-up procedures, participants will be referred to other sources of care available in their community. Some volunteers may have the opportunity to access expedient treatment and decreased morbidity due to early diagnosis and treatment of abnormalities identified during tests, examinations and referrals.

13.5 Informed Consent Process

Written informed consent will be obtained from each study participant prior to screening. Written informed consent also will be obtained for long-term specimen storage and possible future testing, although consent for long-term specimen storage is not required for study participation. In obtaining and documenting informed consent, the IoR and their designees will comply with applicable local and US regulatory requirements and will adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf). Participants will be provided with copies of the ICF if they are willing to receive them.

In addition to the ICF, the Protocol Team will work with study staff and community representatives to develop appropriate materials about the study and a standardized approach to the informed consent process to be implemented at the study site, which will be detailed in the SSP Manual.

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

- The unknown safety and unproven efficacy of the study products
- The need to abstain from sexual intercourse for protocol defined periods
- The importance of participants in both study group sequences to the success of the study
- The importance of adherence to the study visit and procedures schedule
- The potential medical risks of study participation (and what to do if such risks are experienced)
- The potential social harms associated with study participation (and what to do if such harms are experienced)
- The real yet limited benefits of study participation
- The distinction between research and clinical care
- The right to withdraw from the study at any time

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. The 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.

All study-related information will be stored securely. All participant information will be stored in locked areas with access limited to study staff. All laboratory specimens, study data, 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 informed consent forms, 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. 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 authorities
- PPD
- Study staff
- Site IRBs

The MTN has a Certificate of Confidentiality from the US Department of Health and Human Services that is applicable to this study. This Certificate protects study staff from being compelled to disclose study-related information by any US Federal, State or local civil, criminal, administrative, legislative or other proceedings. It thus serves to protect the identity and privacy of study participants.

13.7 Special Populations

13.7.1 Children

The NIH has mandated that children be included in research trials when appropriate. This study meets "Justifications for Exclusion" criteria for younger children as set forth by the NIH. Specifically, "insufficient data are available in adults to judge potential risk in children" and "children should not be the initial group to be involved in research studies." This study does not plan to enroll children under 18 years old.

13.8 Compensation

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

13.9 Communicable Disease Reporting

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

13.10 Access to HIV-related Care

13.10.1 HIV Counseling and Testing

HIV test-related counseling will be provided to all potential study participants who consent to undergo HIV-1 screening to determine their eligibility for this study, and to all enrolled participants at each follow-up HIV-1/2 testing time point. Testing will be performed in accordance with the algorithm in Appendix II. Counseling will be provided in accordance with standard HIV counseling policies and methods at the site and additionally will emphasize the unknown efficacy of the study products in preventing HIV-1 infection. In accordance with the policies of the NIH, participants must receive their HIV-1/2 test results to take part in this study.

13.11 Study Discontinuation

This study may be discontinued at any time by NIAID, the MTN, the US FDA, the OHRP, other government or regulatory authorities, or site IRBs.

14 PUBLICATION POLICY

DAIDS/NIAID and MTN policies 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, NIMH, and IPM for review prior to submission.

15 APPENDICES

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

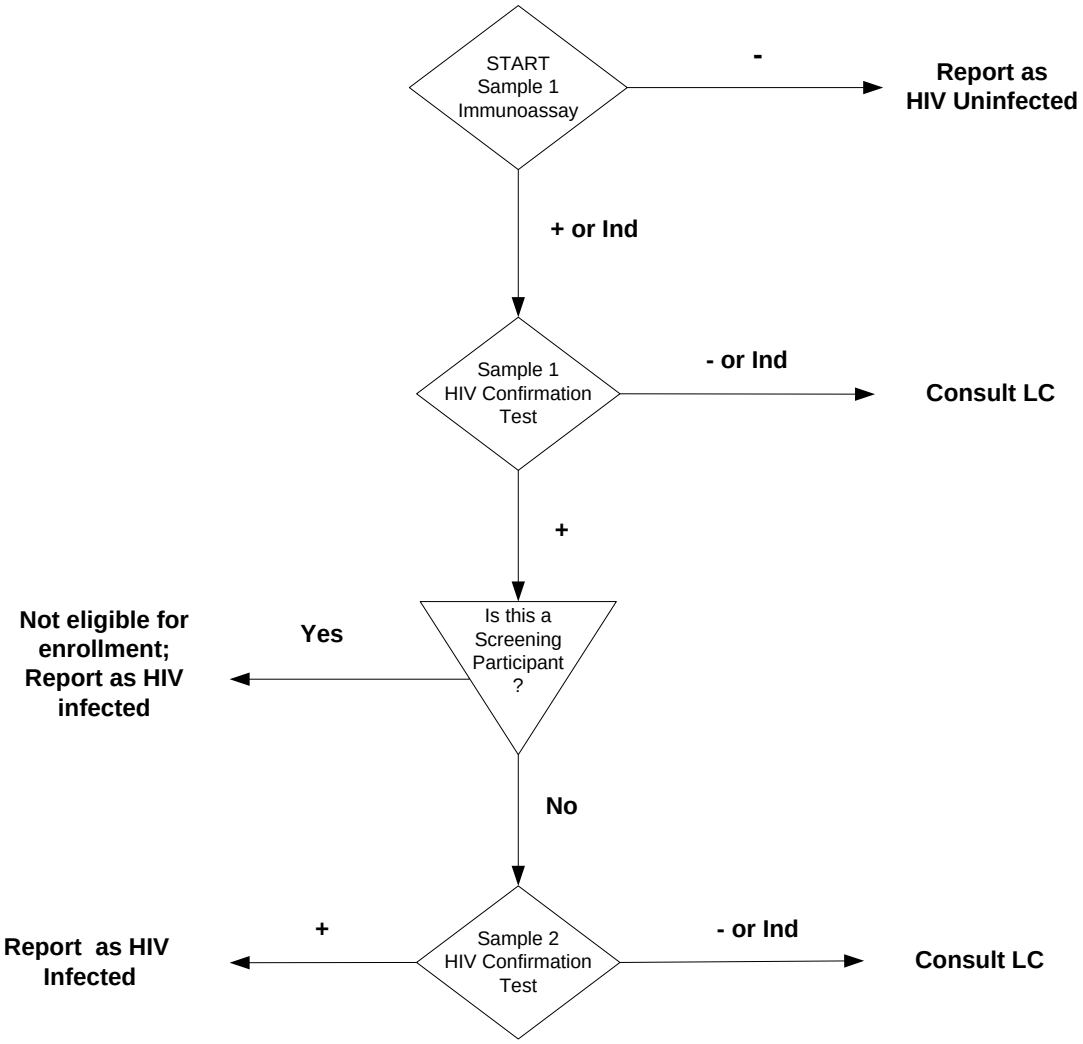
	Visit 1 SCR	Visit 2 ENR	Visit 3 Period 1 Dosing Visit	Visit 4 Sampling Visit	Visit 5 Period 2 Dosing Visit	Visit 6, Sampling Visit/Early Termination Visit	Visit 7 Term Visit/ Contact
ADMINISTRATIVE AND REGULATORY							
Informed consent (SCR/ENR)	X						
Assess consent form comprehension	X						
Review informed consent/Confirm participant willingness to participate in study		X					
Assign PTID	X						
Collect demographic data	X						
Assess/confirm eligibility	X	X					
Locator information	X	X	X	X	X	X	X
Provide reimbursement	X	X	X	X	X	X	~
Schedule next study visit/contact	▲	▲	X	X	X	Xπ	▲
Randomization		X					
BEHAVIORAL/COUNSELING							
HIV pre-/post-test and HIV/STI risk reduction counseling	X	X				X	
Protocol counseling	X	X	X	X	X	X	
Behavioral assessment		X	X		X		
In-depth interview			X		X		
CLINICAL							
Medical history	X	X	X	X	X	X	
General/Targeted physical examination	X	X	▲	▲	▲	▲	
Perform genital examination	X	X	▲	▲	▲	▲	
Perform rectal examination	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	
Treat for UTI/RTI/STI or refer	▲	▲	▲	▲	▲	▲	▲
Disclosure of available test results	X	X	X	X	X	X	X
Record/update AEs			X	X	X	X	X
LABORATORY							
THROAT							
Pharyngeal swab for GC/CT	X	▲	▲	▲	▲	▲	
URINE							
Urine dipstick/culture	▲	▲	▲	▲	▲	▲	
NAAT for GC/CT	X	▲	▲	▲	▲	▲	
BLOOD							
CBC with differential and platelets	X	▲	▲	▲	▲	▲	

	Visit 1 SCR	Visit 2 ENR	Visit 3 Period 1 Dosing Visit	Visit 4 Sampling Visit	Visit 5 Period 2 Dosing Visit	Visit 6, Sampling Visit/Early Termination Visit	Visit 7 Term Visit/ Contact
Chemistries (AST/ALT/Creatinine)	X	▲	▲	▲	▲	X	
Plasma for archive		X					
Plasma PK			X♦	X	X♦	Xπ	
Syphilis Serology	X	▲	▲	▲	▲	▲	
HIV-1/2 test	X	X				X	
HBsAg	X						
HCV serology	X						
Coagulation (PT/INR)	X						
ANORECTAL SAMPLES							
HSV 1/2 detection	▲	▲	▲	▲	▲	▲	
Rectal fluid for PK			X⌂	X	X⌂	Xπ	
Rectal tissue for PK			X⌂	X	X⌂	Xπ	
Rectal tissue for *ex vivo* challenge		X	X⌂		X⌂		
Rectal tissue for histology, transcriptomics, proteomics		X		X		Xπ	
Rectal fluid for microbiome		X		X		Xπ	
Rectal enema effluent for PK and PD prior to biopsy collection		X (PD only)	X⌂	X	X⌂	Xπ	
NAAT for GC/CT	X	▲	▲	▲	▲	▲	
STUDY PRODUCT/SUPPLIES							
Provision of study product and study product use counseling			X		X		
Provision of study lubricant			▲		▲		
Provision of study coital simulation device			▲		▲		
Offer condoms	X	X	X	X	X	X	▲

X =Required, ▲ = As Indicated, ⌂= Participants will be randomized to provide samples either 1 hour or 4 hours after dose administration, ♦= Participants will provide samples at Baseline, 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after dose administration, ~ Site to reference SOPs regarding participant reimbursement, π = Please reference the MTN-033 SSP Manual for additional details (http://www.mtnstopshiv.org/) regarding the appropriate procedures to complete for an Early Termination Visit.

NOTE: Participants will be instructed to call in to the clinic to report any issues related to the collection of samples via the flexible sigmoidoscopy for up to 72 hours following Visits 4 and 6. See SSP Manual for additional details.

APPENDIX II: ALGORITHM FOR HIV TESTING FOR SCREENING AND FOLLOW-UP



Ind: Indeterminate test results
LC: Laboratory Center

APPENDIX III: SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, LONG-TERM STORAGE AND FUTURE TESTING)

DIVISION OF AIDS, NIAID, NIH

MTN-033

An Open Label Randomized Phase 1 Pharmacokinetic Study of Dapivirine Gel Administered Rectally to HIV-1 Seronegative Adults

Version 2.0

December 8, 2017

PRINCIPAL INVESTIGATOR: ***[Site to insert]***
PHONE: ***[Site to insert]***
Short Title for the Study: Rectal PK Study of Dapivirine (DPV) Gel

INFORMED CONSENT

You are being asked to take part in this research study because you are a healthy, HIV-negative man or transgender woman aged 18 or older and reported at least one experience of receptive anal sex in the last year. Approximately 16 people will participate in this study. This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH). The product being used in this study is dapivirine gel. The study gel is supplied by the MTN. At this site, the person in charge of this study is ***[INSERT NAME OF PRINCIPAL INVESTIGATOR]***.

Before you decide if you want to join this study, we want you to learn more about it. This consent form gives you information about the study. Study staff will talk with you and answer any questions you may have. Once you read and understand the study and its requirements, you can decide if you want to join. If you do decide to take part in the trial, you will sign your name on this form. A copy of this document will be offered to you. Signing this consent form does not mean you will be able to join the study. You must first complete the screening tests and exams to see if you are eligible.

It is important to know that your participation in this research is your decision and taking part in this study is completely voluntary (see Your Rights as a Research Participant/Volunteer for more information).

WHAT IS THE PURPOSE OF THIS STUDY?
The main purpose of this research study is to better understand how dapivirine is absorbed by and eliminated from the body when inserted into the rectum (the last 6 to 8 inches of the large intestine) via applicator and with a sexual intercourse simulation device (herein referred to as a dildo). This research study is testing to see if dapivirine gel is safe when inserted into the rectum. Additionally, researchers would like to understand whether you find it acceptable to use the gel when inserted into the rectum via an applicator and with a dildo.

STUDY PRODUCT

Dapivirine has been previously tested for safety, acceptability, and HIV prevention. HIV is the virus that causes AIDS. Now researchers would like to know more about how dapivirine is processed within the body when dapivirine gel is applied rectally using different methods. To do this, they also need to better understand what effect this drug has on the body, including in and around the rectum and anus (the opening of the rectum to the outside of the body).

Dapivirine works in a specific way to potentially prevent HIV; it is thought to prevent HIV from making copies of itself, thereby stopping the spread of HIV in the body.

Dapivirine has been tested before in humans, mostly applied vaginally by women. Vaginal rings containing dapivirine have been previously tested and found to be safe and well-tolerated. Recently, vaginal rings containing dapivirine were tested in two large studies, the MTN-020 (ASPIRE) Study and the IPM 027 (Ring) Study, to see whether dapivirine can help to prevent the spread of HIV. The dapivirine vaginal ring was shown to be safe and to reduce HIV-uninfected women's chances of getting the HIV virus by approximately one third in both studies.

This study is <u>not</u> testing to see if dapivirine prevents HIV infection. Researchers are continuing to study DPV to learn more about how it works in humans to protect against HIV infection. There are only two known effective ways to prevent HIV: condoms and/or the use of pre-exposure prophylaxis (PrEP). PrEP is a new HIV prevention method in which people who do not have HIV take an oral tablet to reduce their risk of becoming infected. Study staff can provide you with additional information about PrEP if you are interested in learning more. If you are currently taking PrEP or plan to take PrEP in the near future, you will not be eligible for this study.

This study is one of two testing the rectal application of the gel. The other study, MTN-026, will enroll approximately 27 male and female participants in the U.S. and Thailand. The main purpose of MTN-026 is to find out if gel containing DPV is safe when inserted into the rectum after a single dose, followed by 7 daily doses. Another purpose of MTN-026 is to better understand how DPV is absorbed by and eliminated from the body. Results of MTN-026 are anticipated in 2017.

STUDY SEQUENCES

All of the eligible participants will be randomized to one of two rectal gel application method study sequences:

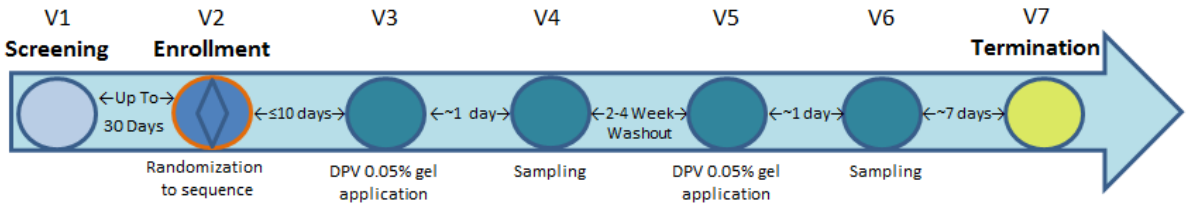
	Study Visit 3	**Study Visit 5**
Sequence A	Single dose of dapivirine gel applied via an applicator	Dapivirine gel applied via dildo
Sequence B	Dapivirine gel applied via dildo	Single dose of dapivirine gel applied via an applicator

Approximately 8 people will be assigned to each sequence. You will be assigned to a sequence by random chance (the equivalent of throwing dice). All participants will receive a gel that contains dapivirine. The study gel is inserted into the rectum using an applicator and, on a separate occasion, using a dildo. Neither you nor the study staff can choose or change the order in which you will apply the study gel. You will be asked to apply the study gel in your rectum two times over the course of this study. Participants in each study group will have the same study visit schedule.

Both study sequences are important to this study. No matter which sequence you are in, you must remember that we do not know the gel will work to protect people from getting HIV.

WHAT WILL HAPPEN DURING THE MTN-033 STUDY VISITS?
The MTN-033 study includes a total of 6 clinic visits and one contact (via phone or in person) including the Screening Visit which is taking place today, if you decide to sign this informed consent form. Multiple visits may be conducted to complete all required screening procedures, if necessary. Visits will take place here, at this study clinic.

[SITE TO UPDATE THE STUDY VISIT/PROCEDURE DESCRIPTIONS TO ALIGN WITH THE FLOW OF STUDY VISITS.]



Screening Visit:

The procedures done today will take about ***[SITE TO INSERT TIME]***.

- Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking), your sexual practices and your understanding of the study requirements.
- You will be asked to provide and/or update study staff with your contact information (i.e. about how we can contact you).
- You will be asked to abstain from some medications during your participation in the study:

  Medication:
  - Anticoagulant medications
  - NSAIDs (nonsteroidal anti-inflammatory drugs)
  - Aspirin (over 81 mg per day)
  - Any other drug that is associated with an increased likelihood of bleeding
  - CYP3A inducer(s) and/or inhibitor(s) (drugs that activate or deactivate an enzyme called CYP3A). Clinic staff can provide you with specific information as to what these drugs are.
  - Hormone-replacement therapy (in pill, needle-injected or gel forms)
  - Rectally-administered medications or products containing nonoxynol-9 or corticosteroids
  - PrEP (oral Truvada®)

Study staff will:
- Perform a physical exam
- Perform a genital exam
- Talk with you about sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex, including use of oral Truvada® for PrEP.

- Talk with you about the requirements of the study including, but not limited to, restrictions on sexual practices:

  Sex for this study is defined as anal intercourse, receptive oral anal stimulation (e.g., partner placing their mouth on your anogenital area), finger stimulation, and the use of sex toys. *You will be asked to abstain from the following activities at these timepoints during the study*:

Activity:	*Abstain For How Long?*

• Receptive anal intercourse
• Receptive oral anal stimulation (e.g., partner placing their mouth on your anal area)
• Rectal stimulation using fingers
• Inserting any non-study products or objects into your rectum, including:
  ○ Rectal medications
  ○ Enemas
  ○ Lubricants
  ○ Sex toys (dildos, anal plugs, etc.)
  ○ Fingers
	• 72 hours (3 days) before and after each study visit

Study staff will also:

- Test your urine for sexually-transmitted diseases and other infections
- Take a blood sample [***SITE TO INSERT AMOUNT***]:
  - To test the health of your blood, liver and kidneys.
  - To test for infections that typically are passed through sex, including HIV, hepatitis B, hepatitis C, and syphilis.
    - You will be told your test results as soon as they are available. You will talk with the study staff about the meaning of your results, how you feel about them, and learn about ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status. To participate in the study, you must receive the results of your HIV test. If the test shows you have HIV, you cannot join the study. We will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.
- Collect a pharyngeal (throat) swab, to test for infections passed through sex.
- Perform a rectal examination, during which rectal fluid will be taken. These will be used to test for infections passed through sex. To collect these samples, study staff will insert a short hollow tube called an anoscope into your rectum. The clinician will insert swabs and/or sponges through the hollow tube to collect the sample.
- Give you treatment or refer you for treatment of sexually transmitted infections, if needed.
- Inform you about other services, if needed.
- Provide you with the results of your tests, when available. It is expected that all your results will be available by [***SITE TO SPECIFY TIMEFRAME***].
- Give you male condoms, if you need them
- Reimburse you for your visit
- Schedule your next visit to enroll in the study, if you are willing and eligible.

If you decide not to join MTN-033, blood and other samples collected at this visit will not be kept or used for any tests other than those listed above.

Enrollment Visit:

Your Enrollment Visit (the visit where you enter the study), will take about ***[SITE TO INSERT TIME.]*** The following procedures are specific to the Enrollment Visit, which will take place up to 30 days after your Screening Visit.

You will:

- Answer questions to confirm you are able and willing to join the study
- Provide and/or update study staff with your contact information (i.e. about where you live and how we can contact you)
- Be assigned to one of two study groups. You will be told the order in which you will use the study product application methods (applicator and dildo).
- Talk with study staff about the following:
  - The rules of the study and how to follow the rules, including the sexual abstinence requirements and use of non-study products/objects. **If you do not think you can be sexually abstinent for the required length of time before and after study visits then you should not join this study.**
  - Sexually transmitted infections (STIs), HIV, HIV/STI testing, and ways to avoid HIV and other infections passed through sex.
- Discuss any health or medical problems you may have had in the past or since your last visit (including what medications you are taking)
- Be asked some questions about your experience and comfort using rectal products, as well as douching or other rectal hygiene practices, among other things. Some of these questions may be asked via computer.
- Be asked to provide a blood sample ***[SITE TO INSERT AMOUNT]***:
  - In case there's a question about your test results at a later time.
  - To test your blood for HIV, the virus that causes AIDS:
    - At this visit and some other visits as noted below, your blood is tested for HIV. You will be told your test results as soon as they are available. You will talk with the study staff about the meaning of your results, how you feel about them, and learn about ways to prevent HIV and other sexually transmitted infections. Sometimes HIV tests are not clearly positive, but also not clearly negative. In that case, we will do more tests until we are sure of your status. If the test shows you have HIV, we will refer you to available sources of medical care and other services you may need. The study staff will tell you about other studies you may be eligible for, if any.
- Have a physical exam
- Have a genital exam
- Have a rectal exam where:
  - Rectal fluid and tissue samples will be collected. The samples collected at this visit (before you receive any doses of study gel) and at other visits will help researchers better understand how the study drug enters and exits the body and/or what effect the drug has. When these samples are collected at future visits, similar tests will be done.
    - To collect rectal fluid and tissue samples: A flexible sigmoidoscopy will be performed. A flexible sigmoidoscope is a flexible, hollow tube is placed inside your rectum so that the study clinician can take samples of tissue. In preparation for the sample collection you will have an enema (rectal lavage). During an

enema, a hollow tube about the thickness of a pencil will be used to put some saline solution (salt water) through your anus and squeeze it into your rectum to flush it out and cleanse the bowel of fecal matter (stool). An enema may be standard procedure prior to insertion of an anoscope or flexible sigmoidoscope, since fecal matter can obscure the test. This may need to be repeated so that any stool that is there is removed. The fluid (effluent) left over from the enema will be collected, and then the study clinician will collect approximately 7 tissue samples, each about the size of a grain of rice.

- Receive treatment or be referred for treatment issues that the study staff may find
- Receive test results, if available
- Give you male condoms, if you need them
- Be reimbursed for your visit
- Schedule your next visit, if applicable.

Dosing Visit (Visit 3):

Your first Dosing Visit is the visit at which you will receive your first dose of the study gel. This visit will take between ***[SITE TO SPECIFY TIMEFRAME]*** to complete.

You will:

- Update study staff with your contact information
- Review the rules of the study and how to follow the rules, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)
- Have a computer-administered interview. This interview may take approximately 45-60 minutes and will occur over video chat, e.g., Google Hangout, Skype, FaceTime, etc. This conversation will be recorded, but your responses will be kept private and confidential, and the audio-recording will be destroyed after it has been transcribed and checked. You will be asked questions about your thoughts on the study product, what might make the product more appealing to use and your experience with administering the gel in the clinic.
- Depending on the study group to which you were assigned, at this visit you will either:
  - Apply one dose of the study gel using an applicator. Study lubricant will be provided to assist with applicator insertion if you need it, or
  - Receive a study-provided dildo. You will be asked to apply the contents of applicator(s) that have been pre-filled with study gel to your dildo. You will be able to use up to 4 applicators. You will be asked to use the device to simulate receptive anal intercourse for approximately 5 minutes. The dildo is yours to keep.
  - At your next dosing visit, you will be asked to use the other study gel application method.
- Have a rectal exam where:
  - Rectal fluid and tissue samples will be collected to help researchers better understand how the study drug enters and exits the body and what effect the drug has.
    - A flexible sigmoidoscopy will be performed. In preparation for sample collection you will have an enema. This may need to be repeated so that any stool that is there is removed. The fluid left over from the enema will be collected, and then the study clinician will collect approximately 9 tissue samples, each about the size of a grain of rice. These tissue samples will be collected either 1 hour or 4 hours after gel administration.

- Be asked some questions about your experience using the study product. Some of these questions may be asked via computer.

Study staff will:
- Take blood samples [***SITE TO INSERT AMOUNT***] at several timepoints including prior to gel administration, every 30 minutes for a three-hour period after gel administration, and 4 hours after gel administration. An intravenous cannula (IV tube) may be placed for 4 hours after you apply the rectal gel for the blood draws. This is done to limit the number of times you will be stuck by a needle.
- Speak with you about any problems that you may be experiencing as a result of using the study gel, applicator, or dildo, or as a result of procedures performed during your visit
- Give you any available test results and provide you with treatment or refer you for treatment if your test results indicate that you require it.
- Give you male condoms, if you need them
- Reimburse you for your visit
- Schedule your next visit or contact.

Sampling Visit (Visit 4):

Your first Sampling Visit will take place approximately 24 hours (1 day) after you receive your first dose of the study gel. This visit will take between ***[SITE TO SPECIFY TIMEFRAME]*** to complete. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

At this visit, you will:
- Update study staff with your contact information
- Review the rules of the study and how to follow the rules, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)
- Have a rectal exam where:
    - Rectal fluid and tissue samples will be collected.
        - A flexible sigmoidoscopy will be performed. In preparation for the sample collection you will have an enema. This may need to be repeated. The fluid left over from the enema will be collected, and then the study clinician will collect approximately 10 tissue samples, each about the size of a grain of rice.

Study staff will:
- Take a blood sample [***SITE TO INSERT AMOUNT***] to help researchers to better understand how the study drug enters and exits the body
- Speak with you about any problems that you may be experiencing as a result of using the study gel, applicator, or dildo, or as a result of procedures performed during your visit
- Give you any available test results
- Give you male condoms, if you need them
- Reimburse you for your visit
- Schedule your next visit or contact.

Dosing Visit (Visit 5):

Your second Dosing Visit will take place after Visit 4, following a washout period of approximately two to four weeks. A washout period is a period of time during a clinical trial when participants receive no active drug (no pharmaceutical product), so as to 'wash out' the drug from the body. This visit will take between ***[SITE TO SPECIFY TIMEFRAME]*** to complete.

You will:

- Update study staff with your contact information
- Review the rules of the study and how to follow the rules, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)
- Have a computer-administered interview. This interview may take approximately 45-60 minutes and will occur over video chat. You will be asked questions about your thoughts on the study product, what might make the product more appealing to use and your experience with administering the gel in the clinic.
- Depending on the study group to which you were assigned, at this visit you will either:
    - Apply one dose of study gel using an applicator. Study lubricant will be provided to assist with applicator insertion if you need it, or
    - Receive a study-provided dildo. You will be asked to apply the contents of applicator(s) that have been pre-filled with study gel to your dildo. You will be able to use up to 4 applicators. You will be asked to use the device to simulate receptive anal intercourse for approximately 5 minutes. The dildo is yours to keep.
- Have a rectal exam where:
    - Rectal fluid and tissue samples will be collected.
        - A flexible sigmoidoscopy will be performed. In preparation for the sample collection you will have an enema. This may need to be repeated. The fluid left over will be collected, and then the study clinician will collect approximately 9 tissue samples, each about the size of a grain of rice. The samples will be collected either 1 hour or 4 hours after gel administration.
- Answer some questions about your experience using the study product. Some of these questions may be asked via computer.

Study staff will:

- Take blood samples [***SITE TO INSERT AMOUNT***] prior to gel administration, every 30 minutes for three hours after gel administration, and 4 hours after gel administration. An IV tube may be placed.
- Speak with you about any problems that you may be experiencing as a result of using the study gel, applicator, or dildo, or as a result of procedures performed during your visit
- Give you any available test results and provide you with treatment or refer you for treatment if your test results indicate that you require it.
- Give you male condoms, if you need them
- Reimburse you for your visit
- Schedule your next visit or contact.

Sampling Visit (Visit 6):

Your second Sampling Visit will take place approximately 24 hours (1 day) after you receive your second dose of the study gel. This visit will take between ***[SITE TO SPECIFY TIMEFRAME]*** to complete. In addition to the procedures listed below, it is possible that study clinicians may need to perform additional tests if medically necessary (for example, you report having symptoms of a urinary, genital, or other infection and/or other issues).

At this visit, you will:

- Update study staff with your contact information
- Review the rules of the study and how to follow the rules, including about sexual abstinence and insertion of non-study products or objects
- Discuss any health or medical problems you may have had since your last visit (including what medications you are taking)
- Have a rectal exam where:
    - Rectal fluid and tissue samples will be collected.
        - A flexible sigmoidoscopy will be performed. You will have an enema, which may need to be repeated. The fluid left over will be collected. Then, the study clinician will collect approximately 10 tissue samples each about the size of a grain of rice.

Study staff will:

- Take a blood sample ***[SITE TO INSERT AMOUNT]:***
    - To test the health of your blood, liver and kidneys.
    - To test your blood for HIV.
        - You will be told your test results as soon as they are available. You will talk with study staff about the meaning of your results, how you feel about them, and learn about ways to prevent HIV and other sexually transmitted infections.
    - To help researchers to better understand how the study drug enters and exits the body
- Speak with you about any problems that you may be experiencing as a result of using the study gel, applicator, or dildo, or as a result of procedures performed during your visit
- Give you any available test results
- Give you male condoms, if you need them
- Reimburse you for your visit
- Schedule your next visit or contact.

Last Study Visit or Contact (Visit 7)

Your Last Study Visit or Contact will take place approximately one week after Visit 6. An in-clinic visit will take place, if needed; if not, your last study contact may take place by phone. This visit/contact will take approximately ***[SITE TO SPECIFY TIMEFRAME]*** to complete.

At this visit, you will:

- Update study staff with your contact information
- Be reimbursed for your visit, if required
- Schedule your next visit or contact (if necessary)
- Be given any available test results
- Discuss any problems that you may be experiencing as a result of using the study gel, applicator, or dildo, or as a result of procedures performed during the study
- Be given male condoms, if you need them

It is important that you remember that at any time during the study, study staff can answer any questions you may have about the procedures mentioned above or any other aspect of this study.

Additional Visits and Procedures

In addition to the procedures listed above, it is possible that study clinicians may need to perform additional tests, if necessary (e.g., if you report having symptoms of a urinary, genital, or other infection and/or other issues). These tests might include the following:

- Physical exam
- Genital exam
- Rectal exam
- Test anal/rectal or throat samples for sexually-transmitted diseases
- Test your urine for sexually-transmitted diseases or other infections
- Test your blood for sexually-transmitted diseases
- Test your blood to check the health of your blood, liver and kidneys
- Give you treatment or refer you for treatment of sexually transmitted infections or other issues, if needed.

Further you may need to provide additional samples if any of the above procedures need to be repeated due to issues with sample processing, and/or testing or shipping. Additional testing may be performed as part of quality control.

If you become infected with HIV

Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities you may become infected with HIV. In the unlikely event that you become infected with HIV, study staff will give you counseling and refer you to available medical care and other services you may need. The study does not pay for this care. Tests will be performed to see if you have HIV drug resistance. This will allow your doctor to know what HIV drugs would be best for the treatment of your type of HIV. If the HIV test shows that you have been infected with HIV, you will stop using the study gel. You may be referred to other research studies. Continued study participation would be of no added benefit to you, so your participation in the study will be discontinued.

RISKS AND/OR DISCOMFORTS

Whenever your blood is drawn, you may have:

- Discomfort
- Feelings of dizziness or faintness
- Bruising, swelling, blood clots, and/or infection
- Excessive bleeding

Use of an applicator or dildo to deliver the study gel into the rectum may be associated with minor trauma in and around the rectum and anus, including lacerations (minor cuts) and bruising. The dildo is flexible and is similar in size and shape to an erect penis. The use of the device itself does not pose any risk beyond what you experience as part of your activities of daily life. Rarely, in other studies use of similar devices has been associated with minor bleeding.

A pharyngeal (throat) swab often causes a momentary gagging reflex.

During rectal exams and collection of rectal fluid and tissue samples, insertion of a lubricated anoscope will likely cause mild discomfort. Insertion of rectal swabs and sponges may also cause mild discomfort, in addition to a slight risk of bleeding. A flexible sigmoidoscopy is a commonly practiced medical procedure where a flexible tube with a light source is used to look inside the rectum and lower colon. The procedures done in this study will not involve any increased risk over usual flexible sigmoidoscopy performed for clinical indications (for routine medical diagnosis or treatment). The risks associated with these procedures include mild discomfort, a sudden urge to relieve the bowels, the feeling of having a "bloated stomach", low blood pressure, light bleeding following a bowel movement, abnormal odor or discharge from the rectum, as well as flatulence (gas passed through the anus/rectum) following the procedure. Endoscopic biopsies (biopsies done using a slender, lighted optical tube) to collect rectal tissue samples are painless and heal quickly within 3 days. On extremely rare occasions, the endoscopic procedure or biopsies may lead to pain, infection (sepsis), bleeding or perforation (small hole or tear) of the gastrointestinal tract. Perforation occurs approximately once out of every 1,000 procedures. If this extremely rare complication occurs, antibiotics and surgery to repair the tear may be necessary. Sexual activity before the biopsy has healed may also lead to an increased risk for STIs and HIV infection, if exposed.

Study Gels

The study rectal gel can cause some side effects. We do not yet know all the side effects of the gels. Some, but not all, participants who used rectal gels (not the gel being used in this study) have had:

- Discharge from the rectum
- Irritation and discomfort
- Abdominal bloating, feeling full, or a sense of abdominal pressure and/or pain
- A sudden, almost uncontrollable need to relieve the bowels
- Diarrhea (loose, frequent stools)
- Passing gas from the intestinal tract
- Feeling a constant need to pass stools, despite an empty bowel
- Muscle spasms or pain in and around the rectum and pelvic area

These side effects may or may not be associated with rectal use of dapivirine gel.

Study Drug

The following side effects have been associated with the use of dapivirine in participants in other studies. These side effects may or may not be associated with the use of dapivirine when the drug is placed into a rectal gel:

- Headache
- Upper respiratory tract infection
- Abdominal pain
- Hypophosphataemia (Abnormally low level of phosphates in the blood)
- Neutropenia (Abnormally low level of white blood cells in the blood)

It is also possible that you may have an allergic reaction to the study product. Signs of allergic reaction may include: rash, dizziness, itching, muscle aches, nausea, fainting, facial flushing, chest tightness, cough, hives, fever, and shortness of breath.

Other Possible Risks
You may become embarrassed and/or worried when discussing your sexual practices, ways to protect against HIV and other infections passed through sex, and your test results. You may feel anxious while waiting for your test results, and after receiving them. Trained study counselors will help you deal with any feelings or questions you have.

We will make every effort to protect your privacy and confidentiality during the study visits. Your visits will take place in private. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community. Finding out your HIV status could cause depression and/or suicidal thoughts. Finding out your HIV status could also cause problems between you and your partner(s). If you have any problems, study counselors will talk with you and/or your partner to try to help resolve them.

It is possible that you and/or your partner(s) may experience problems in your relationship(s) associated with maintenance of the study-required abstinence.

The interviews that take place at some of your clinic visits will be computer-administered and questions of a personal nature may be asked. Responding to these questions may make you uncomfortable. You should NOT identify anyone in the interviews and any names that might be mentioned during the interview will NOT be retained. Instead a generic description will be used in the records (i.e., if you refer to a friend's name, "FRIEND1" will be noted).

BENEFITS
You will receive no direct benefit from receiving study gel during your participation in this study. Information learned from this study may help in the development of ways to prevent the spread of HIV in the future. You will receive rectal exams and counseling and testing for HIV and STIs. You will also have tests to check the overall health of your liver, kidneys, and blood cells.

This study cannot provide you with general medical care, but study staff will refer you to other available sources of care.

You will receive free male condoms, if you need them. If you are infected with HIV, you will be referred for medical care, counseling, and other services available to you. Medical care for HIV infection will not be part of this study. You will need to receive care for HIV infection from your own health care provider or we will provide you with a referral. If you have an STI diagnosed, you will receive medicine or a referral, if needed, and study staff will discuss options available for counseling and treatment of your partner.

NEW INFORMATION
You will be told of any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the gel may be causing bad effects, you will be told about this. You will also be told when study results may be available, and how to learn about them.

WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT
A study clinician may need to remove you from the study early without your permission if:

- The study is cancelled by the US FDA, US NIH, the US Office for Human Research Protections (OHRP), MTN, the local government or regulatory agency, or the Institutional

Review Board (IRB). An IRB is a committee that watches over the safety and rights of research 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 participating in the study)
- You are found to be infected with HIV
- You are not able to keep appointments
- Other reasons that may prevent you from completing the study successfully

In the event that you are removed from or choose to leave this study, you will be asked to complete some of the procedures described for Visit 6, if you are willing to do so.

The study clinician will ask you to stop using the study rectal gel but continue to come in for follow-up visits and procedures if you have a bad reaction to the study gel.

ALTERNATIVE OPTIONS
We do not know if the drug contained within the gel works to protect men and women from getting HIV. Currently there are two known methods to reduce your risk of contracting HIV, the use of condoms and/or the use of oral pre-exposure prophylaxis (PrEP) medication, Truvada®. If you are interested in these alternative options, you may want to discuss them with your doctor.

COSTS TO YOU
[SITE TO COMPLETE ACCORDING TO SITE CAPACITY] There is no cost to you for study related visits, physical/rectal examinations, laboratory tests or other procedures. Treatments available to you from the study site for infections passed through sex will be given to you free of charge or you will be referred for available treatment for the duration of the study.

REIMBURSEMENT
[***SITE TO INSERT INFORMATION ABOUT LOCAL REIMBURSEMENT:***] You will receive [***SITE TO INSERT AMOUNT*** **$xx**] for your time, effort, and travel to and from the clinic at each scheduled visit. You may receive [***SITE TO INSERT AMOUNT*** **$xx**] for any visits which occur in between your normally scheduled visits.

CONFIDENTIALITY
Efforts will be made to keep your information confidential. However, it is not possible to guarantee confidentiality. Your personal information may be disclosed if required by law. The study staff may use your personal information to verify that you are not in any other research studies. This includes studies conducted by other researchers that study staff know about. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by:
- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), US Office for Human Research Protections (OHRP), NIH, and/or contractors of NIH
- Other local, US, and international regulatory authorities
- Study monitors
- Site IRB
- Study staff

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

[Site to include/amend the following:]
The researchers will do everything they can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, we have obtained a Certificate of Confidentiality from the US Federal Government. This Certificate protects study staff from being forced to tell people who are not connected with this study, such as the court system, about your participation or information you give for study purposes. However, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, they will be required to tell the proper authorities. This Certificate does not prevent you from releasing information about yourself and your participation in the study.

RESEARCH-RELATED INJURY
*[**SITE TO SPECIFY INSTITUTIONAL POLICY**:]* It is unlikely that you will be injured as a result of study participation. If you are injured, the *[**institution**]* will give you immediate necessary treatment for your injuries. You *[**will/will not**]* have to pay for this treatment. You will be told where you can receive additional treatment for your injuries. The U.S. National Institutes of Health (NIH) does not have a mechanism to pay money or give other forms of compensation for research related injuries. You do not give up any legal rights by signing this consent form.

CLINICALTRIALS.GOV
A description of this clinical trial will be available on http://www.ClinicalTrials.gov. 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.

YOUR RIGHTS AS A RESEARCH PARTICIPANT/VOLUNTEER
*[**SITE TO SPECIFY INSTITUTIONAL POLICY**:]* Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. If you choose not to participate or to leave the study, you will not lose the benefit of services to which you would otherwise be entitled at this clinic. If you want the results of the study after the study 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 or other organization appropriate for the site]*** **at** ***[insert physical address and telephone number**]*.

CONSENT FOR LONG-TERM STORAGE AND FUTURE TESTING OF SPECIMENS

There might be a small amount of blood, rectal tissue or rectal fluid left over after we have done all of the study related testing. We would like to ask your permission to store these leftover samples and related health information for use in future studies, such as future research to fight HIV and other related diseases. This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range. If you agree, your samples and related health data will be stored safely and securely at facilities that are designed so that only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. You can still enroll in this study if you decide not to have leftover samples stored for future studies. If you do not want the leftover samples stored, we will destroy them. The type of testing planned for your leftover specimens is not yet known. However, samples may be used by the MTN Laboratory Center to complete additional quality assurance testing, ensuring that the tests work correctly and supply accurate data. No genetic testing on either a limited set or the full set of genes is planned for leftover samples that are stored for the purposes of future research. It is important that you know that any future testing or studies planned for these specimens must be approved by an Institutional Review Board before they can be done. You can withdraw your consent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study. However, researchers will not be able to destroy samples or information from research that is already underway.

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

SIGNATURES- VOLUNTARY CONSENT

[INSERT SIGNATURE BLOCKS AS REQUIRED BY THE LOCAL IRB] If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to take part in the study, please sign your name or make your mark below.

_____	_____	_____
Participant Name (print)	Participant Signature/Mark	Date
_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

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