

HPTN 069

NEXT-PREP: Novel Exploration of Therapeutics for PREP

A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC), Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate (MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) for Pre-Exposure Prophylaxis (PrEP) to Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and in At-Risk Women

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LIST OF ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ACTG	AIDS Clinical Trials Group Network
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
AUC	area under the curve
BMD	bone mineral density
BUN	blood urea nitrogen
CASI	computer-assisted self-interview
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
Cl	chloride
CLIA	Clinical Laboratory Improvement Amendments
CO ₂	carbon dioxide
CORE	(HPTN) Coordinating and Operations Center
CPQA	Clinical Pharmacology Quality Assurance
CRF	case report form
CRPMC	(NIAID) Clinical Research Products Management Center
CT	Chlamydia trachomatis
CTU	Clinical Trial Unit
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DXA	dual-energy x-ray absorptiometry
EAE	expedited adverse event
EDM	electronic drug monitoring
EIA	enzyme immunoassay testing
EQA	external quality assurance
FDA	(United States) Food and Drug Administration
FTC	emtricitabine
FTC-TP	emtricitabine triphosphate
GALT	gut-associated lymphoid tissue
GC	gonorrhea
GEE	Generalized Estimating Equation
HCV	hepatitis C

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

HBCoreAB	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HPTN	HIV Prevention Trials Network
Hrs	hours
ICF	informed consent form
ID	identification
IDU	injection drug user
IND	investigational new drug
INR	international normalized ratio
IoR	Investigator of Record
IQA	Immunology Quality Assurance
IRB	institutional review board
ITT	intent to treat
IVR	interactive voice response
K	potassium
LDL	low density lipoprotein
LDMS	Laboratory Data Management System
LFT	liver function test
LL	local laboratory
MOS	Medical Outcomes Study
MSM	men who have sex with men
MVC	maraviroc
Na	sodium
NAAT	nucleic acid amplification test
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NL	(HPTN) Network Laboratory
NRTI	nucleoside reverse transcriptase inhibitor
NSAIDS	non-steroidal anti-inflammatory drugs
O.D.	optical density
OHRP	Office of Human Research Protections

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LIST OF ABBREVIATIONS AND ACRONYMS (continued)

PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PEP	post-exposure prophylaxis
PK	pharmacokinetic
PrEP	pre-exposure prophylaxis
PRO	(DAIDS) Protocol Registration Office
PSRT	Protocol Safety Review Team
PT	prothombin time
PTH	parathyroid hormone
PTT	partial thromboplastin time
QA	quality assurance
QC	quality control
QOL	quality of life
R5-tropic	virus that uses the CCR5 co-receptor
RAI	receptive anal intercourse
RNA	ribonucleic acid
RPR	rapid plasma reagin test for syphilis
RSC	Regulatory Support Center
SAE	serious adverse event
SDMC	(HPTN) Statistical and Data Management Center
SHIV	simian human immunodeficiency virus
SIV	simian immunodeficiency virus
SMC	(HPTN) Study Monitoring Committee
SMS	short message service
SOP	standard operating procedure
SSP	Study Specific Procedures
STI	sexually transmitted infection
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir diphosphate
U.S.	United States
ULN	upper limit of normal
VQA	Virology Quality Assurance
X4-tropic	Virus that used the CXCR4 co-receptor
ZDV	zidovudine

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Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and
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Version 3.0 – January 3, 2013**

A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases

Co-Sponsored by:

Gilead Sciences, Inc.
ViiV Healthcare

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by the Division of AIDS (DAIDS), [the Co-Sponsor(s),] or the HIV Prevention Trials Network (HPTN) Coordinating and Operations Center. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the FDA is notified that the IND is discontinued. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee, DAIDS, [and the Co-Sponsor(s)] for review prior to submission.

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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TERMINOLOGY FOR MARAVIROC, TENOFOVIR DISOPROXIL FUMARATE, EMTRICITABINE, AND THEIR DERIVATIVES

Abbreviation	Compound name	Comments
MVC	maraviroc	This is the active formulation of the drug (trade name, Selzentry [®]) manufactured by ViiV Healthcare. This is the form that is measured in plasma and other fluids. MVC is not measured intracellularly.
TDF	tenofovir disoproxil fumarate	This is the inactive, oral formulation of tenofovir disoproxil fumarate (trade name: Viread [®]) manufactured by Gilead Sciences, Inc. The ester form enhances oral absorption and bioavailability. TDF is rapidly metabolized after dosing to the de-esterified pro-drug, tenofovir (TFV), which is also inactive.
TFV	tenofovir	This is the inactive, de-esterified form of TDF. This form of the drug is measured in plasma and other body fluids.
TFV-DP	tenofovir diphosphate	This is the active, phosphorylated form of tenofovir that is generated in cells. This is the form of the drug that is measured in cells (e.g., PBMCs). It is rapidly dephosphorylated to the inactive form outside of cells, and has a very short half-life outside of cells in tissue.
FTC	emtricitabine	This antiretroviral drug (trade name: Emtriva [®]) is manufactured by Gilead Sciences, Inc. FTC is an inactive pro-drug that is activated in cells by phosphorylation. This is the form of emtricitabine that is measured in plasma and other body fluids.
FTC-TP	emtricitabine triphosphate	This is the active form of FTC that is generated in cells. This is the form measured in cells (e.g., PBMCs).

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SCHEMA

- Purpose:** To assess the safety and tolerability of four antiretroviral (ARV) drug regimens used as pre-exposure prophylaxis (PrEP) to prevent HIV transmission in a population of at-risk men who have sex with men (MSM) and in at-risk women.
- Design:** Phase II, four-arm, multisite, randomized, double-blinded trial.
- Population:** HIV-uninfected at-risk MSM and at-risk women recruited from sites in the United States (U.S.).
- Sites are strongly encouraged to enroll young MSM (aged 18-25) and/or MSM or women of color to maximize representation from these groups. Each site will be asked to work with their Community Advisory Boards (CABs) and outreach, education and recruitment teams to develop a recruitment plan that will focus on the engagement of MSM who are younger and/or MSM and women of color.
- Study Size:** Four hundred (400) MSM and 200 women. Seventy-two (72) participants (18 per arm) will be asked to enroll in a Drug Interaction Subset. Sixty (60) men and 60 women (15 male/15 female per arm) at selected sites will be asked to enroll in a Tissue Subset.
- Study Regimens:** The antiretroviral drugs (ARVs) being used in this study are: maraviroc (MVC) 300 mg, emtricitabine (FTC) 200 mg, tenofovir disoproxil fumarate (TDF) 300 mg, and matching placebos. Participants will be stratified by gender and randomized to one of four arms as follows:
- Arm 1:** MVC 300 mg + [FTC placebo] + [TDF placebo] orally once daily.
Arm 2: MVC 300 mg + FTC 200 mg + [TDF placebo] orally once daily.
Arm 3: MVC 300 mg + [FTC placebo] + TDF 300 mg orally once daily.
Arm 4: [MVC placebo] + FTC 200 mg + TDF 300 mg orally once daily.
- Study Regimen = 3 pills daily; all arms receive at least one active drug.**
- Study Duration:** Approximately 30 months. Accrual will occur in a staggered fashion, with men beginning first, and women beginning several months later. Accrual for the men will require approximately 9 months, and accrual for the women will require approximately 9 months. Each participant will be followed for approximately 12 months (study drug will be stopped at Week 48, with a final post-study drug visit at Week 49).
- Study Sites:** Participating sites will be located in the United States and listed in the Study Specific Procedures (SSP) Manual, and are comprised of HIV Prevention Trials Network (HPTN) – and AIDS Clinical Trials Group Network (ACTG)-affiliated Clinical Research Sites (CRSs). Participants in the Tissue Subset will be recruited at selected study sites.

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SCHEMA (Continued)

Primary objective:

To assess the safety and tolerability of MVC, MVC+FTC, MVC+TDF, and TDF+FTC over 48 weeks. This will be measured by the occurrence of Grade 3 and higher adverse events (safety) and time to permanent discontinuation (tolerability) in each of the four study arms.

The **secondary objectives** of the study are to:

- Assess Grade 2 and higher adverse events, and Grade 1 clinical (non-laboratory) adverse events that lead to a temporary or permanent hold in study drug.
- Assess changes in lipids in each of the four study arms.
- Assess changes in bone mineral density in each of the four study arms.
- Evaluate interactions of MVC, FTC, and TDF in the four study arms in a subset of participants (Drug Interaction Subset).
- Evaluate concentrations of MVC, FTC, tenofovir (TFV) and their phosphorylated derivatives (FTC-triphosphate (FTC-TP) and TFV-diphosphate (TFV-DP) in plasma, peripheral blood mononuclear cells (PBMC), rectal tissue and fluid, and cervical tissue and cervicovaginal fluid, in a subset of participants (Tissue Subset).
- Assess changes in peripheral blood (all participants), and gut-associated lymphoid tissue (GALT) T cell phenotype (Tissue Subset).
- Assess adherence in each of the four study arms as measured by an electronic drug monitoring device (EDM) and self-report.
- Assess and characterize sexual behavior over time as measured by computer-assisted self-interview (CASI).
- Assess the relationship between adherence and sexual risk-taking.
- Evaluate the association of drug concentrations with other adherence measures.
- Assess quality-of-life in each of the four study arms.

The **exploratory objectives** of the study are to:

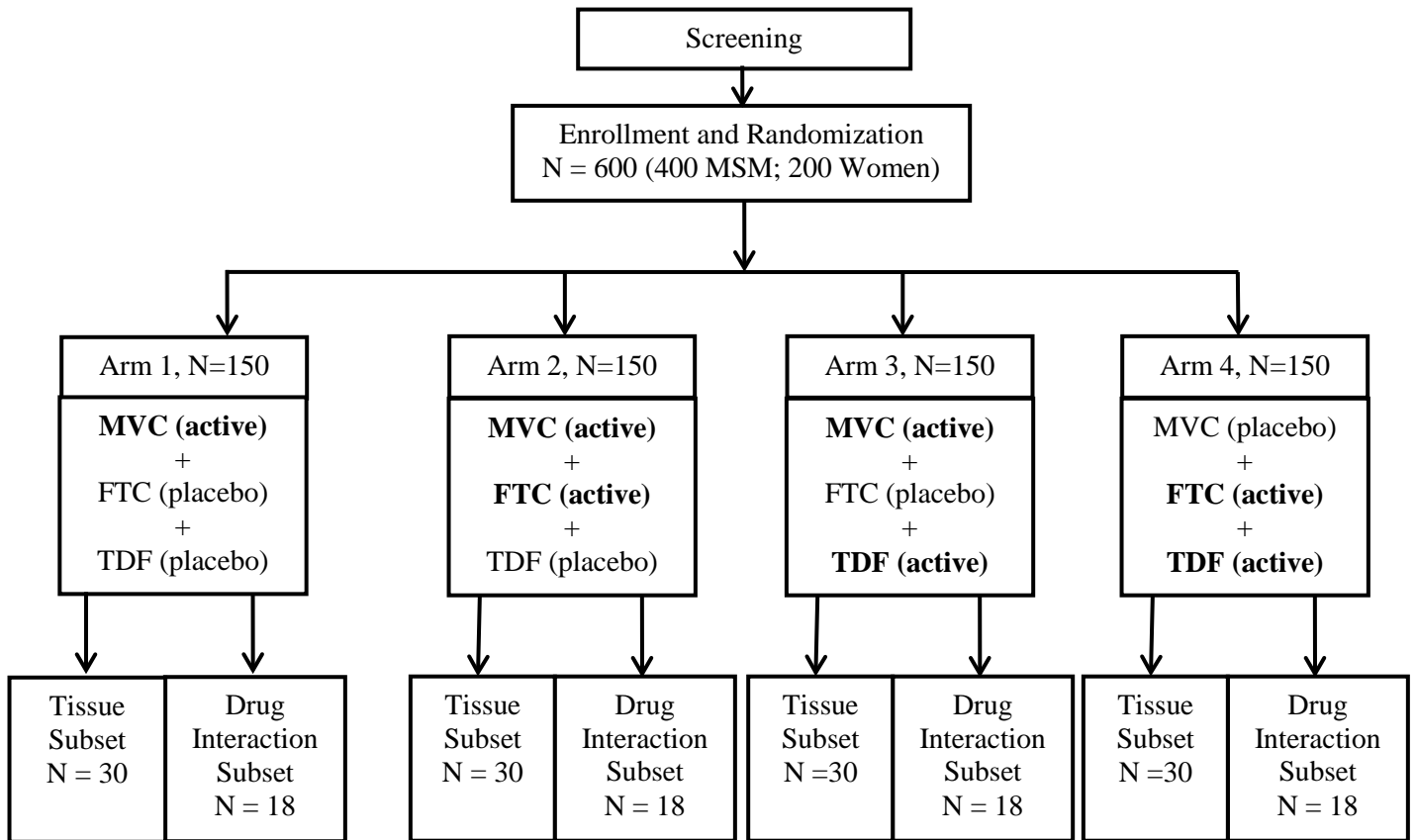
- Characterize HIV (e.g., co-receptor tropism and drug resistance) in any participant who becomes HIV-infected during the study.

- Evaluate the relationship between HIV exposure (assessed using immunologic studies) and behavior.
- Determine whether oral PrEP is associated with suppression of HIV replication in colorectal and cervical explants (*ex vivo* HIV challenge, Tissue Subset).
- Collect hair samples from a subset of participants for possible future studies of drug concentrations in hair.
- Describe gender differences in measured outcomes.
- Assess correlation of drug levels in rectal and cervical samples.
- Characterize host CCR5 polymorphisms and host genetic polymorphisms associated with study drug exposure.
- Describe baseline and incident bacterial sexually transmitted infections (STIs) among participants.

HPTN 069

A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC), Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate (MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) For Pre-Exposure Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and in At-Risk Women

OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



Overview of Study Visit Schedule

		Screening	On Study (Weeks)										
Study Day/Week		45 days	0	2	4	8	16	24	32	40	48	49	TD or SD
All Participants (N=600)		X	X	X	X	X	X	X	X	X	X	X	X
Drug Interaction Subset (N=72)				X ¹									
Tissue Subset	Men (N=60) – plasma, PBMCs, rectal tissue and fluid, hair		X ²				X ⁴	X		X ⁴	X	X	X ³
	Women (N=60) – plasma, PBMCs, cervical tissue, cervicovaginal fluid, and hair (rectal tissue and fluid if woman opts for rectal sampling)		X ⁵				X ⁶	X		X ⁶	X	X	X ³

TD, treatment discontinuation; SD, study discontinuation

¹Includes pre-dosing blood draw, directly observed therapy (DOT) x 1 dose, 6 hour post-DOT blood draw.

²Rectal fluid is not collected at Enrollment (Week 0).

³Plasma, PBMCs and hair samples only at TD or SD

⁴Syphilis testing and GC/CT NAAT (rectal swab and urine) only

⁵Rectal fluid and cervicovaginal fluid are not collected at Enrollment (Week 0).

⁶Syphilis testing and cervical swab for GC/CT NAAT (Note – rectal swab for GC/CT NAAT only in those women electing to participate in rectal tissue sub-study)

1.0 INTRODUCTION

1.1 Background and Rationale

1.1.1 Pre-Exposure Prophylaxis (PrEP)

Globally, HIV is transmitted most commonly through sexual exposure. There are at least seven efficacy studies of PrEP either recently completed or currently underway in 13 countries involving over 20,000 individuals with diverse risk behaviors (discordant couples, at-risk heterosexual persons in high HIV prevalence areas, intravenous drug users [IDUs], MSM). All of these clinical trials evaluate PrEP using either tenofovir disoproxil fumarate (TDF) or the fixed-dose combination of TDF/emtricitabine (FTC).

The U.S. Centers for Disease Control and Prevention (CDC) recruited 400 at risk HIV-uninfected MSM in the U.S. in Atlanta, Boston, and San Francisco in a placebo-controlled safety study of daily oral TDF (300 mg daily) versus placebo (Grohskopf L 2010). Half of the men were randomized to begin taking a daily pill at the start of the study, and the other half were monitored for 9 months, and then began taking a pill. There were no statistically significant differences in Grade 3 or 4 adverse events (regardless of causality with 11% developing at least one Grade 3 or 4 event in each group), serious adverse events, elevated creatinine, or hypophosphatemia between the men taking TDF versus those that were assigned to the placebo. There was no evidence of increased risk compensation/behavioral disinhibition among the men, whether they initiated pill taking earlier or later, nor were significant behavioral differences seen between the men randomized to TDF and those randomized to placebo. Seven incident HIV infections were detected after enrollment, but none were detected among the men who took TDF (P=not significant). The study was not powered to prove the efficacy of TDF for chemoprophylaxis, but the data suggest that TDF was safe, well-tolerated, and that taking pills was not associated with risk compensation in the context of a clinical trial.

TDF given as PrEP also was generally well-tolerated in 469 HIV-uninfected women, without a significant difference in clinical event rates (~5-13%) or selected laboratory abnormalities, compared with placebo (Peterson L 2007). TDF/FTC (or TDF/lamivudine [3TC]) given as post-exposure prophylaxis (PEP) also was generally well-tolerated in high-risk HIV-uninfected MSM, with 72-87% completing a 4-week daily treatment course and approximately 1-12% experiencing a moderate or greater intensity clinical symptom (Mayer KH 2008). The rate of adverse events was much lower, and the completion rates much higher in the TDF-based PEP groups, compared to those seen in the historical controls who took zidovudine (ZDV)-based regimens.

In late 2010, results became available from the first efficacy trial of an antiretroviral-based PrEP, known as “iPrEX” (Grant RM 2010). Close to 2,500 HIV-negative MSM and transgendered women who have sex with men in South Africa, South America, Thailand, and the United States (U.S.) were randomized to daily oral TDF/FTC or placebo. Overall 44% fewer incident HIV infections occurred in the TDF/FTC group (36 incident infections) compared to the placebo group (64 incident infections). A key finding of the study was that drug detection in blood (intracellular and plasma levels) was highly correlated with protection among those whose data indicated use of TDF/FTC on at least 90% of days, incident HIV infection was 73% lower when

compared with the placebo arm. Adverse events were similar between the two groups, with Grade 3 and 4 events occurring among 12% of participants in each arm. Some Grade 2 and higher adverse events were reported significantly more frequently in the TDF/FTC arm than the placebo arm: moderate nausea (22 vs. 10 events) and unintentional weight loss (34 vs. 19 events). Serum creatinine elevations occurred more frequently in the TDF/FTC arm than placebo arm (25 vs. 14 events). All elevations in the serum creatinine level resolved after discontinuation of study drug. There were 10 participants who were infected at enrollment, of whom 3 had FTC-resistant infections. There were no TDF-resistant infections. Of the participants who became infected during follow-up, no FTC or TDF resistance was detected. Of interest, participants in the study reported increased condom use and decreased number of sexual partners.

The Partners PrEP Study enrolled 4,758 HIV serodiscordant African heterosexual couples, and compared TDF once daily and TDF/FTC once daily regimens to placebo. The TDF and TDF/FTC PrEP demonstrated definitive reduced risk of HIV acquisition, by 67% ($P<0.001$) and 75% ($P<0.001$) respectively, in these men and women (Baeten J 2011; Baeten, Donnell et al. 2012)

The CDC TDF-2 trial showed that daily TDF/FTC was safe and effective for prevention of HIV infection among African heterosexual men and women compared to placebo (Thigpen MC 2011). In a modified intent-to-treat analysis that excluded 3 participants who were HIV-infected at enrollment, the overall protective efficacy was 62.2% ($P=0.03$); an “as-treated” analysis demonstrated a protective efficacy of 77.9% ($P=0.01$). (Thigpen, Kebaabetswe et al. 2012) Both studies showed that the PrEP regimens were well-tolerated.

After consideration of these results (primarily iPrEX and Partners PrEP), the U.S. Food and Drug Administration (FDA), in July 2012, approved Truvada (TDF/FTC fixed dose combination) “to be taken once daily and used in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults who do not have HIV but are at high risk of becoming infected (FDA 2012).”

In contrast to the studies outlined above, the FEM-PrEP study was stopped early (April 2011) because the independent Data and Safety Monitoring Board (DSMB) determined that it was highly unlikely to demonstrate that use of TDF/FTC was efficacious in prevention of HIV in a study population of almost 2,000 African women; HIV incidence in the TDF/FTC group was 4.7 per 100 person-years and in the placebo group was 5.0 per 100 persons-years ($P=0.81$) (Van Damme, Corneli et al. 2012). A second study, MTN-003 (VOICE), was designed to compare the efficacy of daily 1% TFV gel, daily oral TFV, and daily oral TDF-FTC among heterosexual African women; both the daily oral TFV arm and the daily 1% TDF gel arms were stopped due to futility (September 2011 and November 2011 respectively) (NIAID 2011; NIAID 2011). The study has completed data collection and is in the process of assessing the impact of TDF-FTC on HIV acquisition. The inconsistent PrEP results in women are presently unexplained and support the need for continued work in this area to better understand causal factors in futility findings and to identify the potential value of alternative PrEP agents for women.

Some additional concerns exist: TDF/FTC is used commonly in ARV regimens for treatment of HIV-infected individuals and viral strains that are resistant to TDF and/or FTC exist and are transmitted in the community. In the Partners PrEP Study, eight participants receiving active PrEP were later found to have been HIV-1 infected at baseline; two of these eight persons developed antiretroviral resistance during the study (one K65R mutation and the other an M184V mutation). (Baeten, Donnell et al. 2012) In the Fem-PrEP study, 4 individuals in the TDF-FTC arm had viral strains with FTC resistance mutations (3 individuals had an M184V mutation and one individual an M184I). (Van Damme, Corneli et al. 2012) In the TDF-2 trial, one individual in the TDF-FTC arm with unrecognized HIV-1 infection at baseline developed multiple resistance mutations (K65R, M184V, and A62B). (Thigpen, 2012)

Although TDF with or without FTC has been generally well-tolerated in both HIV-infected individuals (Arribas JR 2008) and healthy volunteers using PrEP (Peterson L 2007; Grant RM 2010; Grohskopf L 2010; Baeten J 2011; Thigpen MC 2011), the Fem-PrEP trial reported significantly higher proportions of women in the TDF-FTC arm compared to placebo with nausea (4.9% vs. 3.1%; $P=0.04$), vomiting (3.6% vs. 1.2%; $P<0.001$), and elevated (all grades) alanine aminotransferase levels (11.4% vs. 8.6%; $P=0.03$) (Van Damme, Corneli et al. 2012). Higher rates of nausea and vomiting were also observed in the TDF-2 trial among persons in the TDF-FTC arm compared with placebo (nausea: 18.5% vs. 7.1%; $P<0.001$; vomiting: 11.3% vs. 7.1%; $P=0.008$) (Thigpen, Kebaabetswe et al. 2012).

Concerns also remain about longer-term side effects of these drugs, including renal toxicity and decreased bone mineral density (BMD). Renal toxicity occurs with tenofovir disoproxil fumarate use, including acute renal failure and Fanconi's syndrome (Gilead). As noted above, the iPREX study showed more serum creatinine elevations occurred in the TDF/FTC arm than placebo arm (25 vs. 14 events); all elevations in the serum creatinine level resolved after discontinuation of study drug (Grant RM 2010). There were no differences in laboratory abnormalities between the tenofovir disoproxil fumarate-containing arms and the placebo arms in the CDC TDF-2 or Partners PrEP studies (Baeten J 2011; Thigpen MC 2011). However, there was a trend in the Fem-PrEP trial toward higher discontinuations among women in the TDF-FTC arm compared with placebo due to hepatic or renal abnormalities ($P=0.051$) (Van Damme, Corneli et al. 2012).

See Section 1.1.6 regarding the effect of TDF and TDF/FTC on BMD in HIV-uninfected persons.

Given the ongoing concerns about drug resistance and long-term toxicity, as well as conflicting efficacy data in women, further options for ARV PrEP regimens should be explored.

1.1.2 Maraviroc (MVC) for PREP

Maraviroc (MVC) is a CCR5 antagonist that was approved by the FDA in 2007 for treatment of people infected with HIV that utilizes the CCR5 co-receptor for cell entry (R5-tropic virus). FDA approval of MVC was based on large phase III studies that demonstrated the virologic benefits of MVC in HIV-infected, treatment-experienced patients (Gulick RM 2008). The safety of MVC has been established in HIV-infected patients over the past two to five years (Walmsley S 2010) (Gulick 2012) and an estimated >100,000 prescriptions for MVC have been written worldwide. In addition, the hepatic effects of MVC were analyzed across all Pfizer-sponsored

MVC clinical trials (N=2,350), and MVC was not associated with significant hepatic events when taken at the recommended doses (Ayoub A 2010). Additionally, a total of 450 HIV-uninfected individuals have taken MVC in clinical trials, some for up to 3 months, without significant safety issues reported (Fleishaker D 2009).

MVC has a number of potential advantages for use as a PrEP agent: The drug acts early in the life cycle of HIV (prior to entry into a CD4-positive cell) by preventing viral binding to the CCR5 co-receptor. HIV transmission occurs most commonly with R5-tropic virus; in one study of acute HIV infection, 54 of 55 transmitted viruses were R5-tropic (Keele BF 2008).

Although MVC is FDA-approved for twice-daily dosing for HIV treatment, there are pharmacokinetic (PK) data that establish that once-daily dosing of MVC achieves adequate target concentrations and CCR5 co-receptor occupancy (Rosario MC 2008). In fact, the study showed that MVC achieves nearly maximal receptor occupancy with single doses as low as 3 mg in healthy and HIV-infected volunteers. In addition, in the phase III studies of MVC in treatment-experienced HIV-infected patients, virologic outcomes were not significantly different in the once-daily and twice-daily MVC arms (Gulick RM 2008). Furthermore, although the MERIT study of MVC in treatment-naïve patients had a once-daily MVC arm that was stopped early because it did not meet pre-specified non-inferiority criteria, reanalysis of the study with the enhanced tropism assay revealed that excluding patients with newly detected non-R5 virus resulted in similar outcomes with once-daily and twice-daily MVC dosing (Cooper DA 2010; Swenson LC 2010). Additionally, a phase I/II study of MVC in HIV-infected individuals demonstrated a potent antiretroviral effect with 10 days of dosing at 300 mg daily (Fätkenheuer G 2005). Thus, once-daily dosing seems reasonable to test for PrEP.

Twice-daily MVC achieves concentrations that are three times higher in female genital secretions than in blood plasma (Dumond JB 2009) and 7.5 to 26 times higher in rectal tissue compared with blood plasma concentrations (Brown KC 2011). MVC also has a long terminal half-life following oral dosing to steady state in healthy subjects of 14-18 hours (Pfizer). In macaques, a single oral dose of maraviroc achieved concentrations in rectal secretions 4 days later that were 22-fold higher than the IC₅₀ value determined in PBMCs (2.0 ng/mL) and was associated with 100% CCR5 receptor occupancy on the PBMCs (Aung W 2011).

Viral resistance to MVC occurs uncommonly in the community; the most common mechanism of resistance is the selection of HIV that uses the CXCR4 co-receptor (X4-tropic) virus that was most likely present at low levels at the time of MVC treatment initiation. In addition, the drug is not used routinely as first-line treatment in HIV-infected individuals.

MVC prevented infection in macaques with SHIV virus (a chimeric virus that contains the HIV-1 env, rev, tat, and vpu genes in an SIV vector) when administered topically prior to challenge as a vaginal microbicide (Veazey RS 2010). In addition, as a proof of concept, another investigational CCR5 antagonist, CMPD 167, prevented SHIV infection when given orally prior to challenge in macaques (Veazey RS 2005). Oral MVC prevented infection using a vaginal HIV-1 challenge in a RAG-hu humanized mouse model (Neff CP 2010).

In a CDC study (Massud I. 2012), the pharmacokinetic profile of maraviroc in plasma and rectal secretions was evaluated in rhesus macaques given an oral dose of MVC (44 mg/kg). The results produced a similar favorable PK profile in macaques at this dosage as seen in humans receiving a

300 mg dose. The study showed a high MVC concentration in rectal secretions. Six macaques received a dose of maraviroc 24 hours before rectal SHIV challenge and a second dose 2 hours later. Despite the favorable pharmacokinetic profile, 5 of 6 macaques receiving maraviroc (and 3 of 4 controls) were infected following rectal exposure and therefore, no prophylactic efficacy (for the prevention of rectal SHIV) was seen.

Napier et al. showed that although macaque and human CCR5 receptors seem to share the same high binding affinity for chemokines, the CCR5 receptor antagonist, MVC, dissociates from the receptor about 10-fold faster in macaques compared to humans (Napier, Sale et al. 2005). Thus, the duration of action of MVC seems likely to be more sustained in humans and this observation calls into question the applicability of the macaque model for human studies of maraviroc.

In summary, MVC is an FDA-approved drug with a significant safety record in HIV-infected individuals; MVC has a number of favorable mechanistic, PK, and drug resistance properties, and favorable initial animal efficacy data has been obtained using MVC for chemoprophylaxis. However, healthy HIV-uninfected individuals have taken MVC for a maximum of only 28 days in clinical trials, and patients with rheumatoid arthritis (HIV-uninfected) for a maximum of only 12 weeks (Fleishaker D 2009). Because other ARV drugs have occasionally demonstrated greater toxicity in HIV-uninfected individuals than in HIV-infected individuals (e.g., lopinavir/ritonavir, nevirapine, ZDV), the longer-term safety and tolerability of MVC as a PrEP agent in healthy, HIV-uninfected individuals requires further assessment.

1.1.3 MVC + FTC for PrEP

There is some concern that blocking the CCR5 co-receptor when MVC is used as a PrEP agent alone will select for transmission of X4-tropic HIV. However, transmission of X4-tropic HIV is rare in the absence of drug selection (Keele BF 2008). Adding a second active ARV drug with activity against X4-tropic virus to a MVC-based PrEP regimen could address this concern.

Emtricitabine (FTC) is a nucleoside analogue approved for the treatment of HIV infection. FTC is well-tolerated and demonstrates potent virologic activity against both R5- and X4-tropic HIV. FTC is dosed once-daily and has a long mean plasma elimination half-life of approximately 10 hours following a single oral dose (Gilead). FTC has been used in combination with TDF in animal studies of PrEP (García-Lerma JG 2008) as well as human studies (Grant RM 2010).

Although a related compound, lamivudine (3TC), also is potent and well-tolerated in combination with MVC in HIV-infected patients (Gulick RM 2008; Cooper DA 2010), FTC may offer several advantages over 3TC including: a longer serum half-life (10 hours vs. 5-7 hours (Gilead; GlaxoSmithKline), and a higher threshold for drug resistance (Svicher V 2010). Notably, 3TC has not been used in any prior animal or human studies of PrEP. Thus, MVC+FTC appears promising for use as a PrEP regimen in HIV-uninfected individuals.

1.1.4 MVC + TDF for PrEP

As above, adding a second ARV drug with activity against X4-tropic virus to a MVC PrEP regimen would address concerns about infection with X4-tropic virus. TDF would be a favorable candidate for addition to MVC because TFV-resistant viral strains are uncommon in the community and TDF (with or without FTC) is the regimen that has been used most often in

PrEP studies in animals (García-Lerma JG 2008) and humans (Grohskopf LA 2002; Peterson L 2007; Grant RM 2010). In addition, TDF would have activity against FTC-resistant strains with the M184I/V substitution.

1.1.5 Pharmacokinetics of MVC, FTC, and TDF

MVC is a cytochrome 3A4 (CYP3A4) substrate, similar to a number of other FDA-approved ARV agents used for the treatment of HIV infection (Pfizer). CYP3A4 activity can be modulated by other drugs (Brown KC 2009). Thus, MVC plasma concentrations can be influenced by inducers or inhibitors of this pathway. MVC does not inhibit or induce CYP3A activity itself (Pfizer ; Abel S 2008 [2]; Abel S 2008 [3]; Brown KC 2009).

ARV drugs used to treat HIV infection are metabolized primarily by Phase I (CYP450) enzymes (Brown KC 2009). CYP3A4 activity also can be modulated by a number of ARV drugs; therefore, use of other drugs in combination with MVC could affect the level of MVC drug exposure achieved using a given MVC dose (Pfizer; Abel S 2008 [2]; Abel S 2008 [3]; Brown KC 2009). Although MVC is metabolized primarily through the CYP3A4 isoenzyme, renal elimination accounts for approximately 23% of its total clearance, and involves both passive and active processes (Pfizer; Abel S 2008 [3]). Neither FTC nor TDF is a substrate, inhibitor, or inducer of CYP450. Rather, the drugs are mainly eliminated through the renal route (Gilead; Gilead).

A number of drug interaction studies conducted in healthy volunteers characterize the lack of effects of MVC on the renal elimination of nucleoside reverse transcriptase inhibitors (NRTIs) (Abel S 2008 [1]). For instance, two studies showed that MVC did not affect the pharmacokinetics (PK) of ZDV, 3TC, or TFV (Abel S 2008 [1]). Although there are no PK data for MVC and FTC, the lack of interaction with 3TC or TFV makes it unlikely that an important PK interaction would occur with FTC. Clinically important drug interactions between MVC and FTC have not been described and are not expected.

There are also data demonstrating similar MVC and FTC PK when comparing these data in HIV-infected and HIV-uninfected populations (Gilead; Chan PL 2008; Weatherley B 2009). In addition, the safety and tolerability of MVC and FTC dosed separately have also been demonstrated in several healthy volunteer studies (Blum MR 2007; Zong J 2007; Chan PL 2008; Abel S 2008 [1]; Weatherley B 2009). The adverse events (AEs) reported with most of these studies were rated as minor or moderate in severity and overall these drugs were well-tolerated. Hypotension has been described only with doses of MVC \geq 600 mg twice daily (Pfizer). Because this study will be evaluating a lower dose of MVC (300 mg once daily), hypotension is unlikely to occur in this population. Finally, it is important to note that MVC and FTC are frequent components of ARV treatment regimens and concerns about the occurrence of drug interactions or major toxicities with the combination of these two drugs have not been reported.

Despite the lack of evidence of a clinically important drug interaction between MVC and FTC, and data indicating that the PKs of these two drugs do not differ significantly in HIV-infected and HIV-uninfected subjects, the pharmacology and safety of this drug combination have not been formally evaluated in healthy volunteers. In the current study, MVC/FTC and MVC/TFV interactions will be evaluated at the Week 2 visit in the first 72 enrolled participants who provide consent for additional evaluation (18 in each study arm, herein referred to as a “Drug Interaction

Subset”). Participants in all four study arms will be enrolled in the Drug Interaction Subset to maintain blinding of the study regimens. Analyses will include a comparison of MVC levels in the MVC+FTC and MVC+TDF arms to those in the MVC only arm. Analyses will also include a comparison of FTC concentrations in the MVC+FTC and MVC+TDF arms to those in the TDF+FTC arm. Data on MVC, FTC and TFV also will be compared to published data on the concentrations of these drugs obtained when they are used alone.

If this analysis reveals that there are no interactions between MVC and FTC, the safety profile of the combination regimen would be expected to be the same as the safety regimen of each drug used alone, given the same anticipated drug exposure. On the other hand, if use of the drugs in combination results in inhibition of clearance of one drug by the other, that might result in increased concentrations of one drug and potentially increase drug toxicities. Alternatively, if use of the drugs in combination results in induction effects that increase clearance of either drug, that could reduce drug concentrations, possibly below the level associated with ARV effects.

Data from the Drug Interaction Subset described above will be reviewed by the Protocol Safety Review Team (PSRT) in as close to “real-time” as possible, in order to advise the protocol team regarding any important safety concerns. (Refer to the Study Specific Procedures [SSP] Manual for a full description of the PSRT).

In addition to the assessment of drug-drug interactions described above, PK studies will be performed in a subset of participants from each of the four study arms (herein referred to as the “Tissue Subset”). These studies will be conducted in men (N=60) and women (N=60) who will provide additional consent for Tissue Subset participation, 15 participants of each sex from each study arm. Note that tissue from participants in Tissue Subset will also be collected for analysis of gut-associated lymphoid tissue (GALT) T cell phenotype and *ex vivo* HIV challenge studies (see Sections 1.1.11 and 1.1.12, respectively). In the Tissue Subsets, concentrations will be measured for each study drug and/or their derivatives [MVC, FTC, TFV, FTC-TP, TFV-DP] in the following samples: plasma, PBMCs, rectal tissues (men and women subset participants electing to the rectal procedures), and cervical tissues (women’s subset) (from biopsies and homogenate), cervicovaginal fluid (women’s subset), and rectal fluid (from sponge collection in men and women subset participants electing to the rectal procedures). Hair samples will also be collected and stored for possible future analysis of drug levels. These analyses will be performed at Weeks 24 and 48 (to obtain information during steady state) and at Week 49 (to obtain information about drug clearance after cessation of drug use [“wash-out”]). MVC data from rectal tissue and fluid have been reported in a small cohort (Brown KC 2011). FTC has not been assessed in these compartments. With these data, the protocol team will attempt to build multi-compartment models to allow simulation of tissue, cervicovaginal, and rectal lumen concentrations of these drugs in the remainder of study participants. This information will be useful in future efficacy studies, where the concentration of these drugs at the tissue site of action can be estimated based on PK-pharmacodynamic (PD) analyses; these data could be used to guide drug dosing in future studies.

1.1.6 Potential Bone Effects of TDF and MVC

TDF has been associated with decreased bone mineral density (BMD) in multiple randomized, clinical trials in HIV-infected persons, both with initiation of ARV treatment (ART) (Gallant JE

2004; Moyle G 2009; McComsey GA 2011) or switching regimens (Martin, Bloch et al. 2009). The clinical impact of this effect is not clear, but the effect may contribute to the high prevalence of osteoporosis and fractures observed in HIV-infected patients (Brown T 2006; Triant V 2008). Also unclear from existing data are the mechanisms underlying the effect of TDF on BMD. In animal models, high dose TDF exposure is associated with impaired bone mineralization (Castillo AB 2002). TDF also can be associated with renal phosphate wasting, which can present with osteomalacia (Parsonage MJ 2005). An intensive investigation is currently underway to determine the mechanisms and clinical consequences of TDF-induced bone loss in HIV-infected persons.

Two PrEP trials using TDF and investigating the effects on BMD among high-risk groups without HIV-infection were reported in 2011 (Liu, Vittinghoff et al. 2011; Mulligan K 2011). Liu et al. reported results of dual-energy x-ray absorptiometry (DXA) bone densitometry from a subset of men participating in the same CDC study cited in Section 1.1.1 (Grohskopf L 2010). In the intent-to-treat analysis, there was a 1.1% net decrease in mean BMD in the TDF arms pre-treatment or placebo group at the femoral neck, and a 0.8% net decline at the total hip; at the L2 to L4 spine, there was a non-significant trend towards an adverse effect. In summary, TDF use in this study resulted in a small but statistically significant decline in BMD at the total hip and femoral neck in HIV uninfected men participating in the study. Mulligan et al. reported results from iPrEX showing that by Week 24 of the study, BMD tended to increase in the placebo arm, and decrease in the TDF/FTC arm, and while these results were modest, they were statistically significantly different (Mulligan K 2011). No bone mineral density data was collected in the Partners PrEP study (Baeten J 2011). In the TDF-2 study, BMD was measured in a subset of participants (109 in the TDF-FTC arm and 112 in the placebo arm) and demonstrated significant decreases at the forearm, spine, and hip for persons in the TDF-FTC arm as compared with those in the placebo arm (Thigpen, Kebaabetswe et al. 2012). At 12 months, after treatment initiation, for example, 45 of 109 participants in the TDF-FTC group and 44 of 112 participants in the placebo group completed bone mineral density testing. Mean z-scores at this time point were lower in the TDF-FTC group compared to the placebo group at all sites examined: Forearm: -0.72 vs. -0.42; Total Hip: 0.34 vs. 0.55; Lumbar Spine: -0.74 vs. -0.53 (all $P < 0.01$). Similar results were observed at 6, 18, and 24 months.

CCR5 may play an important role in the regulation of bone turnover. Bone is constantly being remodeled through the actions of osteoclasts, which resorb old bone, and osteoblasts, which form new bone. The actions of these two key cells are tightly coupled, such that under normal conditions osteoblast and osteoclast activity are balanced. In addition to other mechanisms, such as the OPG/RANKL system, interaction between osteoblasts and osteoclasts may be mediated in part through CCR5. CCR5 is expressed on osteoblasts and one of its primary ligands is MIP-1 α , a protein secreted in abundance by osteoclasts (Han JH 2001; Yano S 2005). In addition, CCR5 is expressed on osteoclasts (Han JH 2001; Yano S 2005).

Data regarding the functional consequences of CCR5 inhibition appear to be conflicting. In animal models of rheumatoid arthritis, CCR5 inhibitors have been shown to reduce inflammation-induced bone destruction (Yang YF 2002; Vierboom MP 2005; Okamoto H 2006) whereas CCR5-deficient mice showed evidence of increased osteoclast activity and alveolar bone resorption (Andrade I Jr. 2009), perhaps through the loss of osteoblast control over

osteoclast activity. The extent to which the phenotype in CCR5-deficient mice is attributable to compensatory changes in the absence of CCR5 is not clear.

The effect of MVC on BMD in clinical studies is not known. Based on the above data from pre-clinical studies with other CCR5 inhibitors, a beneficial effect on bone turnover can be hypothesized. However, a recent study of MVC in rheumatoid arthritis was terminated because of lack of efficacy on disease endpoints (Fleishaker D 2009), but BMD was not specifically examined. It is therefore important to understand the skeletal effect of this medication, particularly relative to and in combination with TDF. As such, HPTN 069 will not only add to the data set for TDF and TDF/FTC, but will provide data for MVC and its effect on BMD, which has not yet been evaluated in any population.

Rationale for studying BMD in this population: There are multiple reasons to investigate BMD in this study. First, this is a young, healthy population at their peak bone mass and any toxicity related to BMD may not be clinically manifested for many years. Since bone mass during early adulthood is thought to be a major determinant of fracture risk among older individuals (Bonjour JP 2009), investigation of this toxicity is critical in this population. Second, investigation of the bone effects of these medications in an HIV-uninfected population allows for a better evaluation of a drug-specific effect, independent of HIV-infection. This study will add to current data by comparing TDF to MVC and evaluating the combination of these two medications. In addition, with the iPrEX, Partners PrEP and CDC TDF2 studies showing promise for the prevention of HIV-infection, high rates of adherence in the current study could actually result in an increase in drug-related toxicities, such as bone loss.

1.1.7 Potential Effects of TDF and MVC on Blood Lipid Levels

A recent prospective study in HIV-infected individuals demonstrated an antihyperlipidemic effect of tenofovir disoproxil fumarate (Tungsiripat M 2010). Additionally, there are some data to suggest that maraviroc is associated with favorable lipid changes in HIV-infected individuals (MacInnes A 2011). However, there are no data available for either TDF or MVC in HIV-uninfected individuals. For individuals receiving PrEP (who are HIV-uninfected by definition), an understanding of lipid metabolism would be an important finding for prescribing future PrEP regimens.

1.1.8 PrEP Adherence

Biologic efficacy of the PrEP regimens used in this study will require that the study participants achieve sufficient ARV drug levels at the time of sexual exposure and immediately afterwards. iPrEX clearly demonstrated that participants who seroconverted in the TDF/FTC arm generally had lower levels of adherence demonstrated by low to undetectable drug levels near the time of acquiring HIV infection. Adherence clearly impacted the overall efficacy of TDF/FTC PrEP in iPrEX. The reasons for this are unclear. Possible explanations include AEs, use of placebo in the study design, unknown efficacy of study treatment and concerns regarding being mistakenly identified as HIV-infected, in addition to standard adherence challenges associated with any medical regimen. In contrast, the Partners PrEP study reported detectable drug in 81% of participants in the TDF-FTC arm and 83% in the TDF arm. Alternatively, the FEM-PrEP trial analyses of plasma tenofovir levels showed that <27% of participants who seroconverted and <38% of participants that were uninfected demonstrated target tenofovir levels, suggesting low

adherence rates (Van Damme, Corneli et al. 2012). Although low adherence was demonstrated in the iPrEX trial (44% of uninfected participants on drug had detectable tenofovir), efficacy to prevent HIV acquisition was shown in iPrEX. These differences between trial results suggest the possibility of PK differences between rectal and vaginal compartments (Anderson 2012; Van Damme, Corneli et al. 2012) and emphasizing the importance of assessing target tissue levels of PrEP drugs in both men and women.

Levels or patterns of adherence needed to avoid HIV-infection rest both on the pharmacodynamics of the agents employed as well as both the self-directed behavior of following the recommended regimen and patterns of sexual behavior. Behavioral contributions to the efficacy equation include dosing in a pattern(s) that results in drug being present before and after potential HIV exposure(s). The detailed monitoring of sexual and pill-taking behavior are needed to produce estimates of “PrEP coverage” around sex events.

Imprecise measurement of PrEP adherence in clinical trials introduces substantial uncertainty about PrEP feasibility and efficacy. While there is no “gold standard” adherence measure, objective measures of ARV therapy adherence have demonstrated more consistent relations to biomedical outcomes than measures relying on self-report (Berg KM 2006). In iPrEX for example, it was shown that the rate of pill use, as measured by pill-dispensation rates and quantities, decreased during the first year, from 99% to 91%, which was a trend that contrasted with pill counts and self-report data, which indicated an increased rate of use (Grant RM 2010).

In this study, adherence will be assessed in three ways:

- Electronic drug monitoring (EDM) throughout the trial using a single pillbox (Wisepill) containing the three study medications.
- Self-report every 8 weeks via computer-assisted self-interview (CASI).
- Plasma stored on all participants at every visit for selected drug concentration measurements.

Although self-report may be a suboptimal measurement of adherence, inclusion of self-report in this study will allow for exploration of the relative correlation with objective EDM and PK assessments, which may confirm or contrast the high association between self-report and drug detection found in the U.S. cohort of the iPrEX study. In addition, self-report is the most feasible method for assessing adherence in real-world implementation of PrEP, thus gathering additional data on its accuracy is important.

1.1.9 Daily Short Message System (SMS text) Assessments of Sex Events

This will be the first study amongst U.S. participants to characterize fully the relationship between PrEP adherence and sexual exposure in the U.S. in the groups that continue to have the highest rates of incident HIV infections, MSM (Hall HI 2008; Prejean J 2011) and at-risk women. PrEP effectiveness will depend greatly on the dynamic relationship between PrEP pill-taking around sexual exposures. Low overall levels of adherence still may offer a high level of protection if non-use matches times of no or low-risk exposure, and use of PrEP matches times of potential exposure. Thus, adherence below the “perfect” threshold may or may not relate to

actual coverage of sex events. This study will characterize adherence and coverage thus allowing for the role of coverage and its relation to adherence to be better understood. To do this, daily monitoring of both pill intake and sexual behavior will be employed. As described in Section 1.1.8, EDM will be used for monitoring daily pill-taking for all participants through the study. Participants also will be queried randomly about sexual exposure via short message service (SMS) texting (see Appendix III for an example of a sampling strategy) periodically throughout the study.

SMS for assessment of behavior has been successfully employed in previous studies (Harberer JE 2010). With SMS, the participant answers up to two daily questions by cell phone, which is password-protected to ensure confidentiality. The questions for this study are: 1) How many times did you have (anal (for men) or, anal or vaginal (for women)) sex in the last 24 hours?; and, 2) (if ≥ 1) Was a condom used from start to finish each time?. The SMS questions will be sent daily for 7 consecutive days at individualized randomly selected windows throughout the study (see Appendix III).

1.1.10 Sexual Risk Behavior, Quality of Life Measurements and Beliefs about HIV Prevention Research

An underlying concern with all biomedical prevention strategies is that providing some protection against HIV transmission may lead to increased transmission-associated behaviors, such as not using condoms or more high-risk sexual activity. Modeling has suggested that an imperfect HIV prevention strategy (such as PEP or PrEP with oral agents or microbicides) might lead to an increased population-based incidence of HIV-infection if a concomitant effect of the intervention includes increases in risk behavior (Abbas U., Anderson R. et al. 2007). The idea that the effectiveness of a biomedical prevention strategy can be diluted by several mechanisms (Masse BR 2009) including risk compensation, has underscored the need for careful longitudinal, accurate sexual risk behavior assessment in HIV prevention studies; effects are likely to be different for distinct populations and distinct prophylactic strategies. Interestingly, as outlined in Section 1.1.1, transmission-associated behaviors decreased after entry into the iPrEX study (Grant RM 2010), a finding similarly reported in FEM-PrEP, Partners in PrEP, and TDF2. Among FEM-PrEP participants, there was a significant decrease in the numbers of partners, and there was no evidence of increased sexual risk behaviors (Van Damme, Corneli et al. 2012). In addition, in studies of PEP, (Martin JI 1997; Schechter M 2004; Martin, Bloch et al. 2009) and microbicide-based prophylaxis (Abdool Karim, Abdool Karim et al. 2010), ART as prevention in heterosexual serodiscordant couples (Donnell D 2010), and studies of PrEP to date (Grohskopf LA 2002; Peterson L 2007; Grant RM 2010; Baeten J 2011), increased sexual risk-taking has not been reported; rather, more frequently, decreases in risk behaviors have been noted. Results from circumcision (Auvert B, Taljaard D et al. 2005; Bailey RC, Moses S et al. 2007; Gray RH, Kigozi G et al. 2007) and vaccine (Chesney M 1997; Rerks-Ngarm S 2009) studies are more mixed, providing a cautionary note to the above body of literature. Clinical trial settings, however, may not be perfect representations of “real-world” behavior, as trials carefully integrate risk-reduction counseling as part of study conduct; additionally, many of the above mentioned trials were placebo-controlled, allowing the additional argument for ongoing condom use because of the possibility of being randomized to a non-active arm.

This study does not include a placebo-controlled arm, and participants will be counseled on the findings from iPrEX and Partners PREP, particularly that higher levels of adherence were correlated with higher levels of protection. Therefore, this study carries particular relevance to future real-world implementation of PrEP as a biomedical prevention strategy, where effects on mitigated HIV risk perception, use of condoms and other risk-reduction methods, and risk compensation are not tempered by the possibility of inactive placebo treatment. Baseline and serial (every 8 weeks) detailed risk behavior assessments will be employed via CASI in order to optimize methods to reduce social-acceptance bias in sexual behavior reporting. The instruments used will be harmonized across currently planned and enrolling HIV prevention chemoprophylaxis studies in order to optimize cross-study comparisons.

Quality of life (QOL) measures will use the well-validated EQ-5D (Brooks Health Policy 1996) integrated into the CASI platform to minimize participant burden.

Additionally, the study includes an approximately 8-item experimental measure, also integrated into the CASI, of participants' beliefs about HIV prevention research. The PREMIS (PREventive MISconception) Tool assesses beliefs related to study outcomes, study design and HIV risk. Data collected from these items will be used to evaluate their utility in describing beliefs about HIV prevention trials that may include misconceptions and/or may be associated with engagement in risk behaviors.

At selected sites, interviews will take place in a small convenience sample of participants who consent to be interviewed. The purpose of the interviews is to obtain qualitative information about how participants understand the PREMIS items in the Week 4 and Week 40 assessments. Cognitive interviews are one-on-one interviews in which respondents answer queries about how they understood and answered each item; respond to probes that test for likely sources of error in communication of the questions; and discuss key words and phrases, assumptions made by the items, how they generated their responses, and the appropriateness of the response options given.

1.1.11 Effect of Exposure to MVC on T Cell Phenotype

Three recent studies have demonstrated significant changes in T cell phenotype associated with the use of MVC in HIV-infected patients. These changes included an expansion of CCR5+/CD4+ T cells in peripheral blood (Cossarini F 2011), a reduction in T cell activation in peripheral blood (Wilkin T 2011), and in the final study, an increase in both T cell activation and CCR5 expression in both peripheral blood and GALT (Hunt P 2011). The combination of increased T cell activation and CCR5 expansion, especially in GALT, would be an undesirable feature of a PrEP regimen and warrants further evaluation.

Consequently, we will evaluate changes in T cell phenotype in both PBMCs (all participants) and GALT (participants enrolled in the Tissue Subset only, see Section 1.1.5). T cell activation will be characterized by measurement of the proportion of cells expressing CD69, CD38, HLA-DR, and Ki-67. Expression of CCR5 and CXCR4 will be measured in PBMCs and GALT CD3+/CD4+ T cells.

1.1.12 Use of *ex vivo* Colorectal and Cervical Explant Challenge Model to Characterize PrEP Efficacy

Ex vivo HIV challenge studies will be performed using rectal tissue collected from participants (both men and women) enrolled in the Tissue Subset. Intestinal explants are a novel nonclinical surrogate of efficacy for use in rectal microbicide clinical trials. Colorectal explant techniques have been established and used in several laboratories and have undergone a multi-center validation/standardization process conducted within the NIH-sponsored Microbicide Quality Assurance Program (Richardson-Harman N 2009). Currently, there are two colorectal explant models; the ‘sealed edge’ model which provides explant polarization and surrounds the explant with a matrigel cuff to minimize transfer of virus or candidate microbicide around rather than across the explant (Abner SR 2005) and the ‘exposed edge’ model (Fletcher PS 2006) which simply places the explant on a Gelfoam raft. Due to investigators’ belief that the act of receptive anal intercourse (RAI) is traumatic and HIV likely has direct access to sub-epithelial target cells, this second model will be used. Previously in a phase I trial (RMP-01) using UC781, colorectal tissue that was drug-exposed *in vivo* was sampled and studied *ex vivo* for efficacy in suppressing HIV-1 following exposure to laboratory strains of infection. Compared to the participant’s biopsy/explant infection at baseline, the 30-minute drug exposure *in vivo* led to a statistically significant *ex vivo* suppression of high-titer HIV infection (Elliott J 2009). Similar effects were seen in a second phase I study (RMP-02/MTN-006) involving the use of oral and topical TFV (Anton P 2011). Suppression of colorectal explant HIV infection will be evaluated in participants enrolled in the Tissue Subset at selected sites that have experience with these studies. Detailed information about the methods for this analysis and procedures that will be used to harmonize laboratory methods at the sites performing these studies is provided in the SSP Manual.

The rationale for cervical tissue explants is the same as for colorectal explants described above. That is, comparison of the concentration-response relationship *in vitro* may provide useful data to anticipate varied outcomes in future clinical studies. To date, however, there are no published reports of cervicovaginal tissue explants performed after PrEP dosing in women. However, *in vitro* “dosing” of cervical or vaginal tissues followed by incubation with HIV (“challenge”) have been evaluated using varied methods, including both polarized and non-polarized explant methods. In these experiments, a concentration response was described for tenofovir, UC781, and PRO2000 (Richardson-Harman N 2009 75; Rohan 2010; Cost 2012). Cervical tissue biopsies are associated with more consistent infectibility. As an exploratory variable, cervical tissue explants are planned to determine the concentration-response relationship using the explant model which will then be compared among regimens.

1.1.13 Evaluation of HIV Exposure

HIV exposure will be assessed by testing for cytokine release induced by HIV antigens. PBMCs from study participants will be cultured with a panel of peptides derived from HIV genes, and stimulated production of interferon-gamma will be assayed by established protocols for intracellular cytokine staining, including flow cytometry and ELISpot. Cytokine production in HIV-negative individuals is generally quite low but is sometimes detectable. An increase in response during the study would indicate exposure to HIV, and could be useful information to have in a trial of HIV prophylactic interventions, e.g., in preventing or reducing misclassification of individuals who did or did not have such exposures.

Note that the PK and exploratory studies described in Sec 1.1.5, 1.1.11, 1.1.12 and 1.1.13 will be conducted depending on availability of funds.

1.1.14 HIV Seroconversion

Incident HIV infections on this study are expected to occur uncommonly, even in the at-risk study population. However, any participant experiencing an incident HIV infection offers the opportunity to assess the impact of the PrEP regimen. Consequently, these participants will be carefully characterized with regard to their HIV RNA level and CD4 cell count and set points over time, viral co-receptor tropism, antiretroviral drug resistance, and other factors. The relationship between incident HIV infections, reported sexual behaviors, and study drug adherence also will be assessed.

1.1.15 Pharmacogenomic Analysis

The purpose of the pharmacogenomic analysis will be to determine whether genetic polymorphisms play a role in governing the variability among participants in the PK and PD of maraviroc, emtricitabine and tenofovir when used for HIV PrEP. In particular, genotyping and measurement of the expression levels of drug metabolizing enzymes, intracellular kinases and drug transporters will be performed in order to provide a novel informative approach to gaining an understanding of the interindividual differences in exposure to these drugs. In particular, it has yet to be explored whether genetic polymorphisms of intracellular kinases and drug transporters might explain interindividual variability in the activation of tenofovir and/or emtricitabine to the active phosphorylated forms of the drugs.

It has been recently demonstrated that the polymorphic enzyme CYP3A5 plays an important role in the biotransformation of maraviroc (Lu, Hendrix et al. 2012). In this study, formation by of a primary metabolite of maraviroc by human liver microsomes isolated from donors genotyped as homozygous for the loss-of-function CYP3A5*3 alleles was decreased 79% as compared to production by human liver microsomes genotyped as expressing the wild-type allele, CYP3A5*1 allele. The CYP3A5*1 allele is associated with the highest level of protein expression whereas variant alleles such as the loss-of-function CYP3A5*3 allele lead to decreased expression or no activity due to alternative mRNA splicing (Hustert, Haberl et al. 2001; Kuehl, Zhang et al. 2001); interestingly, CYP3A5 protein content accounts for an approximate 50% of the total liver CYP3A content in individuals who carry at least one CYP3A5*1 allele indicating that CYP3A5 can be an important contributor to overall CYP3A-dependent drug metabolism in these individuals (Kuehl, Zhang et al. 2001). In addition, there is ethnic variation in CYP3A5 expression with the CYP3A5*3 allele being present in the European American population with a frequency of 85-98% while the frequency in the African American population is 27-48% (Hustert, Haberl et al. 2001; Kuehl, Zhang et al. 2001; van Schaik, van der Heiden et al. 2002; Daly 2006). Increased risk of certain drug toxicities has been reported in human subjects whom exhibit low expression of CYP3A5 (Egbelakin, Ferguson et al. 2011; Hooper, Fukuda et al. 2012; Takashina, Naito et al. 2012); therefore, gaining an understanding of whether genetic polymorphisms potentially contribute to variability in PK, PD and toxicity of maraviroc is of importance. Taken together, the overall aim of these analyses will be to provide novel insight regarding whether polymorphisms in intracellular kinases and drug metabolizing enzymes

including transporters contribute to differential levels and distribution of ARVs that are relevant to HIV PrEP, which currently remains unexplored.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objective

To assess the safety and tolerability of MVC, MVC+FTC, MVC+TDF, and TDF+FTC over 48 weeks. This will be measured by the occurrence of Grade 3 and higher adverse events (safety) and time to permanent discontinuation (tolerability) in each of the four study arms.

2.2 Secondary Objectives

The secondary objectives of the study are to:

- Assess Grade 2 and higher adverse events and Grade 1 clinical (non-laboratory) adverse events that lead to a temporary or permanent hold of study drug.
- Assess changes in lipids in each of the four study arms.
- Assess changes in bone mineral density in each of the four study arms.
- Evaluate interactions of MVC, FTC, and TDF in the four study arms in a subset of participants (Drug Interaction Subset).
- Evaluate concentrations of MVC, FTC, tenofovir (TFV) and their phosphorylated derivatives (FTC-triphosphate (FTC-TP) and TFV-diphosphate (TFV-DP)) in plasma, peripheral blood mononuclear cells (PBMC), and rectal tissue and fluid, and cervical tissue and cervicovaginal fluid, in a subset of participants (Tissue Subset).
- Assess changes in peripheral blood (all participants) and gut-associated lymphoid tissue (GALT) T cell phenotype (Tissue Subset).
- Assess adherence in each of the four study arms as measured by an electronic drug monitoring device (EDM) and self-report.
- Assess and characterize sexual behavior over time as measured by computer-assisted self-interview (CASI).
- Assess and determine the relationship between adherence and sexual risk-taking.
- Evaluate the association of drug concentrations with other adherence measures.
- Assess quality-of-life in each of the four study arms.

2.3 Exploratory Objectives

The exploratory objectives of the study are to:

- Characterize HIV (e.g., coreceptor tropism and drug resistance) in any participant who becomes HIV-infected during the study.
- Evaluate the relationship between HIV exposure (assessed using immunologic studies) and behavior.
- Determine whether oral PrEP is associated with suppression of HIV replication in colorectal and cervical explants (*ex vivo* HIV challenge, Tissue Subset).
- Collect hair samples from a subset of participants for possible future studies of drug concentrations in hair.
- Describe gender differences in measured outcomes.
- Assess correlation of drug levels in rectal and cervical samples.
- Characterize host CCR5 polymorphisms and host genetic polymorphisms associated with drug exposure.
- Describe baseline and incident STIs among participants.

2.4 Study Design and Overview

This study is a phase II, randomized, multi-site, four-arm, double-blinded study of MVC, MVC+FTC, MVC+TDF and TDF+FTC. Consenting participants will be assessed for eligibility, including assessment of recent medical and sexual history, HIV testing, and laboratory testing for safety. Eligible participants will be randomized to receive MVC, MVC+FTC, MVC+TDF, or TDF+FTC in a 1:1:1:1 ratio. In addition, the study will include several subset evaluations as described in Section 1.1.5. The Drug Interaction Subset evaluation requires 72 participants (18 per arm) evaluated at the Week 2 visit, and the Tissue Subset evaluations require 60 men and 60 women (15 men/15 women per arm) evaluated at enrollment and Weeks 24, 48, and 49 (or at treatment or study discontinuation).

All participants will receive HIV testing with pre- and post-test counseling, in addition to risk-reduction counseling and condoms. All participants will be followed according to the Schedule of Evaluations provided in Appendices I and II.

2.4.1 Participating Sites/Institutions

Participating sites are listed in the SSP Manual.

2.4.2 Study Duration

This study will be approximately 30 months in length. Accrual will occur in a staggered fashion, with men beginning first, and women beginning several months later. Accrual for the men will require approximately 9 months, and accrual for the women will require approximately 9 months. Each participant will be followed for approximately 12 months (with study drug evaluated through 48 weeks, and a final post-drug study visit at Week 49).

3.0 STUDY POPULATION

Four hundred (400) HIV-uninfected MSM and 200 HIV-uninfected women will be included in this study. Sites are strongly encouraged to enroll young MSM (aged 18-25) and/or persons of color to maximize representation from these groups. Each site will be asked to work with their CABs and outreach, education and recruitment teams to develop a recruitment plan that will focus on the engagement of younger MSM and persons of color. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. Study participants will be recruited as described in Section 3.3 and assigned to a study arm as described in Section 7.4. Requirements related to participant retention and withdrawal from the study are described in Sections 3.5 and 3.6, respectively.

Some participants will also be enrolled into two subset groups:

- Drug Interaction Subset. This subset will include 72 participants (18 per arm) and will involve an additional blood draw at one time point.
- Tissue Subset. This subset will include 60 men and 60 women (15 men/15 women per arm), and will involve additional laboratory assessments and additional procedures at four study visits (see Section 5.8 and Appendix I). Rectal and cervical sampling will be performed. For those who consent to participate in this Subset, rectal sampling is required for men and optional for women, and cervical sampling is required for women.

Rectal samples (rectal tissue and rectal fluid) will be used for three different assessments: (1) ARV drug measurement (PK study, see Section 1.1.5), (2) analysis of GALT T cell phenotype (see Section 1.1.11), and (3) *ex vivo* HIV challenge studies (see Section 1.1.12).

Cervical samples (cervical tissue and cervicovaginal fluid) will be used for two different assessments: (1) ARV drug measurement (PK study, see Section 1.1.5) and (2) *ex vivo* HIV challenge studies (see Section 1.1.12).

Participation in the Tissue Subset will require separate (additional) informed consent. Participants may be involved in both the drug interaction subset as well as in the Tissue Subset studies. There are no separate inclusion/exclusion criteria for the Drug Interaction Subset. Special inclusion and exclusion criteria for the Tissue Subset are described in Sections 3.1 and 3.2.

3.1 Inclusion Criteria

Participants who meet all of the following criteria are eligible for inclusion in this study:

- For participants in the men's component of the study, born male. For participants in the women's component of the study, born female
- 18 years or older at the time of screening
- Willing to provide informed consent for the study
- Able to read at a level required for the study components (e.g., CASI and SMS), per the judgment of the study investigator
- For men, a history of receptive or insertive anal intercourse without use of condoms with at least one HIV-infected male partner or male partner of unknown HIV serostatus within 90 days of study entry (provided by self-report)
- For women, a history of vaginal intercourse or receptive anal intercourse without use of condoms with at least one HIV-infected male partner or male partner of unknown HIV serostatus within 90 days of study entry (provided by self-report)
- The following laboratory values must be from specimens obtained within 45 days prior to study enrollment:
 - Non-reactive HIV test results*
 - Hemoglobin (men) > 11 g/dL, absolute; Hemoglobin (women) \geq 10.5 g/dL
 - Absolute neutrophil count > 750 cells/mm³
 - Platelet count \geq 100,000/mm³
 - Calculated creatinine clearance \geq 70 mL/minute using the Cockcroft-Gault equation
 - Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) < 3 times the upper limit of normal (ULN)
 - Total bilirubin < 2.5 ULN
 - Urine protein < 2+
 - Hepatitis B surface antigen (HBsAg) negative

[*Individuals who have one or more reactive HIV test results will not be enrolled, even if subsequent confirmatory testing indicates that they are not HIV-infected]

- No alcohol or substance use that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report, or found upon medical history and examination or in available medical records)
- No medical condition that, in the opinion of the study investigator, would interfere with the conduct of the study (e.g., provided by self-report, or found upon medical history and examination or in available medical records)
- Willing to undergo all required study procedures (including sexual risk behavior assessment by CASI, use of the drug monitoring device, and SMS [i.e., texting])

Additional requirements for all women:

- If of reproductive potential (defined as girls who have reached menarche and pre-menopausal women who have not had a sterilization procedure per self-report (e.g., hysterectomy, bilateral oophorectomy, tubal ligation or salpingectomy)) **must** have a negative serum or urine pregnancy test performed within 48 hours before initiating the protocol-specified medication(s). **Women are considered menopausal if they have not had a menses for at least 12 months and have a FSH of greater than 40 IU/L or if FSH testing is not available, they have had amenorrhea for 24 or more consecutive months.**
- If participating in sexual activity that could lead to pregnancy, women must agree to use a form of contraception from the following list during the trial and for 30 days after stopping the study medication:
 - Condoms (male or female) with or without a spermicidal agent
 - Diaphragm or cervical cap with spermicide
 - IUD
 - Hormone-base contraceptive

For the Tissue Subset:

- For men and women participating in the rectal component, willing to abstain from receptive anal intercourse and practices involving insertion of anything in the rectum (drug, enema, penis, or sex toy) for 3 days prior to rectal biopsy and for 7 days post-biopsy, to minimize risk of HIV-1 infection and bleeding complications after each procedure.
- For women participating in the vaginal component, willing to abstain from vaginal intercourse and practices involving insertion of anything in the vagina (drug, douche, penis, or sex toy) for 3 days prior to cervical biopsy and for 7 days post-biopsy, to minimize risk of HIV-1 infection and bleeding complications after each procedure.

- For women only, per participant report at screening, usual menstrual cycle with at least 21 days between menses (does **not** apply to participants who report using a progestin-only method of contraception at screening, e.g., Depo-Provera).
- For women, satisfactory Pap results in the 12 calendar months prior to Enrollment consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines in the 12 calendar months prior to Enrollment. If there is no document of satisfactory Pap results, the participant should be offered to have the test performed by the site prior to the Enrollment visit. If they refuse, they are not eligible.

3.2 Exclusion Criteria

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

- One or more reactive HIV test results at screening or enrollment, even if HIV infection is not confirmed
- Co-enrollment in any other HIV interventional research study (provided by self-report or other available documentation) or prior enrollment and receipt of active arm (i.e., NOT a placebo) of a HIV vaccine trial (provided by available documentation)
- Use of ARV therapy (e.g., for PEP or PrEP) in the 90 days prior to study entry
- Prior history of a gastrectomy, colostomy, ileostomy, or any other procedure altering the gastrointestinal tract or drug absorption (provided by self-report, or obtained from medical history or records)
- Receipt of prohibited medications as described in the study drug package inserts, or listed in the SSP Manual (provided by self-report, or obtained from medical history or medical records)
- Ongoing intravenous drug use – episodic use or any use in the past 90 days (as assessed by the study investigator)
- Known medical history of allergy to soy (soya or soybeans) or peanuts.
- Weight > 300 lbs. (exceeds weight limit of DXA scanners)
- For women, pregnancy or currently breastfeeding

For the Tissue Subset:

For men and women:

- The following applies to men, and only to women who opt for rectal sampling: Abnormalities of the colorectal mucosa or significant colorectal symptom(s), which in the opinion of the study investigator represent a contraindication to biopsy (including but not limited to presence of any unresolved injury, infectious or inflammatory condition of the local mucosa, and presence of symptomatic external hemorrhoids).
- Per participant report at screening, anticipated use and/or unwillingness to abstain from the following medications during the period of study participation:
 - Heparin, including Lovenox[®]
 - Warfarin
 - Plavix[®] (clopidogrel bisulfate)
 - Any other drugs that are associated with increased risk of bleeding following biopsy procedures in the opinion of the study investigator
- The following applies to men, and only to women who opt for rectal sampling: Per participant report at screening, anticipated use and/or unwillingness to abstain from rectally-administered medications (including over-the-counter products) for 3 days prior to rectal biopsies and for 7 days after biopsies.
- Per participant report at screening, anticipated use and/or unwillingness to abstain from the following medications for a period of 10 days before a biopsy procedure:
 - Aspirin*
 - Non-steroidal anti-inflammatory drugs (NSAIDS)

*Daily use of low-dose aspirin (no more than 81 mg) is allowed at the discretion of the Investigator of Record.

- Abnormal laboratory results for coagulation tests that may indicate an increased risk of bleeding (in the opinion of the investigators).
- Active untreated syphilis, gonorrhea, or chlamydia infection.

For women only:

- Carcinoma in situ of the cervix or invasive cervical cancer. Abnormalities of the vaginal mucosa or significant vaginal symptom(s), which in the opinion of the study investigator represent a contraindication to biopsy (including but not limited to presence of any unresolved injury, and infectious or inflammatory condition of the local mucosa).

- Hysterectomy.
- Per participant report at screening, anticipated use and/or unwillingness to abstain from vaginally-administered medications (including over-the-counter products) and vaginal douching for 3 days prior to cervical biopsies and for 7 days after biopsies.

3.3 Recruitment Process

Participants will be recruited from a variety of venues targeted to MSM and women, including local health clinics, local health departments, and other local establishments geared to meeting the needs of these groups. In order to reach a broader population, advertisements may include college and local newspaper advertisements, fliers posted on frequently visited local venues, electronic advertisements, including craigslist.com, etc. Sites will be responsible for developing appropriate recruitment processes that are geared toward their respective local communities. All advertising materials must undergo approval by each participating site's Institutional Review Board (IRB).

3.4 Co-Enrollment Guidelines

Participants in this study will be encouraged not to take part in other concurrent research studies. Co-enrollment in any HIV vaccine or other interventional prevention trials is prohibited. A participant may be eligible for the study if they were previously enrolled in a HIV vaccine trial that has since been unblinded and documentation is available that demonstrated the receipt of placebo only. This is due in part to concerns about participant study burden, but also to facilitate high levels of adherence and retention in this study (including compliance with study medications), to avoid potential unblinding of this or other studies, and to avoid confounding in the interpretation of the study data.

3.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain him for the entire follow-up period. Optimally, participant retention procedures will be established such that loss rates do not exceed the range that allow the incidence rate of the primary study outcome to be reliably estimated (i.e., a maximum of 10% as assumed in the sample size calculation). Study site staff are responsible for developing and implementing local standard operating procedures to target this goal. Components of such procedures may include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Thorough explanation of the importance of all four study treatment groups to the overall success of the study.
- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit, including where the participant lives and other locator venues.
- Use of appropriate and timely visit-reminder mechanisms.

- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained staff to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness about HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.

3.6 Participant Withdrawal

Regardless of the participant retention methods described in Section 3.5, participants may voluntarily withdraw from the study for any reason at any time. The Investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Safety Review Team (PSRT) which includes the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, representatives from the Network Laboratory, the Operations Center Protocol Specialist, and others.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities (including Office for Human Research Protections [OHRP] and the FDA) or site IRBs terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (as described in Sections 5.4 and 5.5 and Appendix I) of participants who terminate from the study prior to Week 49, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

Participants who discontinue treatment (temporarily or permanently) will be maintained in follow-up as originally scheduled whenever possible.

4.0 STUDY PRODUCT CONSIDERATIONS

4.1 Study Product Regimens/Administration/Formulation Content

The following study products will be used:

- Maraviroc (MCV) tablets 300 mg and matching placebo are provided by ViiV Healthcare. Store tablets at 25°C (77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F).
- Emtricitabine (FTC) capsules 200 mg and matching placebo are provided by Gilead Sciences, Inc. Store capsules at 25°C (77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F).
- Tenofovir disoproxil fumarate (TDF) tablets 300 mg and matching placebo are provided by Gilead Sciences, Inc. Store tablets at 25°C (77°F). Excursions are permitted between 15°C to 30°C (59°F to 86°F).

- In each study arm, participants will take the three study products orally, with or without food.

All study products are medications approved by the U.S. FDA for treatment of HIV-1 infection. Further information on each study product is available in the respective current package insert (available at <http://rsc.tech-res.com/safetyandpharmacovigilance>).

An electronic drug monitoring device (EDM) will be used to assess adherence (Wisepill Technologies, Somerset West, South Africa). The participant will be instructed regarding the use of the monitoring device (See also Section 1.1.8).

4.2 Study Product Acquisition and Accountability

Study Product Acquisition

All study products will be supplied by the NIAID Clinical Research Products Management Center (CRPMC). The study site pharmacist can obtain all the study products through the CRPMC by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks*, and instructions in the SSP Manual. In general, study drugs will be re-supplied to participants every 8 weeks from the time of enrollment.

Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed to study participants. All study products must be stored in the pharmacy. All unused study products must be returned to the CRPMC after the study is completed, terminated or otherwise instructed by the study sponsor. The procedures to be followed are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

4.3 Toxicity Management

Toxicity management is described in Appendix IV.

4.4 Concomitant, Prohibited, and Precautionary Medications

Information regarding recommended, prohibited, and precautionary concomitant medications can be found in the SSP Manual. The SSP Manual will be revised (as a whole or as a Memorandum of Changes) and re-issued whenever changes are made. In order to avoid adverse events caused by drug interactions, whenever a concomitant medication or study treatment is initiated or a dose changed, investigators must review the concomitant medication's and study treatment's most recent package inserts, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

All concomitant medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins, etc.) taken within 30 days prior to enrollment and anytime thereafter during study participation will be collected in the

study participant's chart and on study case report forms (CRFs). Alcohol and recreational or street drug use will be recorded in the participant's study chart only.

5.0 STUDY PROCEDURES

Overviews of the study visit and procedures schedules are presented in Appendices I and II. Presented below is additional information on visit-specific study procedures; the main study procedures appear first, followed by procedures for participants in the Drug Interaction Subset and Tissue Subset. Detailed instructions to guide and standardize all study procedures across sites are included in the SSP Manual. Note that additional procedures are required for participants in the Tissue Subset (see Section 5.8).

5.1 Screening

It is the responsibility of the local site to determine the best approach to screening. For each participant, independent written informed consent for screening and enrollment will be obtained before any study procedures are initiated. Screening procedures may occur over one or more visits. Participants who fail screening for any reason other than a positive HIV test or a positive hepatitis B surface antigen test may rescreen one time. Enrollment is to be completed within 45 days of specimen collection for the laboratory screening tests listed below. The SSP Manual provides additional information regarding the procedures outlined below, including laboratory procedures and requirements.

The following procedures will occur as part of screening:

Administrative, Behavioral, and Regulatory Procedures

- Informed consent
- HIV counseling (pre- and post-test), including risk-reduction counseling
- Condom distribution
- Collection of locator information

Clinical Procedures

- Targeted medical history, physical exam for ascertainment of eligibility, concomitant medications
- Blood collection
- Urine collection

Laboratory Evaluations

- Blood for:
 - Testing for acute HIV infection (using a non-pooled HIV RNA assay) no more than 14 days prior to enrollment, but preferably within 7 days prior to enrollment*
 - HIV testing, with confirmatory testing if necessary**
 - HBsAg, HBsAb, HBCoreAb
 - Complete blood count (CBC) with differential and platelets
 - Chemistry panel (sodium (Na), potassium (K), chloride (Cl), CO₂, glucose, creatinine, blood urea nitrogen (BUN), phosphate, calculated creatinine clearance)
 - LFTs (AST, ALT, total bilirubin, alkaline phosphatase)
 - 25-OH-Vitamin D and parathyroid (PTH) levels (Note: These tests are not required for documentation of inclusion/exclusion, and may be performed at the Enrollment visit at the discretion of the Investigator of Record).
 - Plasma for storage

For women of reproductive potential only: Serum or urine β HCG (must have sensitivity of ≤ 25 mIU/mL) Note: Sites should perform this initial pregnancy testing to rule out pregnancy in order to proceed with the remaining screening testing. Another pregnancy test is required within 48 hours of starting study medication. See Section 5.2.

[*All participants will be tested for acute HIV infection prior to enrollment. This testing can be performed at the same visit as other screening procedures, or at a separate screening visit. See also Section 5.12.]

[** Here and elsewhere in the protocol, “HIV testing” refers to antibody-based testing (e.g., rapid HIV test, EIA), unless other indicated]

- Urinalysis (to include protein and glucose)
- Urinary phosphate and urinary creatinine

Participants who are susceptible to HBV infection will be referred to their primary provider for HBV vaccination.

Screening must be discontinued if a participant is found to be ineligible. HIV counseling and testing will be offered to everyone who consents to screening. Sites will follow the HIV testing algorithm for screening which will be included in the SSP Manual. If a reactive result is obtained for one or both of the HIV tests, the person is not eligible for the study. Additional testing to confirm HIV infection will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be referred for appropriate care.

If all eligibility requirements indicate that an individual is eligible for the study, he will be asked to return to the site for the enrollment visit. Individuals who are not eligible will be informed that they do not meet the requirements of the study and, if necessary, will be referred for appropriate medical services.

5.2 Enrollment

The following procedures will occur as part of enrollment:

Administrative, Behavioral, and Regulatory Procedures

- Confirm eligibility prior to any enrollment procedures
- Randomization assignment
- Demographics information
- Confirm locator information
- HIV counseling (pre-and post-test), including risk-reduction counseling
- Condom distribution
- Adherence counseling (which will include an overview of electronic drug monitoring system)
- Behavioral/QOL assessment using CASI
- Training and review of SMS assessment of sexual exposure

Clinical Procedures

- Complete medical history, concomitant medications, complete physical exam (may be performed during screening in the opinion of the study investigator)
- Urine collection
- Blood collection (participants should be fasting for at least 8 (preferably 12) hours prior to this collection)
- DXA scan (may be performed -30 days/+7 days of enrollment (all women and 200 out of the 400 men will receive a DXA scan)
- Rectal swab (for men, and for women who have reported anal sex within the last year)
- Self-collected vaginal swab or provider-collected cervical swab (at sites that can perform vaginal or cervical gonorrhea [GC] and chlamydia [CT] swab testing in women)
- Provide study drug

NOTE TO SITES: Study product should be initiated within 24 hours of randomization. In cases where the 24 hour time frame cannot be met, contact the PSRT.

Laboratory Procedures

- Blood for:
 - HIV testing, with confirmatory testing if necessary
 - Anti-HCV antibody*
 - Lipid profile (total cholesterol, HDL, triglycerides, LDL – calculated or measured)*
 - CCR5 genotype
 - Syphilis serologic testing
 - Plasma for storage
 - PBMC for storage (immunology studies)
 - Pharmacogenomic testing**

- For women of reproductive potential only: Serum or urine β HCG (must have sensitivity of ≤ 25 mIU/mL)

Note: Negative pregnancy test results must be available within 48 hours of starting study medication. It is the responsibility of sites to determine the best time to perform the pregnancy testing in order to meet this requirement, e.g., if conducting urine pregnancy testing, the testing can be performed at the Enrollment visit, just prior to randomization. Or, if conducting serum testing, the participant might have to report a day before the Enrollment visit to have blood drawn, etc.

- Urine for gonorrhea and chlamydia (GC/CT) NAAT (for men, and for women at sites that do not perform vaginal or cervical swab testing for GC/CT)
- Vaginal or cervical swab for GC/CT NAAT (women only)
- Rectal swab for GC/CT NAAT (for men, and for women who have reported anal sex within the last year)

[*Anti-HCV antibody testing and a lipid profile are required baseline assessments; however, for logistical purposes, sites may perform these tests during screening since they can be performed on the same sample sent for HBV testing and chemistry and LFTs. In these cases, the results obtained during screening will be used as the baseline measurement.]

[**Participants enrolled under Version 2.0 of the protocol can have this test drawn at any follow-up visit.]

NOTE TO ALL SITES: Testing for GC, CT, and syphilis may be performed at screening per site discretion. If not performed at screening, it must be performed at enrollment. For participants enrolled under Version 2.0 of the protocol, refer to the SSP for instructions regarding scheduling of these tests for the first time. In addition, for women, at sites that do not have the clinical or laboratory capacity to perform vaginal or cervical swab testing for GC and CT, urine should be collected and tested for this purpose.

NOTE TO TISSUE SUBSET SITES: For the men and women that are participating in the Tissue Subset, STI testing will follow the Tissue Subset schedule (Screening, Week 16, and Week 40 – See section 5.8).

5.3 Week 2 and Week 4

The following procedures will occur at Weeks 2 and 4.

Administrative, Behavioral, and Regulatory Procedures

- HIV counseling (pre-and post-test), including risk-reduction counseling
- Condom distribution
- Confirm locator information
- Adherence education and follow-up counseling
- Reminder and review of SMS assessment of sexual exposure.
- PREMIS questions only via CASI at all sites and qualitative interviews at selected sites as specified in the SSP (Week 4 only). Qualitative interviews may occur anytime from Week 4 through Week 40.

Clinical Procedures

- Targeted medical history, concomitant medications, targeted physical exam
- Blood collection

Laboratory Procedures

- Blood for:
 - HIV testing, with confirmatory testing if necessary
 - CBC with differential and platelets
 - Chemistry panel (Na, K, Cl, CO₂, glucose, creatinine, BUN, phosphate, calculated creatinine clearance)
 - LFTs (AST, ALT, total bilirubin, alkaline phosphatase)
 - Plasma for storage
- For women of reproductive potential only: Serum or urine β HCG (must have sensitivity of ≤ 25 mIU/mL)

5.4 Weeks 8, 16, 32, 40

Administrative, Behavioral, and Regulatory Procedures

- HIV counseling (pre-and post-test), including risk-reduction counseling
- Condom distribution
- Confirm locator information
- Behavioral/adherence/QOL assessment using computer-assisted structured interviewing
- Adherence education and follow-up counseling
- Reminder and review of SMS assessment of sexual exposure.

Clinical Procedures

- Targeted medical history, concomitant medications, targeted physical exam
- Urine collection (Week 8 only)
- Blood collection
- Provide study drug

Laboratory Procedures

- Urinalysis (to include protein and glucose) (Week 8 only)
- Urinary phosphate and urinary creatinine (Week 8 only)
- Blood for:
 - HIV testing, with confirmatory testing if necessary
 - CBC with differential and platelets
 - Chemistry panel (Na, K, Cl, CO₂, glucose, creatinine, BUN, phosphate, calculated creatinine clearance)
 - LFTs (AST, ALT, total bilirubin, alkaline phosphatase)
 - Plasma for storage
- For women of reproductive potential only: Serum or urine β HCG (must have sensitivity of ≤ 25 mIU/mL)

5.5 Weeks 24 and 48

Administrative, Behavioral, and Regulatory Procedures

- HIV counseling (pre- and post-test), including risk-reduction counseling
- Condom distribution
- Confirm locator information
- Adherence education and follow-up counseling (Week 24 only)
- Behavioral/adherence/QOL assessment using computer-assisted structured interviewing
- Reminder and review of SMS assessment of sexual exposure

Clinical Procedures

- Targeted medical history, concomitant medications, targeted physical exam
- Urine collection
- Blood collection (participants should be fasting for 8 hours prior to blood collection)
- DXA scan (Week 48 only). (The window for completing the DXA scan at this visit is -14 days/+14 days of the Week 48 visit. The other procedures completed at Week 48 will follow the standard allowable window.) **DXA scan is only completed for participants who had a scan completed at enrollment.**
- Provide study drug (Week 24 only [not at Week 48])
- Rectal swab (for men, and for women who have reported anal sex within the last year)
- Self-collected vaginal swab or provider-collected cervical swab (at sites that can perform vaginal/cervical swab testing for GC/CT in women)

Laboratory Procedures

- Urinalysis (to include protein and glucose)
- Urinary phosphate and urinary creatinine
- Urine for GC/CT NAAT (for men, and for women at sites that do not perform vaginal or cervical swab testing for GC/CT)
- Vaginal or cervical swab for GC/CT NAAT (women only)
- Rectal swab for GC/CT NAAT (for men, and for women who have reported anal sex within the last year)

- Blood for:
 - HIV testing, with confirmatory testing if necessary
 - CBC with differential and platelets
 - Chemistry panel (Na, K, Cl, CO₂, glucose, creatinine, BUN, phosphate, calculated creatinine clearance)
 - LFTs (AST, ALT, total bilirubin, alkaline phosphatase)
 - 25-OH-Vitamin D and parathyroid (PTH) levels (Week 48 only)
 - Lipid profile (total cholesterol, HDL, triglycerides, LDL – calculated or measured)
 - Plasma for storage
 - PBMC storage for immunologic studies (Week 24 only [not at Week 48])
 - Syphilis serologic testing*

- For women of reproductive potential only: Serum or urine βHCG (must have sensitivity of ≤25 mIU/mL)

NOTE TO ALL SITES: For women, at sites that do not have the clinical or laboratory capacity to perform vaginal or cervical swab testing for GC and CT, urine should be collected and tested for this purpose.

NOTE TO TISSUE SUBSET SITES: For the men and women that are participating in the Tissue Subset, STI testing will follow the Tissue Subset schedule (Screening, Week 16, and Week 40 – See section 5.8).

5.6 Week 49

Administrative, Behavioral, and Regulatory Procedures

- HIV counseling (pre- and post-test), including risk-reduction counseling
- Condom distribution
- Study termination procedures

Clinical Procedures

- Targeted medical history, concomitant medications, targeted physical exam
- Urine collection
- Blood collection

Laboratory Procedures

- Urinalysis (to include protein and glucose)
- Urinary phosphate and urinary creatinine

- Blood for:
 - HIV testing, with confirmatory testing if necessary*
 - CBC with differential and platelets
 - Chemistry panel (Na, K, Cl, CO₂, glucose, creatinine, BUN, phosphate, calculated creatinine clearance)
 - LFTs (AST, ALT, total bilirubin, alkaline phosphatase)
 - Plasma for storage
- For women of reproductive potential only: Serum or urine βHCG (must have sensitivity of ≤25 mIU/mL)

*If a participant has an initial reactive or positive HIV test at Week 49, the procedures described in Appendix II should be followed and arrangements should be made to provide the participant with the results of the confirmatory HIV testing.

5.7 Additional Procedures for the Drug Interaction Subset

In addition to the procedures for the main study, the following procedures should be performed for this Subset:

At Screening:

- Obtain additional consent for participation in this subset. (Participation in this subset is only needed for the first 72 participants that provide consent to the procedures. The HPTN SDMC will notify sites when participation in this subset is no longer required).

At Enrollment:

- Remind the participant not to take their medication prior to coming to the study site for the Week 2 visit.

At Week 2:

- Pre-dose blood collection
- Directly observed drug dosing
- Post-dose blood collection approximately 6 hours after observed drug dose
- Plasma for drug levels

5.8 Additional Procedures for the Tissue Subset

Only specified sites will participate in this Subset (outlined in the SSP manual). For those enrolled in the Tissue Subset, rectal biopsies are required for men, and are optional for women.

For women enrolled in the Tissue Subset, cervical biopsies are required. In addition to all of the procedures in the main study, the following procedures should be performed for this Subset:

At Screening:

- Obtain additional consent(s) for Tissue Subset
- Coagulation testing (International Normalized Ratio [INR], Prothombin Time [PT], and Partial Thromboplastin Time [PTT]) – to be obtained with results known prior to rectal tissue biopsies. Platelet count cannot be $< 100,000/\text{mm}^3$
- Pap test if the participant does not have documentation of a satisfactory test result in past 12 months
- Syphilis testing, and rectal swab for GC/CT NAAT (men and women), self-collected vaginal swab or provider-collected cervical swab for GC/CT NAAT (women only), and urine for GC/CT NAAT (men only and for women at sites that do not perform vaginal or cervical swabs). This testing must be performed at screening to allow enough time for reporting of results and prior to tissue collection at enrollment

At Enrollment (these procedures should be performed prior to starting study drugs):

- Preparatory enema administered prior to rectal biopsies
- Rectal and cervical tissue collection for GALT T cell phenotype (rectal tissue) and *ex vivo* HIV challenge (rectal and cervicovaginal fluids are not collected at Enrollment)

At Weeks 16 and 40:

- Syphilis testing, and rectal swab for GC/CT NAAT (men and women), self-collected vaginal swab or provider-collected cervical swab for GC/CT NAAT (women only), and urine for GC/CT NAAT (men only and for women at sites that do not perform vaginal or cervical swabs). This testing is in place of Week 24 and Week 48.

At Weeks 24, 48 and 49:

- Plasma storage for drug levels
- PBMC storage for drug levels
- Preparatory enema before biopsies
- Rectal and cervical tissue collection for *ex vivo* HIV challenge and tissue PK and rectal tissue for GALT T cell phenotype
- Rectal and cervicovaginal fluid collection for PK testing
- Hair storage

At study discontinuation (if after Week 24 and before Week 48):

- Collect plasma, PBMCs, and hair samples for PK testing (no tissue collection)

At treatment discontinuation (if after Week 24 and before Week 48):

- Collect all samples that are indicated for the Week 49 visit two weeks after treatment discontinuation. See the SSP Manual for additional details.

5.9 Premature Treatment or Study Discontinuation

Administrative, Behavioral, and Regulatory Procedures

- HIV counseling (pre-and post-test), including risk-reduction counseling
- Condom distribution
- Behavioral/adherence/QOL assessment using computer-assisted structured interviewing

Clinical Procedures

- Targeted medical history, concomitant medications, targeted physical exam
- Urine collection
- Blood collection

Laboratory Procedures

- Urinalysis (to include protein and glucose)
- Urinary phosphate and urinary creatinine
- Blood for:
 - HIV testing, with confirmatory testing if necessary
 - CBC with differential and platelets
 - Chemistry panel (Na, K, Cl, CO₂, glucose, creatinine, BUN, phosphate, calculated creatinine clearance)
 - LFTs (AST, ALT, total bilirubin, alkaline phosphatase)
 - 25-OH-Vitamin D and parathyroid (PTH) levels
 - Lipid profile (total cholesterol, HDL, triglycerides, calculated-LDL)
 - Plasma for storage
- For women of reproductive potential only: Serum or urine β HCG (must have sensitivity of ≤ 25 mIU/mL)

5.10 Participant Assessments via Computer Assisted Structured Interviewing (CASI)

Participants will complete a CASI survey at enrollment and throughout study follow-up which includes assessment of sexual behavior, adherence, QOL assessments and beliefs about HIV prevention research.

See also Sections 1.1.8, 1.1.9, 1.1.10, and the SSP Manual.

5.11 Electronic Drug Monitoring (EDM) and Short Message Service (SMS texting) Components

Daily PrEP adherence data will be collected using an EDM system for the duration of study drug administration. Each participant will be given an EDM device and trained how to use it. The system will automatically capture and report all device openings as date and time of opening. These data will be used to infer ingestion of a dose and estimate adherence to a daily dosing schedule. See Section 1.1.8 and the SSP Manual.

Sexual behavior assessments via SMS texting will occur for the first week post-randomization for training purposes. Sites will be provided with the quality of data for individual participants. This will be reviewed at the Week 2 visit with additional training performed as needed. Participants will be queried periodically throughout study follow-up (see Appendix III for an example of a sampling scheme). Daily messaging for seven (7) consecutive days will occur at 12-13 separate time points. Participants will be regularly reminded that they will undergo these 7-day assessments, and will be offered re-training regarding how to use the system whenever necessary. See Section 1.1.9 and SSP Manual.

5.12 Participants with Suspected or Confirmed HIV at Screening or During the Study

At screening (prior to enrollment and randomization), all participants will undergo HIV RNA testing using a non-pooled assay (note that this testing, performed at screening, can be performed using any FDA-cleared HIV RNA test). This testing will be performed at the site laboratories. If the HIV RNA test performed at screening is positive, or if one of the HIV tests performed at either screening or enrollment is reactive, the participant will not be eligible for enrollment, regardless of subsequent test results. In those cases, HIV infection status will be confirmed using local HIV testing guidelines. Participants who have a reactive HIV test result during follow-up visits will be instructed to discontinue their study medication immediately, and will be further tested using assays such as an FDA-cleared Western blot or the Aptima HIV-1 RNA Qualitative Assay. Further HIV testing will be described in the SSP Manual.

In addition, if a participant has signs or symptoms consistent with acute HIV infection or expresses a concern about recent HIV acquisition, and in the opinion of the investigator the participant history is suggestive of recent HIV acquisition, testing will be performed using an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should select an assay that is FDA-cleared for early HIV diagnosis, such as the AptimaHIV-1 RNA Qualitative Assay. Regardless of whether HIV RNA testing is used for diagnostic testing, HIV infection must be confirmed in all cases using two independent samples.

Any participant who is found to have confirmed HIV infection after enrollment will be followed at all scheduled visits. HIV-infected participants will be followed to contribute information

regarding HIV outcomes after PrEP exposure (including viral set point), to maintain confidentiality, and to comply with expectations of communities. Participants with confirmed HIV infection will be referred for HIV counseling and treatment as appropriate.

Participants with suspected or confirmed HIV infection should follow the procedures outlined in Appendix I and II, and any instructions included in the SSP Manual. The treatment assignment will remain blinded; however, an Investigator can request to the PSRT unblinding for the primary healthcare provider if necessary for the treatment of the participant's HIV infection. If ARV therapy is to be initiated, a regimen containing a ritonavir-boosted protease inhibitor will be recommended to their primary provider, pending the results of the resistance and tropism testing.

In addition, if a participant requests post-exposure prophylaxis (PEP) for HIV exposure, they will be referred to their primary care provider for evaluation. If the participant starts PEP, they should hold study medications until completion of the course of PEP, and documentation of a negative HIV test result. Participants should receive HIV testing at least 14 days after completion of PEP treatment. HIV negative results must be documented before resuming study drug. Refer to the SSP for HIV testing requirements following completion of PEP treatment.

5.13 Hepatitis B and Hepatitis C

Testing for hepatitis B virus (HBV) will be performed at screening (HBsAg, HBsAb, and HBcAb). Persons with a positive HBsAg test will be excluded from the study and will be referred to their primary provider for management. Participants who do not have evidence of immunity to HBV (e.g., negative HBsAb) will be referred for HBV vaccination. For participants who do not have evidence of HBV immunity at screening, HBV testing should be repeated at the discretion of the site investigator during the study if clinically indicated, if the participant has elevated AST/ALT results, or if the participant expresses a concern about having acquired HBV infection after enrollment.

Hepatitis C (HCV) antibody testing will likewise be performed at baseline. However, HCV antibody testing may be completed at Screening since other testing is required at that visit. Persons with a positive HCV antibody test will be referred to their primary provider for management.

5.14 Sexually Transmitted Infections

Participants should be offered testing for any symptomatic STIs in addition to the protocol required testing. That is, in addition to required testing at Enrollment, Week 24, and Week 48 (Screening, Week 16, and Week 40 for participants in the Tissue Subset), a participant will be offered testing if he or she presents at any time with a symptomatic STI. In general, study product need not be held in the event of a STI requiring treatment, unless other product hold guidelines apply. STI testing for participants in the Tissue Subset is described in Section 5.16. Sites should assure appropriate treatment of bacterial STIs.

5.15 Drug Interaction Subset

Participants in the Drug Interaction Subset (18 per arm) will be instructed not to take their study pills prior to reporting to the study clinic for the Week 2 visit. At this visit, a plasma sample will be collected prior to dosing (for steady-state trough levels); after sample collection, a directly-observed dose of the participant's assigned study regimen will be given, followed by a second plasma sample collected approximately 6 hours after the observed dose. See the SSP Manual for additional details.

5.16 Cervical and Rectal Sampling (tissue and fluid collection) in the Tissue Subset

Sixty men and sixty women will be asked to participate in the Tissue Subset. Rectal sampling is required for men and optional for women. Cervical sampling is required for women. Rectal tissues will be obtained at Enrollment and at Weeks 24, 48, and 49. Cervical tissue will be obtained at Enrollment and at Weeks 24, 48, and 49. Plasma, PBMCs, rectal fluid (required for men, optional for women), cervicovaginal fluid and hair will also be collected at Weeks 24, 48, and 49.

All participants in whom rectal sampling is to be performed will be instructed to abstain from receptive anal intercourse for 3 days prior to rectal biopsy, and for 7 days post-biopsy to minimize risk of HIV-1 infection and bleeding complications. Participants also should abstain from administration of rectal medications (including over-the-counter medications) for 3 days prior to rectal biopsies. Women will be instructed to abstain from vaginal intercourse for 3 days prior to cervical biopsies, and for 7 days post-biopsy to minimize risk of HIV-1 infection and bleeding complications. Women also should abstain from douching or administration of vaginal medications (including over-the-counter medications) for 3 days prior to cervical biopsies and 7 days after biopsies. Participants will be contacted by telephone 1-2 days after sample collection to assess for any AEs.

In preparation for the visits where the samples are collected for the Tissue Subset, participants will be tested for PT, PTT, and INR and platelet count at Screening, prior to any biopsy procedure for participants who express interest in enrolling in the Tissue Subset. Participants with abnormal coagulation test results will be ineligible to participate in the Tissue Subset. Participants in the Tissue Subset will be tested at screening, Week 16 and Week 40 for GC/CT using NAAT and for syphilis using a test approved by the HPTN Network Laboratory. Participants with STIs will be provided treatment and have that treatment completed at least 14 days prior to obtaining biopsies.

For women participating in the Vaginal Component, sites will attempt to schedule biopsies during the luteal phase of the menstrual cycle (generally, day 15-28). However, if a participant is attending a study visit earlier in her menstrual cycle (e.g., during the follicular phase, generally day 1-14), the site should attempt to collect the cervical biopsies rather than not performing the procedure. Women in the Vaginal Component will be offered a planner (e.g., a diary or a calendar, or some other tool as determined appropriate by each site) in order to document their menstrual cycle. Refer to the SSP Manual for additional details.

As indicated in Section 5.8, in the event of study discontinuation after the Week 24 visit but before the Week 48 visit, only plasma, PBMCs and hair (no rectal or cervical samples) should be

collected for PK testing. In the event of treatment discontinuation after the Week 24 visit but before the Week 48 visit, the Tissue Subset samples should be collected two weeks following treatment discontinuation, and the procedures and evaluation indicated under Week 49 should be followed. See the SSP Manual for additional details.

5.17 Interim Contacts and Visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff. Interim visits at which no data are collected are not documented on case report forms. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically, record the event on the case report form, and provide or refer the participant to appropriate medical care.

5.18 Criteria for Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. Site IoRs may, with the approval of the PSRT which includes the Protocol Chair, the Division of AIDS (DAIDS) Medical Officer, HPTN Statistical and Data Management Center (SDMC) Protocol Statistician, and the HPTN Operations Center Protocol Specialist and others, withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the OHRP and U.S. FDA), or site IRBs terminate the study prior to its planned end date. Site investigators are required to consult the PSRT prior to the termination of any study participant. Study staff will record the reason(s) for all withdrawals in participants' study records.

6.0 SAFETY MONITORING AND ADVERSE EVENT (AE) REPORTING

6.1 Safety Monitoring

Close cooperation between the Protocol Chair(s), study site Investigator(s), NIAID Medical/Program Officer, HPTN Operations Center Protocol Coordinator, HPTN SDMC Biostatistician, HPTN Network Laboratory (NL), and other study team members will be necessary in order to monitor participant safety and to respond to occurrences of toxicity in a timely manner. The team will have regularly scheduled conference calls during the period of study implementation, and additional ad hoc calls will be convened if required.

The study site investigators are responsible for continuous close monitoring of all AEs that occur among study participants after enrollment, and for alerting the Protocol Safety Review Team (PSRT) if unexpected concerns arise.

A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, one or more site clinicians, and the SDMC Clinical Affairs Safety Associate will serve as the PSRT to be chaired by the Protocol Chair. The HPTN SDMC will prepare routine safety data report for review by the PSRT, which will meet 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. The content, format and frequency of safety data reports will be agreed upon by the PSRT and the HPTN SDMC in advance of study implementation. In addition, for phase II trials such as this with no Data and Safety Monitoring Board (DSMB) oversight, the HPTN Study Monitoring Committee (SMC) may also review safety data, either aggregate or by arm.

6.2 Clinical Data 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 organized and led by the HPTN SDMC Clinical Affairs staff (SMC reviews), the PSRT and study sponsors. The SMC will meet at least yearly to review safety data, in addition to key performance indicators. Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

HPTN SDMC Clinical Affairs 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 for review.

The PSRT will meet regularly via conference call to review clinical data reports generated by the HPTN SDMC. The content, format and frequency of the safety data reports will be agreed upon by the PSRT and the HPTN 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 HPTN representing expertise in the fields of ART, biostatistics, HIV transmission and medical ethics may be invited to join the PSRT safety review. A recommendation to stop the trial may be made by the PSRT at any such time that the team agrees that an unacceptable type and/or frequency of AEs has been observed.

Recommendations regarding permanent discontinuation of study product may involve sponsor consultation with the U.S. FDA.

In the unlikely event that the protocol team or PSRT has serious safety concerns that lead to a decision to permanently discontinue the study product for all participants and stop accrual into the study, the protocol team or PSRT will request a review of the data by the HPTN SMC before recommending that the study be stopped. Additionally, if the total number of incident infections exceeds 10, the protocol team will request a formal SMC review. If at any time, a decision is made to discontinue the study product in all participants, DAIDS will notify the U.S. FDA and the site Investigators of Record (IoR) will notify the responsible IRBs expeditiously.

6.3 Adverse Event Reporting

Information regarding all AEs regardless of seriousness or severity will be recorded in the participant's source files. Grade 1 clinical symptoms (non-laboratory, e.g., headache, nausea) that lead to a temporary or permanent hold of study drug, and all Grade 2 and higher AEs, will be collected on standard case report forms (CRFs) for entry into the study database.

6.4 Expedited Adverse Event Reporting

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 (or latest version) of the DAIDS Expedited Adverse Event (EAE) Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at <http://rsc.tech-res.com/safetyandpharmacovigilance>.

6.4.1 Reporting to DAIDS

The DAIDS Adverse Event Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC at DAIDSRSCSafetyOffice@tech-res.com.

6.4.2 Reporting Requirements for this Study

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 (or latest version) of the DAIDS EAE manual, will be used for this study. This reporting is required for each study participant until their follow-up in the study ends. The study agents for the purposes of EAE reporting are: maraviroc (MVC), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), MVC placebo, FTC placebo and TDF placebo.

6.4.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004, clarification August 2009 (or latest version) must be used for determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance>.

In addition to submitting EAE information to the DAIDS Safety Office via DAERS, the site investigator may be required to submit AE and EAE information to local regulatory agencies or other local authorities.

Information on Grade 2 and higher AEs will be included in reports to the U.S. FDA, and other government and regulatory authorities as applicable. Site staff will report information regarding AEs to their IRB in accordance with all applicable regulations and local IRB requirements.

6.5 Social Impact Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. A social impact that is judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs at least annually, or according to their individual requirements. Social impacts will be collected and reported on CRFs during regular visits. In the event that a participant reports a social impact, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SSP Manual. While maintaining participant confidentiality, study sites may engage their CAB in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

6.6 Pregnancy

Participants who become pregnant after study entry must discontinue study treatment immediately. These participants should be seen for a premature discontinuation evaluation within 7 days. These participants will continue to be followed off treatment, on study until Week 49. The PSRT must be notified of any pregnancies that occur in participants on study.

All pregnancies should be followed until the final outcome can be determined. In the event that the pregnancy has not been completed by the final study visit, then the site should contact the participant through monthly phone calls and review of medical records, if possible, until the pregnancy outcome can be ascertained. Complete the appropriate case report form for pregnancy outcome and obstetric medical complications at the end of the pregnancy, even after the participant is off study.

Participants should also be advised that not all contraceptive choices can prevent HIV transmission and that some may actually increase the risk of HIV acquisition. Study participants who are sexually active with HIV negative or unknown HIV serostatus partners should be advised that they need to consider effective strategies for reducing the risk of HIV transmission, as well as meeting the requirement for effective contraception during their participation in the study. Participants should be instructed to discuss contraceptive choices and HIV risk reduction methods with their health care provider.

Antiretroviral Pregnancy Registry

Pregnancies that occur on study should be reported to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Phone: 800-258-4263; Fax: 800-800-

1052. Intrapartum complications and/or pregnancy outcome will be recorded to The Antiretroviral Pregnancy Registry as well as on study case report forms, if possible.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This study is a phase II, four-arm, multisite, randomized, double-blinded trial of MVC, MVC + FTC, MVC + TDF, or TDF + FTC. The primary objective of the study is to establish the estimates of safety/tolerability of MVC, MVC + FTC, MVC+TDF, and TDF+FTC.

7.2 Endpoints

7.2.1 Primary Endpoints

The safety/tolerability endpoints associated with the primary objective of the study are as follows:

- Safety endpoint: Occurrence of Grade 3 or higher adverse events through 48 weeks.
NOTE: Grade 3 or higher lipid and glucose abnormalities will not be included in the primary endpoint.
- Tolerability endpoint: Time to permanent discontinuation of treatment through 48 weeks.

7.2.2 Secondary Endpoints

The endpoints associated with the secondary objectives of the study are as follows:

- Safety and tolerability endpoints:
 - Occurrence of Grade 2 or higher adverse events through 48 weeks and Grade 1 clinical (non-laboratory) adverse events that lead to a temporary or permanent hold of study drug.
 - Changes in creatinine clearance; fractional excretion of phosphate.
 - Changes in total cholesterol, HDL, LDL (calculated or measured), and triglycerides.
 - Changes in BMD.
 - Changes in peripheral blood and GALT T cell phenotype
- Pharmacokinetic endpoints:
 - Pre-dose and post-dose concentrations of MVC, FTC, and TFV in plasma after 2 weeks of dosing (Drug Interaction Subset).
 - Pre-dose concentrations of drugs (MVC, FTC, TFV, and their phosphorylated derivatives), in plasma, PBMCs, and rectal and cervical samples (Tissue Subset) at 24, 48, and 49 weeks.

- Adherence endpoints:
 - PrEP adherence, proportion of daily doses taken, as measured by electronic drug monitoring.
 - Self-reported number of doses missed in last 30 days and self-reported adherence rating scale.
 - Proportion of doses taken as measured by EDM the day of and day prior to a sexual exposure as detected by SMS assessment.
 - Selected drug concentration measurements in stored plasma samples.
- Self-reported quality of life indicators over time using a standardized assessment tool.
- Self-reported sexual behavior over time using a standardized assessment tool.

7.2.3 Exploratory Study Endpoints

The endpoints associated with the exploratory objective are as follows:

- Evidence of HIV exposure (immunologic studies of PBMC, descriptive only).
- Number of documented HIV seroconversions.
- HIV RNA level and CD4 cell count at seroconversion and set points over time in participants who acquire HIV infection.
- HIV drug resistance and co-receptor tropism in participants who acquire HIV infection.
- Changes in HIV-1 p-24 levels in colorectal and cervicovaginal explant supernatants after oral PrEP.
- Gender differences in measured outcomes.
- Correlation of drug concentrations in rectal and cervicovaginal samples.
- Characterization of host CCR5 polymorphisms and host genetic polymorphisms associated with study drug exposure.
- Presence of syphilis, gonorrhea and chlamydia at Baseline, Week 24 and/or Week 48.

7.3 Accrual, Follow-up, and Sample Size

A total of 600 participants will be enrolled; 400 at-risk MSM and 200 at-risk women. One hundred MSM and 50 women will be enrolled in each of the four arms. The total length of this study is approximately 30 months, with accrual occurring in a staggered fashion, with men beginning first, and women beginning several months later. Accrual for the men will require approximately 9 months, and accrual for the women will require approximately 9 months. Each participant will be followed for approximately 12 months (with study drug evaluated through 48

weeks, and a final post-study drug visit at Week 49). Each site will target a retention rate of 90% over the course of the entire study.

The primary safety endpoint is the occurrence of Grade 3 or higher adverse clinical and laboratory events (per DAIDS grading scale) through 48 weeks. Table A shows two-sided 95% confidence intervals for the true event rate based on various possible observed rates, given the sample size of an individual arm and the sample size of all three MVC-containing arms combined.

Table A. 95% Confidence Intervals for the True Event Rate Given Possibly Observed Event Rates

		MSM	Women	MSM and Women Combined
N	Observed Event Rate	95% CI for True Event Rate	95% CI for True Event Rate	95% CI for True Event Rate
Single Arm	1%	(0.0%, 3.1%)	(0.0%, 3.8%)	(0.0%, 2.6%)
	5%	(0.7%, 9.3%)	(0.0%, 11.0%)	(1.5%, 8.5%)
	10%	(4.1%, 15.9%)	(1.7%, 18.3%)	(5.2%, 14.8%)
	15%	(8.0%, 22.0%)	(5.1%, 24.9%)	(9.3%, 20.7%)
	20%	(12.2%, 27.8%)	(8.9%, 31.1%)	(13.6%, 26.4%)
MVC-containing Arms Combined	1%	(0.0%, 2.3%)	(0.0%, 2.6%)	(0.0%, 2.4%)
	5%	(1.9%, 8.0%)	(1.5%, 8.5%)	(2.0%, 8.0%)
	10%	(5.8%, 14.2%)	(5.2%, 14.8%)	(5.8%, 14.2%)
	15%	(10.1%, 19.9%)	(9.3%, 20.7%)	(10.1%, 19.9%)
	20%	(14.4%, 25.5%)	(13.6%, 26.4%)	(14.5%, 25.5%)

The primary tolerability endpoint is the time to permanent discontinuation of study treatment. Table B shows the power to detect different hazard ratios between the TDF/FTC arm and an individual MVC-containing arm and between the TDF/FTC arm and all three MVC-containing arms combined, assuming the Cox proportional hazards model with a two-sided type-I error of 5%, and 5% annual loss to follow-up (not due to permanent discontinuation). For example, assuming that the incidence rate of permanent discontinuation is 25%, to detect a hazards ratio of 2.0, or 50% incidence reduction, in the combined gender groups, power is 81% when the TDF/FTC arm is compared with an individual MVC-containing arm, and further increase to 98% when the TDF/FTC arm is compared with all three MVC-containing arms combined.

Table B. Power Analysis of Tolerability Endpoints

Comparison between	Incidence Rate*	HR=1.5		HR=1.67		HR=2.0	
		MSM/W	MSM and Women Combined	MSM/W	MSM and Women Combined	MSM/W	MSM and Women Combined
TDF/FTC and an individual MVC-containing arm	15%	18%/8%	25%	27%/10%	37%	44%/15%	60%
	20%	23%/9%	32%	34%/13%	47%	55%/19%	72%
	25%	27%/10%	38%	41%/14%	56%	64%/22%	81%
	30%	32%/11%	45%	47%/16%	64%	72%/45%	88%
TDF/FTC and all MVC-containing arms combined	15%	37%/10%	45%	37%/13%	64%	60%/20%	87%
	20%	47%/12%	56%	47%/17%	76%	72%/27%	95%
	25%	56%/13%	65%	56%/20%	85%	81%/29%	98%
	30%	64%/15%	73%	64%/22%	90%	88%/36%	99%

*This is the overall incidence rate for arms to be compared.

7.3.1 Sample Size Considerations for the Drug Interaction Subset

Table C provides the power to detect one standard deviation from the mean for C_{max} or AUC from historical control data with a given sample size of 72. The calculations are based on using 2-sided t-tests with 0.05 level of significance applied to log-transformed PK parameters. If comparisons are made between study arms, (e.g., MVC versus MVC/FTC looking for FTC effect on MVC) then 17 participants in each arm provides 80% power to detect one standard deviation difference from the mean. If published studies are compared with the largest available historical cohort in the literature, then 16-18 participants in each arm are needed. Based on these sample size assumptions, a total of 72 participants will be required for the Drug Interaction Subset, with 18 participants per arm.

Table C. Power to Detect the Difference of One Standard Deviation for the Given Sample Size of 72 under Various Assumptions

Drug	N (Historical Controls)	Power (%)	C_{max}	AUC
MVC	12	87.9	50-51	33-84
MVC	16	94.0	40	30
FTC	6	64.2	32	16
FTC/TDF	17	94.9	22	19
TDF	27	98.9	26	26

7.3.2 Statistical Considerations for the Tissue Subset

A subset of participants across the four study arms will be asked to provide additional samples (plasma, PBMCs, rectal tissue and fluid, and hair samples); these participants will constitute the “tissue subset.” Three studies will be conducted on these specimens: (1) a compartmental pharmacokinetic (PK) study evaluating systemic and mucosal distribution of the study drugs; (2) a gut associated lymphoid tissue (GALT) study that will characterize T cell phenotype in peripheral blood and GALT-derived T cell populations; and (3) an intestinal tissue explant study where intestinal biopsies from study participants will be challenged *ex vivo* with HIV-1 to

determine whether exposure to study drug regimens is associated with protection from HIV infection.

A total of 120 participants (60 men and 60 women), 30 from each study arm, will take part in the Tissue Subset. Samples will be collected at enrollment, 24, and 48 weeks, and 1 week following study regimen discontinuation (week 49). All three studies will be conducted on tissue specimens from each subset participant. The main objective of this subset is to provide descriptive data.

PK data for MVC, FTC, TFV, FTC-TP, and TFV-DP will be analyzed in selected body compartments. Since PK data comparisons are not being done, and due to a lack of collective information about the study drugs in plasma, PBMCs, rectal, and cervical tissue and fluid, a sample size calculation was not conducted for the PK assessments. Typical non-comparative PK studies range from 6 to 18 subjects per regimen tested. Since MVC is included in three of the study arms, and FTC in two of the study arms, 45 participants will be in an arm including MVC, and 30 will be in the FTC- and TDF-containing arms, respectively. Therefore, it is believed that the proposed sample size of 60 participants (15 per arm to reach an evaluable 12 per each arm) will provide sufficient data for modeling PK parameters.

As women may elect to participate in the rectal studies, including GALT, the sample size for the Rectal Component will likely be at least 60. A minimum sample size of 60 participants (15 per study arm) will provide sufficient power to determine large differences in T cell phenotypic markers for the flow cytometry study, with 80% power to determine an effect size of 0.66 and 99% to determine an effect size of 1.0 between any 2 study regimens. This approach should also provide sufficient power to detect scientifically important changes. The same sample size of 60 will only detect large effect sizes for the explant infection study: 70% power to detect and effect size of 0.8 and 99% power to detect an effect size of 1.4 between any 2 study regimens; this study is considered exploratory and these data will only be used to help power future studies.

7.3.3 Statistical Considerations for DXA Scans

TDF is known to reduce BMD, FTC does not change BMD, and the effect of MVC on BMD is unknown. Based on this knowledge, to improve study power, we plan to combine the 2 non-TDF containing arms (MVC monotherapy and MVC+FTC) and the 2 TDF-containing arms (MVC+TDF and TDF/FTC). Our overall comparison will be the effect of TDF-containing arms vs. MVC-containing arms on bone mineral density.

Power calculations are provided in Table D for the percentage change in BMD comparing MVC/MVC+FTC and MVC+TDF/FTC+TDF arms assuming DXA scanning of 400 trial participants (200 men and 200 women).

Table D. Power Calculation for DXA Scanning

Sample size	Dropouts	s.d.	Effect size to be detected	Power
400	10%	2.50%	1.00%	96.7%
			1.25%	99.7%
			1.50%	99.9%
		3.50%	1.00%	77.4%
			1.25%	92.3%
			1.50%	98.2%
	20%	2.50%	1.00%	87.3%
			1.25%	97.2%
			1.50%	99.6%
		3.50%	1.00%	72.4%
			1.25%	89.1%
			1.50%	96.9%

As shown in the table, when 3.5% sd is assumed, for example, scanning 400 participants would provide a reasonably good power for at least 72%. In addition, if scenarios in Table D were having equal chance to occur, scanning 400 participants would likely have 83% chance (10 out of 12) to have a power more than 85%. Gender differences in DXA results will be assessed.

7.4 Random Assignment

Enrolled participants will be assigned at random to one of four study arms in a 1:1:1:1 ratio. The randomization scheme will be generated and maintained by the HPTN SDMC. Additional details regarding the process of randomization will be included in the SSP Manual.

7.5 Blinding

Study site staff, with exceptions specified otherwise, and participants will be blinded to the random assignments. Blinding will be maintained until all data are entered into the study database, and all study endpoint data and other data included in the final analysis has been cleaned and verified and the data are ready for final analysis. As noted in Section 5.12, an Investigator can request unblinding for the primary healthcare provider in the event a participant seroconverts during the study, and unblinding would assist in the treatment of the participant's HIV infection.

Randomization assignment for all participants (main study and Tissue Subset) will be done according to computer randomly generated treatment coding at the HPTN Statistical and Data Management Center (SDMC), and participant randomization assignments will be accessed through a web-based randomization portal. Study subjects participating in the Tissue Subset will be approached sequentially about participation prior to study treatment randomization. If a subject declines subset participation, they are assigned to a study treatment in the main study and the next subject will be approached about participating in the subset. Because the study is double-blinded and neither study staff (including study investigators) nor participants will know

the randomized treatment assignments, blinding is maintained regardless of subset participation. This is true throughout the study, even as the subset arms complete enrollment.

7.6 Data Analysis

7.6.1 Primary Analyses

Given the nature of this phase II study, primary data analysis will be performed in all participants (men and women) on an intent-to-treat (ITT) basis, as soon as all participants complete their expected follow-up, without findings being unnecessarily delayed for either gender group. Depending on the outcomes to be binary or censored time-to-event, primary data analysis will tabulate the number of primary endpoints observed during the study or plot their Kaplan-Meier curves by treatment arms, respectively; in addition, comparisons between treatment arms will be done by chi-square test/logistic regression analysis, or log-rank test/Cox regression analysis, whichever is appropriate.

Those who are lost-to-follow-up prior to the study end would be considered “censored” for the safety endpoint, but they would be considered as “treatment discontinuation” and included in the tolerability endpoint. Risk sets would be adjusted in the partial likelihood method for an extended Cox proportional hazards model, i.e., the Andersen-Gill proportional intensity model, to accommodate those who are on-and-off for the tolerability endpoint. They will be compared among the 3 individual MVC-containing arms and the TDF/FTC arm.

7.6.2 Secondary Analyses

Secondary data analyses include “as-treated” analyses of the primary endpoints and additional analyses on the secondary endpoints described earlier, for individual or combined gender groups as in the primary analyses. Exploratory analyses will be performed to characterize the distribution of secondary endpoints and their potentially associated predictors by treatment arms. Time-to-event secondary endpoints will be analyzed by the Kaplan-Meier curves, stratified log-rank tests and the Cox proportional hazards model. Binary secondary endpoints will be analyzed by chi-square tests and the logistic regression model. Repeated measurements will be analyzed by Generalized Estimating Equation (GEE) methods.

Drug Interaction Subset

All statistical analyses for the Drug Interaction Subset will be performed using Stata (College Station, TX). C_{tau} will be summarized using descriptive statistics (means, standard deviation, minimum value, and maximum value). Prior to analysis, the AUC and C_{tau} will be transformed using the natural logarithm. The geometric mean with 90% confidence intervals will be calculated for FTC and MVC C_{tau} . The number and severity of any adverse events, serious adverse events, clinical laboratory abnormalities, and reasons for discontinuation due to an adverse event will be used to assess the preliminary safety of combined MVC + FTC in healthy volunteers. Clinical significance of analysis results will follow the FDA recommendations and the ICH guidelines.

Tissue Subset – PK Study

Concentrations will be measured for each study drug and/or their derivatives (MVC, FTC, TFV, FTC-TP, TFV-DP) in the samples (plasma, PBMCs, hair, rectal samples). These analyses will be performed in samples obtained at Weeks 24 and 48 (to obtain data during steady state) and at Week 49 (to obtain data about clearance after cessation of study drug use [“wash-out”]). A multi-compartment PK model will be built with these data to allow simulation of tissue and rectal lumen concentrations of these drugs in the remainder of study participants.

In addition, sparse sampling population PK assessments will be done by nonlinear mixed effects models. These models will produce subject-specific PK parameter estimates (i.e., AUC, C_{min} , C_{max}). The ratio between observed concentrations and expected concentrations (based on Pop PK modeling) will be calculated. These estimates along with raw PK parameter estimates will then be compared among the study drugs and the four biological matrices (plasma, PBMCs, hair, rectal samples).

Tissue Subset – GALT Phenotype Study

The following T cell phenotypic markers will be characterized: CD45, CD3, CD4, CD8, CCR5, CXCR4, CD38, HLA-DR, CD-69, and Ki-67. Analysis of baseline variability among the four treatment groups will be performed for continuous measure using analysis of variance and Kruskal-Wallis tests. To analyze the treatment effect of the four study drugs, changes in the percentage of T cell phenotypic markers from baseline to 24, 48, and 49 weeks will be compared between each of the treatment groups. A two sample t-test will be used for continuous variables such as T cell phenotype. Because of the relatively small number of participants planned, assessments to look for changes will be done using two-sided tests with a significance level of 0.05. Hence, any significant results will need to be followed with confirmatory studies and discussion of their clinical relevance. Assuming normally distributed differences, and a paired t-test with a sample size of approximately 15 participants, there will be 80% power to detect an effect size (Cohen’s d) of 0.66 and 99% power to detect an effect size of 1 between any two regimens. To convert the effect size d , into measured units, the derived standard deviations for each assay change is multiplied by d . Thus, for example, based on the results from the RMP-01 UC781 trial (Anton PA 2011), there was a 98% power to detect an average decrease of 6.34% in CD4-lymphocytes, and higher power for larger differences. This approach will provide sufficient power to detect any scientifically important changes.

Tissue Subset – *ex vivo* HIV Challenge Study

The main question of interest for the explant studies is whether the various treatment arms are able to reduce explant infectivity post-treatment. As virus growth varies according to the day of observation, comparisons will be made once exponential virus growth is being observed, using an improved statistical method (“soft endpoint”), developed for the Microbicide Quality Assurance Program (MQAP-NICHD) (Richardson-Harman N 2009). Optical Density (O.D.) data from all p24 assays will be compared to a universal standard curve for O.D. values within a 95% confidence interval of the plate standards. Differences between study products will be determined using Repeated Measures ANOVA and ANCOVA (adjusting for baseline differences). Changes in cumulative p24 antigen will be the primary outcome in the explant studies. A two-sided paired t-test with a significance level of 0.05 will be used. The previous

UC781 study (RMP-01) showed effect sizes of 1.4 for 0.25% at 104 TCID50 (corresponding to an average difference of 5240) and an effect size of 0.8 for 0.1% at 104 TCID50 (corresponding to an average difference of 1110). However, while nearly all 36 participants' tissues were infectible at baseline with the higher 104 titer, only 2/3 of those same 36 participants' tissues were infectible with the 102 viral titer at baseline (Anton, Saunders et al. 2011). Consequently, only the high viral titer will be used in the current study. Using a two-sided paired t-test with $\alpha=0.05$, the study will have 70% power for an effect size of 0.80 and 99% power for an effect size of 1.4. Comparisons between baseline and each study regimen will be done using multi-level models, but given the extremely small sample sizes, this will only be done for powering further studies, as there will not be sufficient power to detect a difference in changes, except for very extreme outcomes.

Adherence

PrEP execution. PrEP execution will be defined as the number of EDM events/number of prescribed doses prior to treatment discontinuation. Because participants may have several periods of PrEP discontinuation and re-initiation, each execution during each PrEP episode will be examined. Participants will be categorized according to low, medium, and high adherence. When examined as an outcome, a dichotomous variable ($<90\%$, $\geq 90\%$) or a continuous outcome will be used. Participant-reported numbers of missed doses over the 30 days will be used as additional adherence measures to provide comparable measures with other studies.

PrEP persistence time, which is defined as the time from randomization to PrEP discontinuation (>30 consecutive days without an EDM event) will also be examined.

PrEP adherence patterns, such as the frequency and duration of interruptions, are defined as >48 hrs without an EDM event and will be characterized.

Coverage

The median number of days will be reported with reported risk events (defined as anal sex without condom use). The proportion of doses will be reported as those taken as measured by EDM the day the participant reports the risk event and the day prior to reporting a risk event. Participants will be categorized as taking 0, 1 or 2 doses. The differences between arms and changes over time for the entire population will be examined. Additional analyses will consider anal sex without regard to condom use and pill-taking for up to 7 days prior and 7 days after a risk event.

Quality of Life (QOL)

QOL indicators will include individual EQ-5D response items, and a summary indicator representing the U.S. societal perspective (Shaw JW 2005).

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent form(s) contained in Appendices V-VII — and any subsequent modifications — will be reviewed and approved by the HPTN Protocol Review Committee and DAIDS Prevention Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs at least annually, and within three months of 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. Study sites are responsible for the submission of continuing review to the DAIDS Protocol Registration Office, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

8.2 Informed Consent

Written informed consent will be obtained from each study participant. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendices V-VII that describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. If applicable, the study site also is responsible for translating the template form into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Participants will document their provision of informed consent by signing their informed consent forms. (Further details regarding DAIDS requirements for documenting the informed consent process can be found in the DAIDS Standard Operating Procedure for Source Documentation.)

All participants will be offered a copy of their informed consent form.

8.3 Incentives

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

8.4 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All

laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a 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 separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; Gilead Sciences, Inc. and ViiV Healthcare; representatives of the HPTN CORE, SDMC, and/or NL; ACTG; the U.S. FDA, OHRP, other government and regulatory authorities, and/or site IRBs.

The HPTN will obtain a Certificate of Confidentiality from the U.S. Department of Health and Human Services that will be applicable for this study. Sites may register under the Certificate through the HPTN CORE once they have obtained local IRB approvals for the study. This Certificate protects study staff from being compelled to disclose study-related information by any Federal, State or local civil, criminal, administrative, legislative, or other body.

8.5 Communicable Disease Reporting Requirements

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

8.6 Study Discontinuation

The study also may be discontinued at any time by NIAID, the HPTN or ACTG, the pharmaceutical sponsors, the U.S. FDA, other government or regulatory authorities (OHRP), or site IRBs.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described in Appendix I and Section 5.0; additional tests to be performed for participants with confirmed HIV infection are described in Appendix II.

9.1 Local Laboratory Specimens

Specimens to be processed at the local site laboratories may include HIV rapid testing, HIV enzyme immunoassay testing (EIA), HIV confirmatory testing (e.g., Western blot, if needed), hepatitis serology testing (HBsAg, HBsAb, HBCoreAb, anti-HCV antibody), CBC with differential and platelet count, chemistry panel (sodium, potassium, chloride, CO₂, glucose, creatinine, blood urea nitrogen, phosphorous), calculated creatinine clearance, LFTs (ALT and AST, total bilirubin, alkaline phosphatase), syphilis testing (using rapid plasma reagin (RPR) or other tests approved by the HPTN Network Laboratory), lipid profile (with total cholesterol, HDL, calculated or measured LDL and triglycerides), 25-OH-vitamin D level, parathyroid (PTH) level, rectal and cervical swabs for NAAT for GC/CT (these can also be done at the Network Lab if unavailable at the site), urinalysis, urinary phosphate and urinary creatinine, HIV viral

load (used to screen all participants for acute HIV infection prior to enrollment, and for participants who have confirmed HIV infection after study enrollment); CD4 cell count (for participants with confirmed HIV infection), and HIV RNA testing (for participants who have possible acute HIV infection after study enrollment, performed at the site laboratory or a CLIA-certified laboratory if the test is not available on site). Testing will be performed using an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should select an assay that is FDA-cleared for early HIV diagnosis such as the AptimaHIV-1 RNA Qualitative Assay. Sites will be required to prepare and store PBMCs for immunology studies (all participants) and for CCR5 genotyping (all consenting participants). Selected sites will also process rectal and cervical samples (tissue and fluid for PK and immunology studies, Tissue Subset only) and will store hair samples (Tissue Subset only).

All women of reproductive potential will have either a serum or urine β HCG test for pregnancy (sensitivity of ≤ 25 mIU/mL) at each visit. Additionally, if a woman does not have satisfactory Pap result in the past 12 months and wishes to join the Tissue Subset, a Pap smear will be completed.

9.2 Network Laboratory Specimens

9.2.1 Virology

The HPTN Network Laboratory (NL) will perform testing to determine HIV infection status in selected cases (e.g., indeterminate Western blot). Additional assays may be performed at the HPTN NL or at an outside laboratory designated by the HPTN NL. This testing may include HIV genotyping, HIV phenotyping, HIV tropism testing, HIV subtyping, minority variants assays, or other tests to characterize HIV viruses and/or the host response to HIV infection.

Samples from participants who become HIV-infected during the study will be shipped to the HPTN NL. A sample collected at the time of HIV diagnosis will be sent to Monogram Biosciences (South San Francisco, CA, a subsidiary of LabCorp) for HIV resistance and HIV tropism testing. If they are not able to perform the testing, another laboratory will be selected by the HPTN NL. Results from this testing will be made available to study sites at study closure. Results may be provided to study sites prior to study closure upon request, with approval of the HPTN NL and the Protocol Chairs. Results from any other resistance testing (e.g., minority variants analysis, if performed, see above) will not be returned to study sites.

9.2.2 Pharmacology

In order to avoid excessive phlebotomy and minimize the cost and complexity of the protocol, only sparse sampling will be done. In the Drug Interaction Subset, only plasma samples will be collected and analyzed (Week 2 visit, two samples per participant). In the Tissue Subset, plasma, PBMC and rectal, and cervical samples (tissue and fluid) will be collected and analyzed. Hair samples will also be collected for possible future studies. Sample collections for the Tissue Subset will occur at Enrollment and at the 24, 48, and 49-week study visits (note that samples collected at Enrollment are only for the GALT T cell phenotype analysis and the *ex vivo* HIV challenge; no PK samples are collected at Enrollment). These visits were selected to coincide with the most intensive adherence assessment visits, allowing for comparison of adherence and PK parameters. The following substances will be measured in different sample types:

- Plasma: MVC, FTC, TFV
- PBMCs: FTC-TP, TFV-DP
- Rectal fluid (from sponge collection): MVC, FTC-TP, TFV-DP
- Rectal tissue homogenate (from biopsy samples): MVC, FTC, TFV, FTC-TP, TFV-DP
- Cervicovaginal fluid: MVC, FTC, TFV (no phosphates)
- Cervical tissue homogenate (from biopsy samples): MVC, FTC, TFV, FTC-TP, TFV-DP

[*Note that samples will be unblinded in the Pharmacology Laboratory (only), so the relevant assays can be identified and performed.]

All drug concentrations will be measured using assays that are validated and approved by the Clinical Pharmacology Quality Assurance (CPQA) Committee. Testing of hair will be performed at the HPTN NL or at an outside laboratory designated by the HPTN NL. All other pharmacology assays will be performed at the HPTN NL. Test results will not be returned to study sites.

9.2.3 Immunology

PBMC samples from Enrollment and the Week 24 visit will be used to seek evidence of HIV exposure in participants who do not develop established HIV infection. Testing for HIV exposure may include analysis of HIV- or peptide-induced immunological responses, such as cytokine production, in cultured PBMCs. Those data could be correlated with behavioral data. Testing will be performed at the HPTN NL or at a laboratory designated by the HPTN NL. Test results will not be returned to study sites.

9.2.4 Rectal and Cervical NAAT for GC/CT

Rectal and cervical swabs will be tested for GC/CT using a NAAT. The expectation is that this testing will be performed locally. Sites should contact the HPTN NL if local testing is not possible. Sites should also contact the HPTN NL for approval if they plan to use an alternate laboratory for testing.

9.2.5 Pharmacogenomics

Samples collected for pharmacogenomic testing will be analyzed for genetic polymorphisms associated with study drug exposure. Assays will be performed at the HPTN NL. Test results will not be returned to the sites.

9.3 Quality Control and Quality Assurance Procedures

9.3.1 QC for HIV Diagnostic Testing

Local laboratories will perform testing for HIV diagnosis at screening, enrollment, and other scheduled visits. Algorithms for HIV diagnostic testing are provided in the SSP Manual.

9.3.2 QC for HIV RNA Monitoring

Quantitative HIV RNA (viral load) testing will be performed at local laboratories to monitor HIV infection in any subject with confirmed HIV infection. Note that this is distinct from use of qualitative HIV RNA testing that is performed to determine HIV infection status (see above). Local laboratories must be certified under the Continuous Laboratory Improvement Amendment (CLIA-certified); participation in the DAIDS Virology Quality Assurance (VQA) program is recommended.

9.3.3 QC for CD4 Cell Count Determination

CD4 cell count testing will be performed at local laboratories in any subject with confirmed HIV infection. Local laboratories must be CLIA-certified; participation in the DAIDS Immunology Quality Assurance (IQA) program is recommended.

9.3.4 QC for Safety Testing

Local laboratories performing safety testing, e.g., HBV and HCV serologies, CBC with differential, chemistry testing (including liver function tests) must be CLIA-certified and must participate in appropriate external quality control (EQA) programs.

9.4 Tissue Subset Processing

Selected sites will process rectal and cervical tissue and fluid for special studies. This includes processing luminal fluid for the PK subset, and processing tissue for GALT T cell phenotype analysis (rectal biopsies only) and *ex vivo* HIV challenge studies. Different methods of tissue processing are needed for each of these three analyses.

Peripheral blood and tissue for GALT T cell phenotype will be processed at selected clinical sites. The sites will ship the samples overnight to a centralized laboratory in RPMI transport medium and the central lab will isolate the T cells and stain and run the samples for flow cytometric analysis.

- Plasma, PBMCs, rectal and cervical tissue and rectal and cervicovaginal fluid will be processed and frozen for subsequent shipment to the HPTN NL. Measurement of ARV drugs for the PK subset will be performed at the HPTN NL.
- Rectal and cervical tissue will be processed for *ex vivo* explant infection. This analysis will be performed at each of the sites enrolling the tissue subset. The explant infections will be performed using methods similar to those described previously (Dezzutti, Uranker et al. 2012).

- All sites will use aliquots of the same viral stock (may be unique to rectal and cervical) and the same laboratory procedures. Explant supernatant will be collected from the cultures and will be analyzed for HIV p24 antigen; p24 antigen assays will be measured at a centralized laboratory designated by the HPTN Network Lab. Further details are provided in the Study Specific Procedures Manual.

9.5 CCR5 Genotype

PBMC samples collected for CCR5 genotyping will be sent to a centralized laboratory designated by the HPTN NL for testing.

9.6 Specimen Storage and Possible Future Research Testing

Study sites will store PBMC, plasma, and where applicable, hair, rectal tissue and fluids collected in this study at least through the end of the study. In addition, study participants will be asked to provide written informed consent for these samples to be stored after the end of the study for possible future non-protocol listed testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed at the end of the study.

9.7 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the United States Centers for Disease Control and Prevention. All infectious specimens will be transported in accordance with United States regulations (42 CFR 72).

10.0 ADMINISTRATIVE PROCEDURES

10.1 Protocol Registration

Initial Registration of the protocol by the DAIDS Protocol Registration Office (DAIDS PRO) is required prior to implementation of this protocol. As part of this process, each site must have the protocol and protocol informed consent form(s) approved, as appropriate, by their local institutional review board (IRB) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. In the case of Initial Registration, site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO. Sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Following Initial Registration, any full protocol amendments require submission of a protocol registration packet to the DAIDS PRO as described above; however, the DAIDS PRO *WILL NOT* review and approve site-specific ICFs. Sites will receive a Registration Notification when the DAIDS PRO receives a complete registration packet.

There may be cases where a site submits as their Initial Registration a protocol amendment (Version 2.0 or higher of a protocol); in such cases, the instructions for Initial Registration will be followed.

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, which can be found at <http://rsc.tech-res.com/protocolregistration/>.

10.2 Study Activation

Pending successful protocol registration and submission of all required documents, the HPTN Operations Center staff will “activate” a site. Study implementation may not be initiated until a study activation notice is provided to the site by the HPTN Operations Center. (In some cases the Division of AIDS has provided activation approval via email, which is also acceptable documentation of activation.) In addition, if study “activation” is determined to be necessary for any subsequent amendments, study implementation may not be initiated until a study activation notice is provided to the site by the HPTN Operations Center.

10.3 Study Coordination

DAIDS holds the Investigational New Drug (IND) application for this study (IND# 113,655). Copies of all regulatory documents submitted to this IND by DAIDS will be forwarded to Gilead Sciences, Inc. and ViiV Healthcare for cross-referencing with the company’s other INDs for the study product(s). Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS and Gilead Sciences, Inc. and ViiV Healthcare.

Study implementation will be directed by this protocol as well as the SSP Manual. The SSP Manual, which will include links to the DAIDS SOPs for Source Documentation and Essential Documents, as well as links to the Manual for Expedited Reporting of Adverse Events to DAIDS and the DAIDS Toxicity Tables, will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations.

Study case report forms will be developed by the study team and HPTN SDMC. Data will be transferred to the HPTN SDMC, entered, and cleaned using the HPTN SDMC DataFax data management system. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team as well as the HPTN Study Monitoring Committee. The Protocol Chair, DAIDS Medical Officer, Protocol Biostatistician, and HPTN Operations Center Protocol Specialist will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

10.4 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN Operations Center, HPTN SDMC, HPTN NL, NIAID, ACTG, Gilead Sciences, Inc., ViiV Healthcare, site IRBs, and U.S. regulatory authorities (OHRP and U.S.FDA). A site visit log will be maintained at each study site to document all visits.

10.5 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) and the DAIDS Regulatory Support Center (RSC) prior to implementing the amendment.

10.6 Investigator's Records

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with Federal regulations, for each of the investigational products tested, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the U.S. FDA is notified that the IND is discontinued. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

10.7 Use of Information and Publications

Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, DAIDS, Gilead Sciences, Inc. and Viiv Healthcare, for review prior to submission.

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APPENDICES I - VII

APPENDIX I: SCHEDULE OF PROCEDURES AND EVALUATIONS										
	Screening	Enr	Wk 2	Wk4	Wk 8, 16, 32, 40	Wk 24, 48	Wk 49	T/D ¹ or S/D ¹	Suspected infection ²	Confirmed Infection ²
ADMINISTRATIVE, BEHAVIORAL, REGULATORY										
Informed consent (including consent for the Drug Interaction Subset [all sites] and the Tissue Subset [designated sites])	X									
Randomization ²⁸		X								
Demographic information		X								
HIV counseling (pre-and post-test), including risk-reduction counseling	X	X	X	X	X	X	X	X	X	X
Condom distribution	X	X	X	X	X	X	X	X	X	X
Locator information	X	X	X	X	X	X			X	
Behavioral/adherence/QOL assessment/Beliefs (PREMIS) ³		X		X	X	X		X		
SMS assessment ⁴	Random sampling at 12-13 different time points up to Week 48									
Adherence education and follow-up counseling		X	X	X	X	X ¹²				
CLINICAL EVALUATIONS & PROCEDURES										
History, con meds, physical exam (complete history and PE at enrollment, targeted at all other visits)	X	X	X	X	X	X	X	X	X	X
Blood collection	X	X	X	X	X	X	X	X	X	X
Urine collection	X	X			X ⁵	X	X	X		
Rectal and vaginal or cervical swab collection ²⁹		X				X				
Provide study drug		X	X ⁶		X	X ¹²				
DOT - Drug Interaction Subset only ⁶ (first 72 who consent)			X ⁶							
DXA scan		X ²¹				X ⁷				
LOCAL LABORATORY EVALUATIONS										
HIV RNA for acute HIV infection ⁸	X									
HIV testing ²	X	X	X	X	X	X	X	X	X	
HBV serology ⁹	X									
HCV serology ⁹		X								
CBC with differential and platelets	X		X	X	X	X	X	X		
Chemistry panel ¹⁰	X		X	X	X	X	X	X		
LFTs (AST, ALT, total bilirubin, alkaline phosphatase)	X		X	X	X	X	X	X		
Lipid profile (fasting 8 -- or preferably, 12-- hrs - see Section 5.2)		X				X		X		
25-OH-Vitamin D level (may be performed at Enrollment at IoR discretion)	X					X ⁷		X		
Parathyroid (PTH) level (may be performed at Enrollment at IOR discretion)	X					X ⁷		X		
Serum or urine βHCG pregnancy test (women only) ²³	X	X	X	X	X	X	X	X	X	X
Urinalysis ¹¹	X				X ⁵	X	X	X		
Urinary phosphate and urinary creatinine	X				X ⁵	X	X	X		
Urine for GC/CT (for men, and for women at sites that do not perform swabs) ²⁶		X				X				

APPENDIX I: SCHEDULE OF PROCEDURES AND EVALUATIONS (continued)

	Screening	Enr	Wk 2	Wk 4	Wk 8, 16, 32, 40	Wk 24, 48	Wk 49	T/D ¹ or S/D ¹	Suspected infection ²	Confirmed Infection ²
Syphilis serologic testing ²⁶		X				X				
Cervicovaginal/Rectal GC/CT NAAT ²⁶		X				X				
ALL PARTICIPANTS										
Plasma for storage ¹³	X	X	X	X	X	X	X	X	X	X
Plasma for drug levels			X ⁶							X
PBMC for pharmacogenomic testing		X ²²								
PBMC for immunology testing ¹⁴		X				X ¹⁵				
PBMC for CCR5 genotyping		X								
TISSUE SUBSET¹⁶										
Coagulation testing (INR/PT/PTT) – perform after consenting to Tissue Subset	X									
Pap Test ²⁴	X									
Syphilis serologic testing	X				X ¹⁷					
Cervicovaginal/Rectal GC/CT NAAT ^{26,27}	X				X ¹⁷					
Urine GC/CT NAAT (men only) ^{26,27}	X				X ¹⁷					
Plasma for drug levels (PK) ¹⁸						X	X	X ¹⁹		X
PBMC for drug levels (PK) ¹⁸						X	X	X ¹⁹		X
Rectal and cervicovaginal fluid for drug levels (PK) ¹⁸						X	X	X ¹⁹		
Preparatory enema		X				X	X	X ¹⁹		
Rectal and cervical tissue for drug levels (PK) ^{18,20}						X	X	X ¹⁹		
Rectal and cervical tissue for ex vivo HIV challenge ²⁰		X				X	X	X ¹⁹		
Rectal and cervical tissue for GALT T cell phenotyping ²⁰		X				X	X	X ¹⁹		
Hair – store for future studies						X	X	X ¹⁹		
Post-biopsy phone call for adverse event assessment ²⁵		X				X	X	X ¹⁹		

FOOTNOTES FOR APPENDIX I

¹T/D = Treatment Discontinuation; S/D = Study Discontinuation

²HIV diagnostic testing must be performed according to the instructions and algorithms provided in the SSP Manual. In all cases, HIV diagnosis must be confirmed by testing two samples collected on different dates. The HPTN NL should be consulted in any case where HIV infection status is unclear, if any HIV test (e.g., rapid HIV test or EIA) is reactive, if HIV seroconversion is documented, or if acute HIV infection is suspected after enrollment. Additional testing must be performed for participants who have suspected acute HIV infection after enrollment or confirmed HIV infection (see Appendix II). Participants who are confirmed to be HIV-infected according to the SSP Manual will have no further HIV diagnostic testing performed at subsequent study visits. If any participant has an initial reactive or positive HIV test at Week 48, confirmatory testing should be performed 1-2 weeks later. The results of confirmatory testing should be communicated to the participant at their final visit at Week 49. If any participant has an initial reactive or positive HIV test at Week 49, follow the procedures in Appendix II and make arrangements to provide the participant with results of the confirmatory testing. Additional laboratory evaluations for participants with confirmed HIV infection are detailed in Appendix II. Also see SSP Manual for additional details.

³The enrollment assessments will include a brief sexual behavioral assessment and QOL via CASI. This assessment must be completed before the SMS training (see Footnote 4). Adherence assessments will begin at Week 8. Only PREMIS questions will be asked at Week 4. In addition, qualitative interviews will take place following the PREMIS-related questions at any time from Week 4 through week 40 at selected sites in a subset of participants who agree. See SSP for more details.

⁴Participants will undergo sexual-behavior assessments via SMS at 12-13 random time points during the study, each time point lasting a total of 7 days. A 7-day assessment will also occur starting at the enrollment visit for training purposes in order to familiarize the participant with the device and the assessment. A reminder and review of the SMS assessment should occur at each study visit.

⁵Week 8 only.

⁶Participants in the Drug Interaction Subset only. This subset will include the first 72 participants enrolled in the study who consent for participation in the Drug Interaction Subset (18 in each study arm). For these participants, this evaluation will involve three steps: (1) collection of a pre-dose (trough) sample, (2) administration of a single, directly observed dose, and (3) collection of a post-dose sample 6 hours after the observed dosing. Note that the appropriate window periods for the 6-hour sample collection are defined in the SSP Manual. Participant must bring their study product to the clinic for DOT dosing. The DOT dose is not routinely supplied by the pharmacy; however, the site should have a plan in place in the event that the participant forgets to bring his/her study medication.

⁷Week 48 only. The window for completing the DXA scan at this visit is -14 days/+14 days of the Week 48 visit. The other procedures completed at Week 48 will follow the standard allowable window. Only participants that received a DXA scan at Enrollment will receive a scan at Week 48.

⁸All participants will be tested for acute HIV infection prior to enrollment. This testing will be performed using a non-pooled HIV RNA assay. This testing must be completed no more than 14 days prior to enrollment, but preferably within 7 days prior to enrollment. This testing can be performed at the same visit as other screening procedures, or at a separate screening visit.

⁹HBsAg, HBsAb, and HBCoreAb tests will be performed at Screening and anti-HCV antibody tests will be performed at Enrollment. However, for logistical purposes, the anti-HCV antibody testing may be completed at Screening. In these cases, the results obtained during screening will be used as the Baseline measurement. Participants who are HBsAg positive will be referred for care and are not eligible for enrollment. Participants who do not have evidence of immunity to HBV (e.g., negative HBsAb) will be referred for HBV vaccination. Evidence of immunity to HBV is not required for enrollment. Participants who test positive for the anti-HCV antibody are eligible to be on the study and will be referred for care.

¹⁰The chemistry panel includes: sodium, potassium, chloride, CO₂, glucose, creatinine, blood urea nitrogen, phosphate, creatinine clearance calculated using the Cockcroft-Gault formula, where CrCl (male) in mL/min = $[(140 - \text{age in years}) \times (\text{actual body weight in kg})] / (72 \times \text{serum creatinine in mg/dL})$. If any abnormalities are observed at screening that do not meet the criteria for exclusion from the study, repeat testing and/or further evaluation may be performed at the discretion of study personnel prior to enrollment.

¹¹Urinalysis includes protein and glucose measurements.

¹²Week 24 only.

¹³Plasma will be collected from all participants at these visits. These samples will be used for QC testing and may also be used for retrospective analysis of HIV in participants who acquire HIV infection. These samples may also be used for future analysis of random drug levels as a possible measure of adherence.

- ¹⁴PBMCs will be collected for all participants at Enrollment and Week 24 (no collection at Week 48) for immunologic studies that will seek evidence of HIV exposure in participants who do not have evidence HIV infection. Testing for HIV exposure may include analysis of HIV- or peptide-induced immunological responses, such as cytokine production, in cultured PBMCs.
- ¹⁵Week 24 only.
- ¹⁶Participants in the Tissue Subset only. Sixty (60) male participants (15 in each study arm) will comprise the Rectal Component of the Tissue Subset. Women may elect to participate in the Rectal Component, therefore, the Rectal Component may contain more than 60 participants depending on the number of women who elect to join that component. Sixty (60) female participants will comprise the Vaginal Component of the Tissue Subset. Participants in the Tissue Subset will be enrolled at selected sites that have the clinical capacity and expertise for rectal and/or cervical sampling as well as the laboratory capacity and expertise for processing these tissue and fluid samples. See the SSP Manual for additional details, including procedures for collecting and processing rectal and cervical samples. Rectal and cervical tissue will be collected at Enrollment, and at Weeks 24, 48, and 49. Rectal and cervicovaginal fluid will be collected at Weeks 24, 48 and 49. At Enrollment, Week 16 and Week 40, a rectal swab and cervicovaginal testing for GC/CT NAAT, and blood for syphilis testing will be collected in preparation for the tissue and fluid collection.
- ¹⁷Weeks 16 and 40 only.
- ¹⁸PK samples (Weeks 24, 48 and 49) must be collected prior to drug dosing (trough levels).
- ¹⁹In the event of study discontinuation after the Week 24 visit but before the Week 48 visit, only plasma, PBMCs, and hair (no rectal samples) should be collected for PK testing. In the event of treatment discontinuation after the Week 24 visit but before the Week 48 visit, all of the Tissue subset samples should be collected per the schedule of events and procedures at Week 49, two weeks following the time of treatment discontinuation. Post-biopsy phone call should occur 1-2 days after the biopsy procedure. See the SSP Manual for additional details.
- ²⁰Tissue processing methods for PK analysis, *ex vivo* HIV challenge, and GALT cell phenotype are different. See the SSP Manual.
- ²¹The DXA required for enrollment may be performed at -30 days/+7 days, i.e., during screening or after enrollment. All of the women and 200 of the 400 men enrolled will have a DXA scan. The SDMC will inform the sites when the men's DXA cohort is enrolled.
- ²²Participants who were enrolled under Version 2.0 will have to consent to this particular test since it is a new test included under Version 3.0 (i.e. was not included in Version 2.0). For those participants, if consent is given, the pharmacogenomics plasma sample may be drawn at any scheduled follow-up visit. For participants newly enrolling under Version 3.0 and who have given consent, the pharmacogenomics plasma sample will be drawn at Enrollment.
- ²³Because the screening window is 45 days, two pregnancy tests are required during screening. While it is a site's discretion to determine the best process for screening, it is recommended that the initial pregnancy test be performed early in the screening process to rule out pregnancy prior to initiating other screening tests. An additional pregnancy test must be performed with documented negative results within 48 of initiating study medication. For participants who become pregnant during the study, once the initial positive test is documented, additional pregnancy testing need not be performed.
- ²⁴Test is to be offered if a woman does not have a documented satisfactory result within the past 12 months. It must be completed prior to the Enrollment visit. See Section 3.1.
- ²⁵Adverse event assessment should occur about 24-48 hours after biopsies via phone call to participant.
- ²⁶Refer to the SSP for instructions regarding scheduling of these tests for participants enrolled under Version 2.0 of the protocol. For participants enrolled under Version 3.0, these tests may be completed at Screening per site discretion. In these cases, the results obtained during screening will be used as the Baseline measurement.
- ²⁷Testing at Week 16 and Week 40 will be completed in place of the Week 24 and Week 48 testing.
- ²⁸Study product should be initiated within 24 hours of randomization. In case that the 24 hour frame cannot be met, contact the PSRT.
- ²⁹These swab collections pertain to the main study participants (not the Tissue Subset participants) for GC/CT testing. Rectal swabs will be collected in all men, and in women who report having had anal sex in the last year (from the time the swab is collected). At sites that have the clinical and laboratory capacity to collect and test cervical or vaginal swabs for GC/CT, this swab should be collected. A woman may opt to self-collect a vaginal swab specimen; if she does, this must be done at the study clinic. For sites that cannot collect and test vaginal or cervical swabs for GC/CT testing, urine should be collected for this purpose.

APPENDIX II: ADDITIONAL PROCEDURES FOR PARTICIPANTS WITH CONFIRMED HIV*

	Time of diagnosis	Week 49 or last study visit
CD4 cell count testing	X	X
HIV viral load testing	X	X
Plasma and PBMC for PK⁵	X	
Shipment of samples to the HPTN NL¹	X	X
Specialized HIV testing²	X	X ³
Other testing⁴	X	X
Additional plasma storage	X	X

*These procedures are indicated for participants with confirmed HIV infection, or for any participant who has an initial reactive or positive HIV test at Week 49. Participants who have confirmed HIV infection during the study will continue in the study, off of study drug.

¹Samples from HIV seroconverters will be shipped to the HPTN NL; sites should store samples until they receive a request for shipping from the SDMC. At the discretion of the HPTN NL, samples may be transferred to a DAIDS-approved repository.

²The HPTN NL will coordinate specialized HIV testing using samples shipped to the HPTN NL. This testing will include the following assays performed at Monogram Biosciences: PhenoSense GT (for NRTIs, NNRTIs, PIs), PhenoSense Entry (for MVC susceptibility) and Trofile (HIV tropism assay). Env sequencing may also be performed (retrospective for research use only).

³For participants whose first positive HIV test is obtained prior to Week 48, samples collected at Week 49 may be used to evaluate changes in ARV resistance patterns.

⁴Additional testing may be performed at the HPTN NL or at another laboratory designated by the HPTN laboratory for research purposes; those results will not be returned to study sites or study participants. This testing may include additional HIV genotyping/sequencing assays, HIV phenotyping, HIV subtyping, minority variants assays, other assays to characterize HIV viruses and/or the host response to HIV infection.

⁵Blood collection for plasma storage for PK is completed for all participants with confirmed HIV infection. PBMC storage for PK is only completed for those individuals participating in the Tissue Subset.

APPENDIX III: DESCRIPTION OF SMS SAMPLING STRATEGY, ADHERENCE, AND COVERAGE

Potential SMS Sampling Schemes¹

Week ²	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
A	X				X				X				X		
B	X						X				X			X	
C	X		X			X						X			
D	X		X		X					X					X
E	X						X		X				X		
F	X			X				X		X				X	
G	X							X				X			
H	X			X		X					X				X

¹ 25% of the population is sampled during any given study week after Week 2. All participants will be queried about sexual exposure for the first week post-randomization, which will serve as a training period. Sites will receive data on the quality of responses (*i.e.*, number of days with successful responses). Participants will receive additional training at the Week 2 visit and at any subsequent visit as needed.

² Weeks are depicted as 0-14 for illustrative purposes and do not match the actual visit schedule of the study.

Potential patterns of pill taking.³

Week	1	2	3	4	5	6	7
Excellent adherence with risk events: Adherence: 100%. Coverage: 2/2 and 2/2							
Pill taken?	X	X	X	X	X	X	X
Sex event?		X		X			
Poor adherence with risk events: Adherence: 3/7 =43%. Coverage: 1/2 and 0/2							
Pill taken?	X					X	X
Sex event?		X		X			
Poor adherence with no risk events: Adherence: 3/7 =43%. Coverage: no sex events							
Pill taken?	X					X	X
Sex event?							
Excellent adherence with no risk events: Adherence: 100%. Coverage: no sex events							
Pill taken?	X	X	X	X	X	X	X
Sex event?							
Excellent adherence around risk event: Adherence: 57%. Coverage: 2/2							
Pill taken?	X	X	X	X			
Sex event?		X					

³ Adherence is defined as the proportion of doses taken as measured by EDM. Coverage is the proportion of doses taken the day of and a day prior to a sex event.

APPENDIX IV: TOXICITY MANAGEMENT

Toxicity Management General Guidance

In general, the site Investigator has the discretion to hold study product at any time if she/he feels that continued product use would be harmful to the participant, or interfere with treatment deemed clinically necessary according to the judgment of the investigator. In addition, a Protocol Safety Review Team (PSRT) will be established for this study, and will review safety data on a regular basis. The PSRT's responsibilities will include consultation and decision-making regarding management of toxicities and study product administration, including product resumption following the occurrence of certain types of toxicities and/or permanent discontinuation. Investigators should consult the PSRT for further guidance in restarting study drug or progressing to permanent discontinuation. Revealing a participant's blinded status will occur only for individuals who seroconvert and choose to initiate antiretroviral therapy. (A full description of the PSRT's role and responsibilities is included in the SSP Manual).

Grade 1 or 2

In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product, and that is not specifically addressed in the Table below may continue use of the study product per protocol.

Grade 3

Participants who develop a Grade 3 AE or toxicity that is not specifically addressed in the Table below and is judged to be related to study drug by the Investigator, study drug use should be temporarily discontinued in consultation with the PSRT. In general, and unless otherwise decided in consultation with the PSRT, the investigator should re-evaluate the participant until resolution of the toxicity. The study drug should be permanently discontinued if improvement to severity \leq Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study drug use is resumed and the same Grade 3 AE recurs at any time, the Investigator must consult the PSRT for further guidance on holding of study drug, frequency of reevaluation or progression to permanent discontinuation of the study drug.

Grade 4

Participants who develop a Grade 4 AE or toxicity that is not specifically addressed below (regardless of relationship to study drug) should have the study drug temporarily discontinued. The Investigator must consult the PSRT and continue the temporary study drug hold until a recommendation is obtained from the PSRT. In general, study drug use will not be resumed if the Grade 4 AE is considered related to study drug use. If, in consultation with the PSRT, study drug use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study drug must then be permanently discontinued.

General Criteria for Discontinuation of Study Product

Participants may voluntarily discontinue the study products for any reason at any time. Investigators will permanently discontinue participants from study product per protocol for any of the specific criteria below, which may be further clarified in the SSP Manual. Investigators also may permanently discontinue participants from study product for use of prohibited medication (see SSP Manual), or for reasons not shown here or in the SSP Manual (e.g., to protect participants' safety and/or if participants are unable or unwilling to comply with study product use procedures). In such cases, the Investigator must first query the PSRT for review. The PSRT will provide a written response to the site indicating whether the PSRT has recommended permanent discontinuation of study product based on careful review of all relevant data. It should be noted that the safety of the participant should always take precedence, and therefore, an Investigator of Record may determine that study drug be permanently discontinued before the PSRT has time to respond. This is acceptable, and in such cases, the PSRT should be notified as soon as possible regarding the nature of the case and the course of action taken.

The criteria for permanent discontinuation of study product use for an individual participant are:

- Study product-related toxicity requiring permanent discontinuation of study product per the guidelines above and below
- Completion of regimen as defined in the protocol
- Request by participant to terminate study product
- Clinical reasons determined by the Investigator
- Acquires HIV infection or hepatitis B virus (HBV) infection
- Pregnancy

Any participant who prematurely discontinues study drug should be followed according to the procedures in the Schedule of Evaluations in Appendix I, with the exception of study drug dispensation, counseling, and adherence measurements.

Study drug will be temporarily withheld from a participant for any of the following reasons:

- Report of use of prohibited concomitant medications described in the SSP Manual. Study drug use may resume when the participant reports that he is no longer taking the prohibited medication, provided other reasons for temporary study drug hold/permanent discontinuation do not apply.
- The participant is unable or unwilling to comply with required study procedures such as HIV testing and routine laboratory assessments, or otherwise might be put at undue risk to their safety and well-being by continuing study drug use, according to the judgment of the Investigator. The Investigator must consult the PSRT on all temporary study drug holds instituted for this reason for further guidance on resuming study drug use, continuing the temporary hold, or progressing to permanent discontinuation. If study

drug use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the Investigator should consult the PSRT to resume study drug use at that time.

- The participant has one or more reactive HIV test results, or expresses a concern about having acute HIV infection. Criteria for resuming use of study drug in these circumstances are defined in the SSP.

Participants who temporarily or permanently discontinue study drug will be instructed to return all study drugs as soon as possible.

**Guidance on Toxicity Management for Specified Toxicities:
Nausea, Vomiting, and Diarrhea**

CONDITION AND SEVERITY ¹	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT ²
Nausea, Vomiting, and Diarrhea		
Grade 1 and 2	Continue study drug (reminder to take study drug with food)	Treat symptomatically with hydration, oral antiemetic therapies or antiemetic suppositories at the discretion of the Investigator. The Investigator should order any clinically relevant laboratory analyses (per judgment of the Investigator).
Grade \geq 3	Discontinue study drug temporarily	Participants with Grade \geq 3 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, must discontinue the study drug temporarily until Grade 2 or lower and be treated symptomatically. Should condition(s) not improve to Grade \leq 2 within 7 days, the Investigator should consult the PSRT for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug.

**Guidance on Toxicity Management for Specified Toxicities:
AST or ALT**

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
ELEVATIONS in AST or ALT (New clinical finding or increase from baseline clinical finding only)		
Grade 1	Continue study drug unless participant is symptomatic	AST and ALT must be repeated every 4 weeks until they are < Grade 1. Study drug may be continued while repeating AST and ALT at the discretion of the investigator provided the participant is asymptomatic. In the case of symptomatic participants, study drug will be held temporarily, and management (including resumption of study drug) should be arranged in consultation with the PSRT.
Grade 2	Continue study drug unless participant is symptomatic	Participants should have AST/ALT re-checked as soon as possible (ideally within 1 week of the receipt of the results) and then be followed weekly until levels are Grade ≤ 1. The frequency of follow up may be altered at the discretion of the site investigator following consultation with the PSRT. Study drug may continue at the discretion of the investigator provided the participant is asymptomatic. In the case of symptomatic participants, study drug will be held temporarily, and management (including resumption of study drug) should be arranged in consultation with the PSRT.

**Guidance on Toxicity Management for Specified Toxicities:
AST or ALT (Cont'd)**

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
ELEVATIONS in AST or ALT (New clinical finding or increase from baseline clinical finding only)		
Grade 3	Discontinue study drug temporarily	Study drug should be temporarily held for any Grade 3 AST or ALT. Participants should have AST/ALT re-checked as soon as possible (ideally within 1 week of the receipt of the results). Participants should then be followed weekly until levels are Grade ≤ 1. Resumption of study drug should be arranged in consultation with the PSRT. If improvement to Grade ≤1 cannot be documented within three weeks of receiving the Grade 3 results, study drug must be permanently discontinued. If following a Grade 3 event(s) the participant is permitted to resume study drug, but has an additional event (AST and/or ALT) at a Grade 3 level, the Investigator must permanently discontinue the study drug, offer symptomatic treatment (if appropriate), and order any clinically relevant laboratory analyses (per judgment of the Investigator).
Grade 4	Permanently discontinue study drug	Study drug should be permanently discontinued for any Grade 4 AST or ALT and the PSRT should be immediately notified. Participants should have AST/ALT re-checked as soon as possible (at most within 1 week of the receipt of the results). Participants should then be followed weekly until levels are Grade ≤ 1 unless indicated by the PSRT.

Note for all grades: All study participants will be negative for HBsAg at study entry, and that participants who enter the study without evidence of immunity to HBV will be referred for HBV vaccination. Therefore, pre-existing HBV infection is not likely to be a cause of AST/ALT elevations.

Careful assessments should be done to rule out the use of alcohol, lactic acidosis syndrome, non-study medication-related drug toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST or ALT of any grade. The participant must be carefully assessed for any symptoms or signs of hepatotoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acolic stools, right upper quadrant pain, or hepatomegaly. If the AST/ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent, if possible, should be undertaken. If symptoms or signs of clinical hepatitis are present, study drug must be held or discontinued. In addition, all participants with elevated values should be considered for testing for Hepatitis A, B, and C infection.

If the investigator has determined in consultation with the PSRT that the case has stabilized, it may be possible to decrease the frequency of follow-up laboratory testing in addition to resumption of study drug.

Guidance on Toxicity Management for Specified Toxicities:

Creatinine Clearance

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
CREATININE CLEARANCE		
Estimated CrCl < 50 mL/min	Discontinue study drug temporarily	If the calculated creatinine clearance is <50mL/min, it should be confirmed within 1 week of the receipt of the results, and the PSRT should be consulted
Confirmed CrCl < 50 mL/min	Permanently discontinue study drug	If the calculated creatinine clearance is confirmed to be <50 mL/min, the study drug must be permanently discontinued and the PSRT notified. Participants who fail to have a confirmed test within 2 weeks of receiving the initial result, should be permanently discontinued from use of the study drug and the PSRT is notified.
Re-testing result is ≥50 mL/min	Consult PSRT for guidance	If re-testing yields a result ≥ 50 mL/min, the Investigator must consult the PSRT for further guidance on resuming study drug use, continuing the hold temporarily, or progressing to permanent discontinuation. If the investigator in consultation with the PSRT has determined that the case has stabilized, it may be possible to decrease the frequency of follow-up laboratory testing in addition to resumption of study drug.

**Guidance on Toxicity Management for Specified Toxicities:
Hypophosphatemia**

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
Hypophosphatemia		
Grade 2	Continue study drug	<p>The phosphate should be repeated ideally within 4 weeks of the receipt of any initially abnormal results. If hypophosphatemia is confirmed, then a fractional excretion of phosphate should be calculated. Fractional excretion of phosphate is measured as:</p> $FEPO_4 = \frac{\text{fractional excretion of phosphate} = \frac{\text{urine } [PO_4] \times \text{plasma } [Cr]}{\text{urine } [Cr] \times \text{plasma } [PO_4]} \times 100$ <p>When the FEPO4 result is received, contact the PSRT for management instructions.</p> <ul style="list-style-type: none"> • Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution. Other causes of phosphate loss should be evaluated. Unless other temporary study drug hold requirements apply, study drug need not be held.

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
Grade 3	Continue study drug until repeat test results are available	<p>The phosphate should be repeated ideally within 1 week of receipt of any initially abnormal results, and should be accompanied by serum or plasma creatinine testing and urine dipstick for protein/glucose, and fractional excretion of phosphate. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution, and other causes of low phosphate should be investigated. Participants with any of the following results (of tests accompanying the repeat phosphate test) will have study drug held:</p> <ul style="list-style-type: none"> • Proteinuria $\geq 3+$ • Glycosuria $\geq 3+$ • Creatinine $\geq 1.5 \times \text{ULN}$ • Creatinine clearance $< 50 \text{ mL/min}$ • Fractional excretion of phosphate $> 5\%$. <p>Participants may continue study drug provided that: Study drug hold is not otherwise indicated (<i>e.g.</i>, due to the results of creatinine, creatinine clearance, urine protein, and/or urine glucose)</p> <p>Phosphate levels will be retested approximately weekly until return to \leq Grade 2, unless other retesting schedule has been advised by the PSRT.</p>

**Guidance on Toxicity Management for Specified Toxicities:
Hypophosphatemia (Con't)**

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
Hypophosphatemia		
Grade 4	Permanently discontinue study treatment	<p>Study drug should be permanently discontinued for Grade 4 hypophosphatemia, and the PSRT must be immediately contacted. Participants should have phosphate checked within 1 week and should be accompanied by serum or plasma creatinine testing and urine dipstick for protein/glucose, and fractional excretion of phosphate. Supplemental phosphate should be given with phosphate-rich food or fluid with or without neutral phosphate solution. Other causes of low phosphate should be investigated.</p> <p>Phosphate levels will be retested approximately weekly until return to < Grade 2.</p>

**Guidance on Toxicity Management for Specified Toxicities:
Proteinuria**

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
Proteinuria		
Proteinuria 2+	Temporarily hold study drug as per follow-up and management	<p>Proteinuria of 2+ or greater does not need to be confirmed at a separate visit.</p> <p>Study drug should be held if hold criteria outlined for serum creatinine and/or phosphorus are met. If neither value meets criteria for study product hold, study drug should continue.</p>
Proteinuria 3+ or greater	Permanently discontinue	Study drug should be permanently discontinued regardless of serum or plasma creatinine or phosphorus results obtained at the time of proteinuria detection. Inform the PSRT. Urine dipstick testing and serum or plasma creatinine and phosphate should then be performed monthly for at least three months.

**Guidance on Toxicity Management for Specified Toxicities:
Glycosuria**

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
Glycosuria (The toxicity management guidelines outlined in this section do not apply to diabetes mellitus.)		
Glycosuria 1+	Continue unless management states otherwise	<p>A finding of 1+ glycosuria should be confirmed with a second urine dipstick performed no earlier than one week, but no later than 2 weeks after detection of the first 1+ glycosuria.</p> <p>If detection of 1+ glycosuria confirmed on two separate visits, study drug should be held only if serum or plasma creatinine or phosphorus results obtained at the time of detection of glycosuria meet hold criteria.</p>
Glycosuria 2+	Temporarily hold study drug as per follow-up and management	<p>Glycosuria of 2+ or greater does not need to be confirmed at a separate visit. Glycosuria secondary due to known diabetes mellitus does not need to be confirmed.</p> <p>If detection of 2+ glycosuria, study drug should be held until results of serum or plasma creatinine and phosphorus results obtained at the time of glycosuria detection are available. Study drug hold should continue if hold criteria outlined for serum creatinine and/or phosphorus are met (refer to creatinine clearance and hypophosphatemia). If neither of these values meets criteria for study drug hold, study drug should be resumed.</p>
Glycosuria 3+ or greater	Permanently discontinue	<p>If detection of 3+ or greater glycosuria at any visit, study drug should be permanently discontinued regardless of serum or plasma creatinine or phosphorus results obtained at the time of proteinuria detection. Urine dipstick testing and serum creatinine and phosphorus should then be performed monthly for at least three months.</p>

**Guidance on Toxicity Management for Specified Toxicities:
Hypertriglyceridemia/hyperlipidemia**

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
Hypertriglyceridemia/hyperlipidemia		
Grade ≥ 3	Continue study drug at the discretion of the site investigator	If elevated triglyceride or lipid levels are from a non-fasting blood draw, repeat the draw after an 8-(or preferably, 12-) hour fast. Only levels done in a fasting state should be used to determine toxicity management. Participants with asymptomatic ≥ Grade 3 triglyceride, total cholesterol, or LDL elevations may continue study medications at the discretion of the site investigator. The investigator should consider baseline lipid abnormalities in this decision. Participants should be referred for management of cholesterol abnormalities. Please refer to the National Cholesterol Education Program guidelines for current recommendations for treating cholesterol abnormalities at www.nhlbi.nih.gov/about/ncep .

¹The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 (with Clarification dated August 2009), (which is available at the following website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>) must be followed.

²If study drug is held or stopped due to toxicity, participant should have repeat clinical and laboratory evaluations every 10-14 days or as determined in the table above, if possible, until toxicity resolves or on a schedule determined by the PSRT.

APPENDIX V: SAMPLE SCREENING AND ENROLLMENT INFORMED CONSENT FORM

A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC), Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate (MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) For Pre-Exposure Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and in At-Risk Women

(HPTN 069)

Version 3.0

January 3, 2013

DAIDS Document ID: 11789

Sponsored by: Division of AIDS, U.S. National Institute of Allergy and Infectious Diseases, US National Institutes of Health. Study products are provided by Gilead Sciences, Inc. and Viiiv Healthcare.

PRINCIPAL INVESTIGATOR: *[Insert Name]*

PHONE: *[Insert Number]*

INTRODUCTION

You are being asked to take part in a research study. Joining this study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason. This research study is for men and women who may be at risk for getting Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decided whether to join the study, we would like to explain the purpose of the study, the risks and benefits to you, and what is expected of you.

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

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign your name or make your mark on this form. You will be offered a copy of this form to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary. You do not have to take part in any of the tests or procedures in the study.
- You may decide not to take part in the study, or you may decide to leave the study at any time without losing your regular medical care.

- If you decide not to take part in the study, you can still join another study at a later time if there is one available and you qualify.
- You cannot join this study if you are taking part in another study of drugs or medical devices. You are asked to tell the study staff about any other studies you are taking part in or thinking of taking part in. This is very important for your safety.

PURPOSE OF THE STUDY

This study will help us to understand the safety of the drugs being used in the study, as well as how well people who take them can handle them (meaning, do they make you feel sick, which is referred to as “tolerability”). The drugs used in this study are approved for treatment of people with HIV infection. We want to know if these same drugs are safe to take in people who are not HIV-infected. The study is being done in both men who have sex with men and in women who may be at risk for getting HIV infection through having sex. The drugs in this study are called maraviroc (also called Selzentry or MVC), emtricitabine (also called Emtriva or FTC), and tenofovir (also called Viread or TDF). These are all a type of drug called antiretrovirals.

Other studies have been done or are being done to see if antiretrovirals can prevent HIV infection. We do not yet know the results of all of these studies. One study, called the iPrEX study, was completed in 2011. The iPrEX study showed that FTC and TDF taken together might lower the chances of getting HIV in men who have sex with men. Some of the men given these two drugs in the iPrEX study took the drugs more regularly; these men seem to have been less likely to get infected with HIV. The iPrEX study found no serious safety concerns. These findings are encouraging, but other studies are needed. First, we need to confirm the iPrEX results. Second, we need to see if other antiretrovirals or combinations of antiretrovirals are safe and might be better at preventing HIV infection.

Additionally, two studies showed support for the use of antiretrovirals for HIV prevention. The CDC TDF-2 trial showed that daily TDF/FTC was safe and effective for prevention of HIV infection among African heterosexual men and women compared to placebo. The Partners PrEP Study, which enrolled African heterosexual couples (one HIV positive and the other HIV negative), compared TDF once daily and TDF/FTC once daily regimens versus placebo. The TDF and TDF/FTC PrEP demonstrated a lower chance of getting HIV. Both studies showed that taking these drugs in this manner was safe and well-tolerated.

After consideration of the iPrEX results, the United States Food and Drug Administration (FDA), in July 2012, approved Truvada (TDF/FTC fixed dose combination) “to be taken once daily and used in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 infection in adults who do not have HIV but are at high risk of becoming infected.” No new side effects were identified in the iPrEX study. The most common side effects reported with Truvada included diarrhea, nausea, abdominal pain, headache, and weight loss. Serious adverse events in general, as well as those specifically related to kidney or bone toxicity, were uncommon.

HIV comes in 2 types, R5 virus and X4 virus. Almost all new HIV infections occur with R5 virus. Maraviroc is a drug that prevents R5 viruses from entering cells; however, it has no effect on X4 viruses. Other HIV drugs, including tenofovir and emtricitabine, work against both R5 and X4 viruses. It is possible that someone taking maraviroc (alone) could get infected with X4 virus. Adding tenofovir or emtricitabine to maraviroc could work against both R5 and X4 viruses. We do not know if having drugs

that work against both kinds of HIV viruses is important in trying to prevent infection by using antiretrovirals.

The three drugs being used in this study have all been shown to be safe in people with HIV. Two of the drugs, FTC and TDF, also appear to be safe in people without HIV and to protect against HIV, but more research is needed to confirm this. The third drug, maraviroc, has not yet been studied very much in people without HIV. In this study we will look at safety and tolerability when using different combinations of these three drugs in people without HIV. The results of this study will help us decide whether maraviroc could be used in a larger study to see if it prevents people from getting HIV.

The FDA has been informed of this study and has permitted it to be conducted. The United States National Institutes of Health (NIH) is funding this study. About 400 men and 200 women in the United States will be in this study. About [approximate site-specific accrual target to be inserted here if required by IRB] participants will be in the study here at [insert study site]. The whole study will take about 2.5 years to finish. Each person will be in the study for about a year.

There may be no direct benefits for you if you participate in this study. There also may be some risks with taking part in the study. If you are a woman and are pregnant, you are not eligible to be in this study. Before you can make an informed decision about whether to take part in this study, you should understand the possible risks and potential benefits of being in this study. This informed consent form gives information about the study that will be discussed with you. Once you understand the study, and if you agree to take part, you will be asked to sign your name on this form.

You will be offered a copy of this form to keep.

STUDY GROUPS

If you decide to take part in the study, you will be placed in 1 of 4 groups. Each group will have 150 people. Each group will get a combination of the study drug(s) and placebo pills. Each group contains one or more of the active (“real”) study drugs. As mentioned above, placebo pills look and feel like the active or “real” drugs but they do not have the drugs or any other medicine in them. The groups will look like this:

- One group will get maraviroc + placebo pill + placebo pill
- One group will get maraviroc + FTC + placebo pill
- One group will get maraviroc + TDF + placebo pill
- One group will get TDF + FTC + placebo pill

All 4 groups will get 3 pills. The 3 pills are to be taken every day. The study staff and you will not know which group or drugs you are taking. This is because we do not want to have any influence on how the results of the study will come out. Within about 6 months after the study ends, you will be told which drugs you got. Until then, no one will be told.

The study group that you will be in will be chosen randomly, like flipping a coin. You cannot choose your group, and the study staff cannot choose your group for you. You have an equal chance of being placed in each group.

No matter what group you are in, you must remember that we only know that TDF and FTC when taken together might lower the chances of getting HIV. And in this study, you will not know which group you are in until the study is over. We also do not know if the other combination of study drugs we are using in this study will protect you from getting HIV. One of the best things you can do to protect yourself against getting HIV during sex is to use a condom every time you have sex.

STUDY PROCEDURES

[Note to sites: Due to variations in screening procedures across sites, or the use of private local laboratories, or other local laboratory testing requirements, the per visit blood and urine amounts will vary across sites. Sites will fill in the volumes per their local requirements, but approximate volumes are provided here as general guidance:

RNA for acute infection: 10 mL

HIV testing: 20 mL

HBV serology: 10 mL

CBC: 10 mL

Chem/LFT/Lipid/Vitamin D/PTH: 10 mL

Plasma for storage: 10 mL

PBMC for immunology: 20 mL

Plasma or serum for drug levels: 10 mL

Pharmacogenomics testing: 5 mL

Syphilis testing: 10 mL

Pregnancy testing: 1 mL serum or 10 mL urine

If you decide to join the study, you will be asked to come to this clinic over the course of a year for approximately 10 times. If you are a woman of childbearing potential, you will be tested for pregnancy at every visit.

Screening Visit

Your screening visit will happen after you read, discuss, understand, and sign this form. We will help you understand the form and answer your questions before you sign this form. The procedures done at this visit will take about 1-2 hours.

The study staff will:

- Ask you where you live and other questions about you, your medical health, your sexual practices, and whether you use alcohol or drugs.
- Give you a brief physical exam to make sure you are healthy.
- Talk with you about HIV and ways to protect yourself from getting it.

[NOTE TO SITES: ADD THE FOLLOWING HERE UNDER THE SCREENING SECTION IF YOU INTEND TO PERFORM THIS STI TESTING AT SCREENING. IF NOT, INCLUDE THIS UNDER THE ENROLLMENT SECTION.]

- For men, we will test for three sexually transmitted infections called gonorrhea, chlamydia, and syphilis at three different times in the study - for enrollment, and at Week 24 and 48 (every 6

months). For gonorrhea and chlamydia, this will be done by performing a swab of your rectum and collecting urine. Blood will be collected for syphilis testing as outlined below.

- *[Note to sites: Swab testing is the preferred method for testing for GC and CT in women, but can also be performed with urine. Add which method you will perform for these tests: For women, we will test for three sexually transmitted diseases called gonorrhea, chlamydia, and syphilis at three different times in this study – for enrollment, and at Week 24 and 48 (every 6 months). For gonorrhea and chlamydia, this will be done by performing [sites to fill in method: a swab of your cervix, and a swab of your rectum if you have had anal sex in the last year OR will be done by collecting urine]. Blood will be collected for syphilis testing as outlined below.*
- We will also collect urine to check the health of your kidneys.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, hepatitis B testing, syphilis to check your general health and the health of your liver and kidneys, and for storage for study-related testing and long-term storage (if you provide consent).
- For women of childbearing potential: Collect ~XX mL of *[blood or urine]* for pregnancy testing
- Give you condoms.

The results of the HIV test will be available *[site to insert timeframe of RNA testing, and also EIA testing if being used]*. You will be contacted about the results of your other tests when they are available. If you have gonorrhea, chlamydia, or syphilis, you will be referred for treatment (*sites to add specifics about this here as necessary*). A small amount of blood will be stored from this visit. No other samples collected at the time of screening will be kept or used for any other tests other than those listed above.

Confirmation of Eligibility:

Once all the results of the screening tests are known, the following will happen:

- You will be told your test results and what they mean.
- If you have a positive HIV test or a positive test for hepatitis B infection, you will not be eligible for the study, and you will be referred for the appropriate medical care.
- If you are negative for both HIV, hepatitis B infection, but the results from the other blood or urine tests show that you might have some health problems, you may not be eligible for the study. Study staff will refer you to available sources of medical care and other services you may need. Later, if these problems resolve, you can come back to find out if you are eligible at that time.
- We will ask whether you would be interested in agreeing to some additional procedures that require a smaller number of people to participate (not the full 600 enrolled in the study). The procedures are identified as a Drug Interaction Subset (requires 72 people), and a Tissue subset (requires 60 men and 60 women) *[only the sites participating in the Tissue subset should list this here]* If the slots for participating in the main study or for these additional procedures are full, we will let you know. One of the additional procedures is described here and under the Week 2 visit information, and the other is described in another consent form *[only the sites participating in the Tissue subset should include the statement “and the others are described in another consent form”.]* We will ask you to check a box if you are interested in the Drug Interaction Subset (*sites*

participating in Tissue Subset to add – or sign another consent form for the Tissue Subset). You can still be in the study and not undergo these additional procedures.

- Give you referrals for other health services if you need them.

Enrollment Visit

If you are eligible for this study and decide to take part in the study, you will be asked to return for the enrollment visit. This visit will last about 2-3 hours. During the visit, the study staff will:

- Confirm where you live and how to contact you.
- Ask you some questions about yourself, like your age, and your ethnic group.
- Ask you to answer questions on a computer about your sexual practices, and how you feel about how your life is going.
- Talk with you about HIV and ways to protect yourself from getting it.
- Give you a complete physical exam, to include measuring your height, weight, temperature, blood pressure, and ask you about any other medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood for: HIV testing, anti-Hepatitis C Virus (HCV) antibody testing, to check how much cholesterol is in your blood (a fatty substance in your blood), to check on a protein in your body called CCR5 (if you provide consent), and for storage for study-related testing and long-term storage (if you provide consent). Additionally, if you provide consent, we will use a sample of your blood to see how the drugs work in your body by looking at your genes. [*Note to sites: Anti-HCV antibody and lipid profile tests may be performed at screening per note in Section 5.2. If this testing is performed during screening, insert this item in the screening section above.*] [*Note to sites: Pharmacogenomic testing can be performed at any visit for participants originally consented under Version 2.0*] Information about the CCR5 testing and the other testing related to your genes is found later in this consent form. For the cholesterol test, you will be instructed to not eat or drink anything other than what the study staff tell you is acceptable for 8-12 hours before your blood is drawn.
- For women of childbearing potential: Collect ~XX mL of [*blood or urine*] for pregnancy testing
- Randomize you into one of the four study groups.
- Give you your study pills, and explain how to take them, and any side effects they may cause. We will also give you an electronic pill box to put your pills in. The box sends an electronic message to our system when it is opened. We will explain to you how this pill box works and give you enough study drugs to last until your next visit.
- Explain and provide instructions about a text-message system (SMS) we will be using in the study. This system will send you up to four text messages to your cell phone. The first message asks you to enter your chosen password (you will choose this password when you enter the study). You cannot get any messages from the system unless you enter your own password. The next two questions are about your sexual practices. The last text message is a reminder to delete the text messages to protect your privacy. The system is confidential and safe. We will ask you to use this system everyday for 7 days in a row during your first week on the study so that you can learn the system. After that, we will be using this system at approximately 12-13 different

random times up to the end of the study. Each time you receive will be asked the same two questions everyday for 7 days. You may receive up to approximately 392 text messages over the course of the study (up to 196 questions + up to 196 instruction texts).

- Ask you to have a bone mineral density dual-energy x-ray absorptiometry (DXA) scan. All of the women (200) and 200 of the 400 men who agree to be on this study will have these scans done. You will be told if you will not have a DXA scan. A DXA scan is a special kind of x-ray using a small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. During the DXA scan, you will lie very still on a table for about 15 minutes. The machine will then take the x-rays. This test will be done at this visit (Enrollment), and also at one visit toward the end of the study (Week 48). [*Note to sites: If you choose to perform the baseline DXA during screening, remove it from here and add it to the screening section.*]
- Give you the results of your tests (HIV, sexually transmitted infections, [*note to sites: “and DXA” if you intend to provide those results to your participants*]) when they are available.

[NOTE TO SITES: ADD INFORMATION HERE ABOUT STI TESTING AS OUTLINED UNDER SCREENING IF YOU INTEND TO DO THIS AT ENROLLMENT AND NOT AT SCREENING. BE SURE TO INCLUDE UNDER BLOOD ABOVE THAT SYPHILIS WILL BE TESTED USING BLOOD “AS EXPLAINED ABOVE”.]

- Give you condoms.

Week 2 Visit

This visit will last about 45 minutes – 1 hour (longer if you agree to the Drug Interaction Subset procedures). During this visit, the study staff will:

- Confirm where you live and how to contact you.
- Give you a brief physical exam, ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, to check your general health, the health of your liver and kidneys, and for storage for study-related testing and long-term storage (if you provide consent).
- For women of childbearing potential: Collect ~XX mL of [*blood or urine*] for pregnancy testing
- Talk with you about HIV and ways to protect yourself from getting it.
- Ask you whether you have questions about taking your study pills.
- Give you the results of your blood tests when they are available.
- Remind you about how the SMS system works.
- Give you condoms.
- Explain to you the additional procedure for the Drug Interaction Subset. The purpose of the Drug Interaction Subset is so that we can measure the amount of the study drugs in your blood

right before and soon after you take them. The procedures involve the following: You will be asked to bring your study pills with you to the visit, but not to take them before you come to the visit. Once you get to the clinic for the visit, we will collect ~ XX mL (about x teaspoons) of blood. We will then ask you to take your study pills in front of a staff person. We will then ask you to come back to the clinic about 6 hours later to have ~ XX mL (about x teaspoons) of your blood drawn. [Sites to insert here any additional information, e.g., additional reimbursement, refreshments provided, etc.].

Week 4 Visit

This visit will last about 1 hour. During this visit, the study staff will:

- Confirm where you live and how to contact you.
- Give you a brief physical exam, ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking.
- Talk with you about HIV and ways to protect yourself from getting it.
- Ask you whether you have questions about taking your study pills.
- Ask you to answer questions on a computer about how you feel about this research study.
- [Sites participating in qualitative interviews for PREMIS to add here: Ask if you are willing to take part in a face-to-face interview with a trained staff member who will ask you questions about how you feel about this research after you have answered the questions on a computer. These interviews will be recorded. These interviews will take place when convenient for you some time between this visit and the Week 40 visit.]
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, to check your general health and the health of your liver and kidneys, and for storage for study-related testing and long-term storage (if you provide consent).
- For women of childbearing potential: Collect ~XX mL of [*blood or urine*] for pregnancy testing
- Give you the results of your blood tests when they are available.
- Remind you about how the SMS system works.
- Give you condoms.

Week 8, 16, 32, and 40 Visits

These visits will last up to 2 hours. During these visits, the study staff will:

- Confirm where you live and how to contact you.
- Ask you to answer questions on a computer about your sexual practices, and your experiences taking your study pills.
- Talk with you about HIV and ways to protect yourself from getting it.
- Give you a brief physical exam, ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking.

- Collect urine from you to check the health of your kidneys (at the Week 8 visit only).
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, to check your general health and the health of your liver and kidneys, and for storage for study-related testing and long-term storage (if you provide consent).
- For women of childbearing potential: Collect ~XX mL of [*blood or urine*] for pregnancy testing
- Give you your study pills, and ask you if you have any questions about taking them.
- Give you the results of your tests when they are available.
- Remind you about how the SMS system works.
- Give you condoms.

Week 24 and 48 Visits

This visit will last about 2-3 hours. During these visits, the study staff will:

- Confirm where you live and how to contact you.
- Ask you to answer questions on a computer about your sexual practices, your experiences taking your study pills, and how you feel about how your life is going.
- Talk with you about HIV and ways to protect yourself from getting it.
- Give you a brief physical exam, ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking.
- For men, perform a swab of your rectum and collect urine for gonorrhea and chlamydia. Blood will be collected for syphilis testing as outlined below.
- [*Note to sites: Add which method you will perform for these tests in women:* For women, we will perform a swab of your cervix for gonorrhea and chlamydia, and a swab of your rectum if you have had anal sex in the last year *OR* we will collect urine for gonorrhea and chlamydia. Blood will be collected for syphilis testing as outlined below.
- [*Tissue Subset sites only to add*]: If you opt to participate in the Tissue Subset, you will follow that schedule for the collection of these specimens for gonorrhea, chlamydia, and sphyilis.
- Collect urine to check the health of your kidneys.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing, to check your general health and the health of your liver and kidneys, to check how much cholesterol is in your blood (a fatty substance in your blood), and for storage for study-related testing and long-term storage (if you provide consent). For the cholesterol test, you will be instructed to not eat or drink anything other than what the study staff tells you is acceptable for 8-12 hours before your blood is drawn.
- For women of childbearing potential: Collect ~XX mL of [*blood or urine*] for pregnancy testing
- Ask you to have a DXA scan (x-ray), if you received one at Enrollment (Week 48 only).
- Give you your study pills, and ask you if you have any questions about taking them (Week 24 only)

- Give you the results of your tests when they are available.
- Remind you about how the SMS system works (Week 24 only).
- Give you condoms.

Week 49 Visit

This visit will last about 1 hour. During this visit, the study staff will:

- Talk with you about the end of the study, and when you will know what drugs you were taking, and when the results of the study will be available.
- Give you a brief physical exam, ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking.
- Collect urine from you to check the health of your kidneys.
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, to check your general health and the health of your liver and kidneys, and for storage for study-related testing and long-term storage (if you provide consent).
- For women of childbearing potential: Collect ~XX mL of [*blood or urine*] for pregnancy testing
- Give you the results of your tests when they are available.
- Give you condoms.

What will happen if you permanently stop taking your study medications

If you permanently stop taking the study drugs during the study for any reason, we will ask you to continue to come for your regular study visits, but you will no longer have to undergo certain procedures, like answering questions about taking the study pills, talking to us about taking the study pills, etc. We will fully explain to you what will happen if you permanently stop taking your study drugs.

POSSIBLE FUTURE TESTS

Some of the blood that you give during this study may be left over after all of the study tests are completed. We would like to keep this blood for an indefinite amount of time for future testing that may be unrelated to this study, but still related to HIV. You will be asked to sign at the end of this consent form to give permission for this. Even if you do not give permission to store your blood after the study, you can still be in this study. You may also withdraw your consent for specimen storage at any time.

RISKS AND/OR DISCOMFORTS

Pregnancy

There are no adequate or well-controlled studies of pregnant women taking the medicines used in this study. If you are currently pregnant, you are not eligible to be in this study..

If you can get pregnant and are engaging in sexual activity that could lead to pregnancy, you must agree to use a form of contraception (condoms with or without a spermicidal agent; diaphragm or cervical cap with spermicide; IUD; Hormone-base contraceptive) during the trial and for 30 days after stopping the study medication.

If you become pregnant after joining the study, you will be asked to discontinue study treatment immediately. You will be asked to come to the clinic within 7 days of the site knowing of your pregnancy in order for the clinician to examine you. You will continue to be followed on study, but you will no longer take any study medicine. In addition, all pregnancies will be registered in the Antiretroviral Pregnancy Registry. This registry does not include any identifiers, so none of your personal information will be provided. You can learn more about this registry at www.apregistry.com.

If you are still pregnant when the study ends, we will still contact you and/or review your medical records until the outcome of your pregnancy is known by site staff.

Not all contraceptive choices can prevent HIV transmission, and some may actually increase the risk of getting HIV. We will talk with you throughout the study about ways to protect yourself from getting HIV. You should also discuss with your health care provider and the study clinic staff ways to maintain effective contraception during your participation in the study.

Blood Draws

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases you may faint. There is also a slight chance of infection when blood is drawn. You may be nervous while you are waiting for your HIV test result. If the tests show that you have HIV, you may worry about your health and future. You will receive counseling before and after the test to help address your concerns. We will make every effort to protect your confidentiality during the study. However, it is possible that others may learn that you are part of this study and they may think that you are infected with HIV or are at high risk for infection with HIV. Because of this you could have trouble finding or keeping a job. You could also have problems with your family, friends and community.

Rectal and Cervical Swabs

You may experience pain or discomfort from the rectal or cervical swab. In some cases, you may have some bleeding.

Sensitive Questions

The questions we will ask you about your sexual behavior may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time.

DXA Scan

We are exposed to radiation on a daily basis both from natural (sun and earth) and man-made sources. The average radiation dose from these sources for those living in the United States is 363 millirem per year. Exposure of up to 5,000 millirem of radiation is allowed in individuals who use radiation in their work (such as Radiologic Technologists and radiologists). Also, there is no evidence that a dose up to 5,000 millirem per year is associated with any risk. By comparison, the radiation dose that you will

receive from the DXA scans done for this research is less than 1% of this annual limit for radiation workers (if you receive the scans). The scanning machines will not cause any physical discomfort other than from having to lie still on the table for the duration of the test. [*Note to sites: State here if you intend to provide the results of these scans to your participants*].

CCR5 Testing

We want to test to see if your body makes the CCR5 protein. This is done by testing your DNA (your genes). Genes, called DNA, tell us about the way your body is programmed to work. For instance a person that is very tall probably has different genes than a person who is very short. HIV uses the CCR5 protein to attach to cells. Some strains of HIV use another protein to attach to cells. One of the drugs we are using in this study, maraviroc, works by blocking the ability of HIV to attach to the CCR5 protein. Since maraviroc blocks the way the CCR5 protein works, it might interfere with the normal function of CCR5 in your body and may increase your risk of infections or cancer. The study researchers do not plan to contact you or your regular doctor with any results from this test. This is because research tests are often done using experimental procedures, so the results may not help for making decisions on managing your health.

Other Genetic Testing

We also want to look at your genes that affect how your body changes and removes the drugs used in this study. Gene differences between people can lead to different amounts of drug in the body; this may affect how well a drug protects people from HIV infection. If you consent, we will test your blood to get information about how your genes may have affected the drug levels in your body. The tests we will use to look at your genes are research tests and will be performed in a research laboratory. All of the samples will be identified with a coded number. The laboratory doing the testing will not know who you are. The results obtained for individual study participants (like you) will not be reported to the study sites or back to you. However, the combined results of the testing from all of the study participants will be available to the study sites and to the study participants at their request, once the analysis has been completed.

Study Medications

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site. It should be noted that these are the risks that are seen in HIV positive people taking these medications. It is not known if these side effects will occur as often and it could be that some of these side effects might be more or less serious HIV negative people.

Maraviroc (MVC, Selzentry[®]) – Entry Inhibitor-CCR5 Co-Receptor Antagonist

The following serious side effects have been associated with the use of maraviroc:

- Liver problems (liver toxicity) have occurred in people who took maraviroc. An allergic reaction may happen before liver problems occur, and includes a rash on your body (allergic reaction), yellowing of the skin or whites of your eyes, dark urine, vomiting, stomach pain, or elevated

liver related function tests. People who have hepatitis B or C might be at higher risk of having liver problems.

- Heart problems, including heart attack.
- Low blood pressure when standing up, which can cause dizziness or fainting. People who have serious kidney problems may be at increased risk.

In addition to the serious side effects listed above, additional side effects include:

- Colds
- Cough
- Fever
- Rash
- Dizziness
- Diarrhea
- Swelling of parts of the body
- Flu and flu-like symptoms
- Muscle aches, spasms and pain
- Stomach pain and bloating
- Sleeping problems
- Runny, congested nose
- Problems with urination
- Low amounts of white blood cell counts (neutropenia)

NOTE: Because of how the drug works in your body, there is a possible increased risk for getting other infections or cancer, although there is no evidence from other studies of an increase in serious infections or cancer.

Maraviroc contains soy lecithin. If you have a medical history of allergy to soy (soya or soybeans) or peanuts, you may develop an allergic reaction to maraviroc. Before starting maraviroc, you should inform your health care provider if you are allergic to soy or peanuts.

Nucleoside Analogue (this applies only to Emtriva and Viread)

In HIV-infected patients, redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving combination antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

Lactic acidosis (elevated lactic acid levels in the blood) and severe hepatomegaly (enlarged liver) with steatosis (fatty liver) that may result in liver failure, other complications or death have been reported

with the use of antiretroviral nucleoside analogues alone or in combination. The liver complications and death have been seen more often in women on these drug regimens. Some nonspecific symptoms that might indicate lactic acidosis include: unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness, dizziness and shortness of breath.

Emtricitabine (FTC, Emtriva[®])

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

- Headache
- Dizziness
- Tiredness
- Inability to sleep, unusual dreams
- Loose or watery stools
- Upset stomach (nausea) or vomiting
- Abdominal pain
- Rash, itching, which sometimes can be a sign of an allergic reaction
- Skin darkening of the palms and/or soles
- Increased cough
- Runny nose
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage

NOTE: If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if emtricitabine is stopped.

Tenofovir Disoproxil Fumarate (Tenofovir DF, TDF, Viread[®])

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

- Upset stomach, vomiting, gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Headache

- Abdominal pain
- Worsening or new kidney damage or failure
- Inflammation or swelling and possible damage to the pancreas and liver
- Shortness of breath
- Rash
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Muscle pain and muscle weakness

NOTE: If you are infected with both Hepatitis B and HIV, you should be aware that your liver function tests may increase, and symptoms associated with hepatitis (an acute inflammation of the liver) may worsen if tenofovir is stopped. You could have these side effects or other side effects that we do not know about.

Other Possible Risks

We do not know if there are other risks if you use herbal treatments or supplements while you are using the tablets. Please tell study staff if you are using any herbal treatments or supplements.

We will perform an HIV test, which is routinely done before HIV drugs are tested in non-HIV subjects. You will be counseled before and after this test is done. [Sites to insert reporting responsibilities in the state the site is located in. Also include whether if a participant tests positive, the results will become part of public health records, or any other record (medical file, etc.)]

You will be tested for gonorrhea, chlamydia and syphilis. [*Note to sites: Insert here any reporting responsibilities for your state or local jurisdictions or reporting of these infections to public health authorities.*]

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers immediately.

There may also be some social risks to participating in this study. You may feel embarrassed or uncomfortable with some of the questions you will be asked, some of the procedures that will be done, or some of the test results that you will receive. You may also experience stigma as a result of being involved in a study about HIV because people may assume that you are HIV-infected.

If you test positive for HIV during the study you will be asked to stop taking your study medication. If you continue to take the study medication after HIV infection has occurred, there is a chance that drug resistance may occur.

BENEFITS

We will test you for HIV and other sexually transmitted infections throughout this study. The counseling you get during this study may help you to avoid HIV and other sexually transmitted infections. If you have or become infected with HIV, this counseling may help you to learn how to better care for yourself and avoid passing HIV to your sexual partners. If you become HIV infected, or have another sexually transmitted infection, we will refer you for care and/or treatment. At the screening visit we will also check if you have hepatitis B infection. If needed, we will refer you for hepatitis B vaccination. During the study you will have tests to check on the health of your blood, liver, and kidneys. If any health problems are found, you will be referred for care. At every visit you will receive condoms free of charge.

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

NEW INFORMATION

You will be told 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 medication may be causing bad effects, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

You may be withdrawn from the study without your consent if any of the following occur:

- You are unable or unwilling to follow all of the study procedures or instructions.
- You could be harmed by continuing to take tablets.
- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- You are not able to attend clinic visits or complete all of the study procedures.
- Other reasons, as decided by the study staff.

ALTERNATIVES TO PARTICIPATION

[Sites to include/amend the following if applicable: There may be other studies going on here or in the community that you may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.] In addition, maraviroc, emtricitabine, tenofovir, and/or the combination pill, Truvada (TDF+FTC), are all available by prescription from your healthcare provider to treat HIV infection. As indicated previously in this consent form, the FDA has approved Truvada (TDF+FTC) for the prevention of HIV, and may be available by prescription from your health care provider.

COSTS TO YOU

There will be no cost to you for study related visits, study products, physical examinations, laboratory tests, or other procedures.

REIMBURSEMENT

You will receive [\$xx] for your time, effort, and travel to and from the clinic at each scheduled visit. *[Sites to insert information about local reimbursement for the study. In addition, note that reimbursement for the SMS component needs to be standardized across all sites. Sites should insert here the following: Each participant will receive \$2.00 per day (for completing all of the questions for that single day) for 7 days, and an \$11.00 bonus for fully completing and answering all questions for all 7 days, for a total of \$25.00]. Additional note to sites: It is up to each site as to how they want to manage this payment scheme, e.g., it may be folded into the site's overall participant reimbursement schedule, but participants should be notified of the amount they will get each day for this component plus the bonus.*

CONFIDENTIALITY

To keep your information private, your samples will be labeled with a code that can only be traced back to your study clinic. Your name, where you live, and other personal information will be protected by the study clinic. The results of any tests done on these samples will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. Any publication of this study will not use your name or identify you personally. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act, by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB), study staff, study monitors, the companies that make the drugs used in this study, and *(insert applicable local authorities)*.

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

The study staff will also use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes other studies conducted by *[site name]* and 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:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- the United States Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- [insert names of applicable IRBs]
- study staff
- study monitors
- the companies that makes the study drugs (Gilead Sciences, Inc. and ViiV Healthcare)

[Sites to include/amend the following if applicable:] [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 [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].

RESEARCH-RELATED INJURY

[Sites 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 get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries either through this institution or the NIH. You do not give up any legal rights by signing this consent form.

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].

If you have questions about who to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member] at [insert physical address and telephone number].

SIGNATURE PAGE

A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC), Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate (MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) For Pre-Exposure Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and in At-Risk Women, Version 3.0 (HPTN 069)

SCREENING AND ENROLLMENT 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 join the study, please sign your name or make your mark below. Also, please indicate by providing your initials in the spaces below the additional sample collection, genetic testing, or long-term storage that you agree to.

- _____ I agree to take part in this study.
- _____ I agree to take part in the Drug Interaction Subset, where I will have an additional blood draw at the Week 2 visit.
- _____ Site staff to fill in “N/A” here (and initial and date) if the slots for the Drug Interaction Subset are filled.
- _____ I agree to have samples of my blood stored and used for future testing related to HIV infection.
- _____ I do not agree to have samples of my blood stored and used for future testing related to HIV infection.
- _____ I agree to allow my blood to be tested to see if my genes make the CCR5 protein.
- _____ I do not agree to allow my blood to be tested to see if my genes make the CCR5 protein.
- _____ I agree to allow my blood to be tested to see how my genes make the drugs work in my body.
- _____ I not agree to allow my blood to be tested to see how my genes make the drugs work in my body.

[Selected sites participating in qualitative interviews to add]:

- _____ I agree to participate in an interview where I will be asked questions about this research, and the interview will be recorded.
- _____ I do not agree to participate in an interview where I will be asked questions about this research, and the interview will be recorded.

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness Name (print)
(As appropriate)

Witness Signature and Date

**APPENDIX VI: SAMPLE INFORMED CONSENT FORM FOR TISSUE SUBSET
(RECTAL COMPONENT)**

**A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC),
Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate
(MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) For Pre-Exposure
Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and
in At-Risk Women
(HPTN 069)**

**Version 3.0
January 3, 2013
DAIDS Document ID: 11789**

Sponsored by: Division of AIDS, U.S. National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health. Study products are provided by Gilead Sciences, Inc. and ViiV Healthcare.

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

INTRODUCTION:

You have decided to take part in the research study named above. During this study, we also want to learn how the drugs that you will be taking interact with each other, what changes occur to your immune system, and whether taking the study drugs protect you from HIV infection. Your immune system helps to keep you from getting infections. We need 60 male participants and up to 60 female participants (15 men and up to 15 women from each study arm) to participate in this study subset. You will be asked to give blood, hair, rectal tissue and rectal fluid samples for use in this part of the study. Rectal tissues are very tiny pieces of the lining of your rectum. You will also be tested to see whether your blood can clot normally. Your blood contains platelets, and platelets help make blood clot. A clot is when the liquid blood becomes solid. The body makes a blood clot when the skin or somewhere inside the body is cut. This stops blood from going out too much. It is essential that blood be able to clot.

We will also test for sexually transmitted infections before we collect samples from you. This consent form gives you information about the collection, and the use of these samples. The study staff will talk to you about this information. Please ask if you have any questions. You will be asked to sign or make your mark on this form to indicate whether you agree to participate in this portion of the study. You will be offered a copy of this form to keep.

YOUR PARTICIPATION IS VOLUNTARY:

Participation in the Tissue Subset of this study is completely voluntary. You may decide not to participate. Your decision not to participate in the Tissue Subset will not have any impact on your participation in the main study, and will not result in any penalty or loss of benefits to which you are otherwise entitled. Even if you decide now that you wish to participate in this part of the study, you may

change your mind at any time. If this happens, you must tell the study staff that you have changed your mind.

PURPOSE:

If you decide to participate in the Tissue subset study, your samples will be used to help us learn how the drugs you are taking work and how they interact with each other. The drugs are not only found in your blood but in other body tissues as well, and that is why in addition to blood, hair and rectal tissues and fluid will be collected and tested in this Tissue subset study. The samples will be collected four times - at screening (and prior to receiving study drugs), Weeks 24, 48 and 49. You will also undergo testing for sexually transmitted infections called gonorrhea, Chlamydia, and syphilis at screening, and Weeks 16 and 40. If you have any of these infections, you will be referred for treatment.

The study researchers do not plan to contact you or your regular doctor with any results from tests done on your samples. This is because research tests are often done using experimental procedures, so the results may not help for making decisions on managing your health.

PROCEDURES:

Screening

We will draw XX mL of blood (about x teaspoons) to make sure that your blood is healthy and can clot normally since biopsies can cause bleeding. This testing will happen during the screening visit only and before you start study drugs.

[Note to sites: Coagulation testing generally requires 10 mL].

Enrollment

You will have an enema to prepare the rectum for the rectal biopsy. A rectal biopsy is a procedure to remove a small piece of rectal tissue for examination. A rectal exam is done first, followed by collecting a fluid sample from your anal area using a small sponge. The sponge draws the sample of the rectal fluid through a short hollow lubricated tube called an anoscope, which is placed into the rectum. After the anoscope is removed, then a lubricated instrument called a flexible sigmoidoscope is placed into the rectum. The biopsy can be taken through this instrument. The flexible sigmoidoscope lets your doctor examine the inside of your large intestine from the rectum and through the lower part of your colon. Rectal tissue will be collected. These samples will be stored. You should not have anal sexual intercourse or insert anything in to your rectum for 3 days before the tissue sampling, and for 7 days after the tissue sampling. We will also call you one or two days after the procedures to check on how you are feeling. *[Note to sites: Insert specifics regarding how this procedure is performed in your institution and whether an additional consent form is required at the clinic where it will be performed].*

These procedures will take about [sites to insert length of time necessary], and the full visit should last about [sites to insert length of time for the full visit].

Screening, Week 16 and 40 Visits

At each of these visits, we will use a cotton swab to collect a sample from your anus. This will be used to test for the gonorrhea and chlamydia. Additionally, if you are male, we will ask for a urine sample for these tests. We will also draw XX mL of blood (about x teaspoons) to test for syphilis. We need to

know whether you have these infections, and treat you for them, before we collect the rectal tissue and fluids.

[Note to sites: Syphilis testing will depend on the test used. RPR generally requires 10 mL and another 10 mL if confirming it is treated prior to procedure].

Week 24, 48 and 49 visits

At each of these visits, in addition to the procedures for which you have already consented, your blood will be drawn, up to 150 mL (which is about 30 teaspoons). A hair sample (about 100 hairs) will be collected and rectal tissues and fluids will be collected as described above. All of these samples will be stored. You should not have anal sexual intercourse or insert anything into your rectum for 3 days before the tissue sampling, and for 7 days after the tissue sampling. We will also call you one or two days after these procedures to check on how you are feeling.

If you permanently stop taking the study medications after the Week 24 visit but before the end of the study, we want to be able to collect the same samples as listed here approximately two weeks after you stop taking the drugs.

Each of these visits will last [insert length of time here].

Possible Risks or Discomforts:

Blood and hair samples

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases, you may faint. There is also a slight chance of infection when blood is drawn.

Taking a sample of your hair may cause some discomfort. You may worry that this is painful or affects how you look. About 100 strands of hair are needed for this procedure. This is about the number of hairs that a person loses from their body every day. The collection procedure involves cutting the shaft of the hairs near the scalp; the root of the hair will not be collected. Each hair will be cut carefully and will be sampled around your scalp, this way people will not be able to tell that you hair has been removed. We can also take a hair sample from another part of your body other than your scalp if you wish.

Enemas

You may experience some mild discomfort and a bloated or “crampy” feeling. If you have any hemorrhoids or other painful conditions, you might feel anal or rectal discomfort.

Rectal tissues and fluids

There may be some discomfort during the collection of tissue samples. You may feel an urge to have a bowel movement. Cramping sometimes occurs as the instrument is placed into the rectal area. You may have the feeling of a “bloated stomach”. On extremely rare occasions, you may have pain, infection, bleeding or perforation of the gastrointestinal tract (occurs about once out of every 1,000 procedures and may require hospitalization and surgical management). It is important that you do not put anything in your rectum for the 3 days before and 7 days after having tissue samples taken, because you may be at a higher risk for bleeding or getting or spreading an infection until the biopsy sites have healed.

Rectal swabs

You may experience pain or discomfort from the rectal swab. In some cases, you may have some bleeding.

POTENTIAL BENEFITS:

There are no direct benefits to you from participating in the Tissue Subset portion of this study. However, you and others could benefit in the future from this research. You will also be treated for any sexually transmitted infections if you have them.

CONFIDENTIALITY:

To keep your information private, your samples will be labeled with a code that can only be traced back to your study clinic. Your name, where you live, and other personal information will be protected by the study clinic. The results of any tests done on these samples will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. Any publication of this study will not use your name or identify you personally. However, your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- the United States Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- [insert names of applicable IRBs]
- [insert applicable local authorities]
- study staff
- study monitors
- the companies that makes the study drugs (Gilead Sciences, Inc. and ViiV Healthcare)

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of

Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

PROBLEMS OR QUESTIONS:

If you have questions about the study, or if you have a research-related injury, you should contact:

- [site insert name of the investigator or other study staff]
- [site insert telephone number and physical address of above]

For questions about your rights related to the study, contact:

- [site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [site insert telephone number and physical address of above]

SIGNATURE PAGE: TISSUE SUBSET (RECTAL COMPONENT)

**A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC),
Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate
(MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) For Pre-Exposure
Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and
in At-Risk Women, Version 3.0
(HPTN 069)**

CONSENT FOR TISSUE SUBSET (RECTAL COMPONENT)

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 join the study, please sign your name or make your mark below.

It should be noted that all relevant information (e.g. compensation and treatment of injury, involuntary withdrawal, cost to subjects, new findings) from the Main study consent still applies to this consent form.

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness Name (print)
(As appropriate)

Witness Signature and Date

**APPENDIX VII: SAMPLE INFORMED CONSENT FORM FOR TISSUE SUBSET
(VAGINAL COMPONENT)**

**A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC),
Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate
(MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) For Pre-Exposure
Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and
in At-Risk Women
(HPTN 069)**

**Version 3.0
January 3, 2013
DAIDS Document ID: 11789**

Sponsored by: Division of AIDS, U.S. National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health. Study products are provided by Gilead Sciences, Inc. and ViiV Healthcare.

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

INTRODUCTION:

You have decided to take part in the research study named above. This research, in addition to the main study, is part of a Tissue Subset study. The Tissue Subset study has two parts. One part is a rectal study and the other is a vaginal study. As a woman, to be in the Tissue Subset you must agree to be a part of the vaginal part. You can also join the Rectal part of the Tissue Subset, but it is not required. During this study, we also want to learn how the drugs that you will be taking interact with each other, what changes occur to your immune system, and whether taking the study drugs protect you from HIV infection. Your immune system helps to keep you from getting infections. We need 60 female participants (15 from each study arm) to participate in this study subset. You will be asked to give blood, hair, and cervical tissue and fluid samples for use in this part of the study. These tissues are very tiny pieces of the lining of your cervix. You will also be tested to see whether your blood can clot normally. Your blood contains platelets, and platelets help make blood clot. A clot is when the liquid blood becomes solid. The body makes a blood clot when the skin or somewhere inside the body is cut. This stops blood from going out too much. It is essential that blood be able to clot.

We will also test for sexually transmitted infections before we collect samples from you. This consent form gives you information about the collection, and the use of the samples that will be collected from you if you decide to participate. The study staff will talk to you about this information. Please ask if you have any questions. You will be asked to sign or make your mark on this form to indicate whether you agree to participate in this portion of the study. You will be offered a copy of this form to keep.

YOUR PARTICIPATION IS VOLUNTARY:

Participation in the Tissue Subset of this study is completely voluntary. You may decide not to participate. Your decision not to participate in the Tissue Subset will not have any impact on your participation in the main study, and will not result in any penalty or loss of benefits to which you are otherwise entitled. Even if you decide now that you wish to participate in this part of the study, you may change your mind at any time. If this happens, you must tell the study staff that you have changed your mind. Additionally, you may elect to participate in the Rectal Component of the Tissue subset. However, it is not required and you may still be in this Vaginal Component if you choose not to be in the Rectal Component. If you do want to be in the Rectal Component, you will have those procedures explained to you and you will need to sign a separate consent form.

PURPOSE:

If you decide to participate in the Tissue subset study, your samples will be used to help us learn how the drugs you are taking work and how they interact with each other. The drugs are not only found in your blood but in other body tissues as well. This is why we also want to test your blood, hair, vaginal fluid and cervical biopsies. The samples will be collected four times - at screening (and prior to receiving study drugs), Weeks 24, 48 and 49. All of these samples will be tested to measure the amount of study drug that are found in each of these places. One cervical biopsy from each of these visits will be tested in a laboratory to see if it can be infected with HIV in a test tube. We want to see if the study drugs protect the cervical biopsies from getting infected with HIV.

The study researchers do not plan to contact you or your regular doctor with any results from tests done on your samples. This is because research tests are often done using experimental procedures, so the results may not help for making decisions on managing your health.

PROCEDURES:

Screening

We will draw XX mL of blood (about x teaspoons) to make sure that your blood can clot normally. Clots are how the body stops bleeding. This testing will happen during the screening visit only and before you start study drugs. You will be given the results of this test.

[Note to sites: Coagulation testing generally requires 10 mL].

If you have not have a PAP smear within the past year, then a PAP smear test will be done at this visit. A pap smear is a brushing of the cervix to look for atypical (or damaged) cells that may mean you are at risk for cervical cancer. You will be given the results of this test.

We will also test for sexually transmitted infections. This will include a blood test for syphilis, and either a urine test or a swab of the cervix to test for gonorrhea and chlamydia. You will be given these test results. If any of these infections are found, we will arrange for you to get treatment *[or provide treatment to you]*. You are able to continue participation in this substudy one week after you have completed this treatment.

Enrollment

Collection of Cervical Biopsies and Vaginal Fluids

A clinician will ask you about your menstrual cycle. These specimen collections will not occur during your menstrual period. We will offer you a planner (for example, a diary or a calendar) to help track your menstrual cycle. This will help us to schedule your biopsy appointments.

A clinician will insert a speculum into your vagina to allow the clinician to see your vagina and cervix. Then the clinician will place a small sponge next to your cervix. The sponge will stay in place for a few minutes and will collect vaginal fluid. Then this will be removed. Next, the clinician will collect up to three biopsies of the cervix using forceps. This instrument will pinch and cut out a small piece of the skin from the cervix (about the size of a grain of rice).

These samples will be stored. You should not have vaginal sex or insert anything in to your vagina for 3 days before these tests, and for 7 days after the tests. We will also call you one or two days after the procedures to check on how you are feeling. *[Note to sites: Insert specifics regarding how this procedure is performed in your institution and whether an additional consent form is required at the clinic where it will be performed].*

These procedures will take about *[sites to insert length of time necessary]*, and the full visit should last about *[sites to insert length of time for the full visit]*.

Screening, Week 16 and 40 Visits

At each of these visits, we will test you for gonorrhea and chlamydia using either a swab of the cervix, or sample of urine. We will also draw XX mL of blood (about x teaspoons) to test for syphilis. If any of these infections are found, we will arrange for you to get treatment *[note to sites: add whether treatment will be provided by the site]*. You are able to continue participation in this substudy one week after you have completed this treatment.

[Note to sites: Syphilis testing will depend on the test used. RPR generally requires 10 mL and another 10 mL if confirming it is treated prior to procedure].

Week 24, 48 and 49 visits

At each of these visits, in addition to the procedures for which you have already consented, your blood will be drawn, up to 150 mL (which is about 30 teaspoons). A hair sample (about 100 hairs) will be collected. The vaginal fluid and cervical biopsies will be collected as described above. Please note that up to three cervical biopsies will be collected at each of these visits. All of these samples will be stored. You should not have vaginal sex or insert anything in to your vagina for 3 days before these tests, and for 7 days after the tests. We will also call you one or two days after the procedures to check on how you are feeling. *[Note to sites: Insert specifics regarding how this procedure is performed in your institution and whether an additional consent form is required at the clinic where it will be performed].*

If you permanently stop taking the study medications after the Week 24 visit but before the end of the study, we want to be able to collect the same samples as listed here approximately two weeks after you stop taking the drugs.

Each of these visits will last [insert length of time here].

Possible Risks or Discomforts:

Blood and hair samples

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases, you may faint. There is also a slight chance of infection when blood is drawn.

Taking a sample of your hair may cause some discomfort. You may worry that this is painful or affects how you look. About 100 strands of hair are needed for this procedure. This is about the number of hairs that a person loses from their body every day. The collection procedure involves cutting the shaft of the hairs near the scalp; the root of the hair will not be collected. Each hair will be cut carefully and will be sampled around your scalp, this way people will not be able to tell that your hair has been removed. We can also take a hair sample from another part of your body other than your scalp if you wish.

Cervical biopsies and fluids

You may feel some discomfort when the vaginal speculum is inserted. There may be some discomfort during the collection of cervical biopsies. You may feel a pinch and have some cramping when the biopsy sample is taken. If you have a biopsy, you may feel some soreness in your vagina for a day or two. Some vaginal bleeding or discharge is normal for up to a week after a biopsy.

On extremely rare occasions, you may have significant pain, infection or bleeding where the biopsies were taken. It is important that you do not put anything in your vagina for the 3 days before and 7 days after having the biopsies taken, because you may be at a higher risk for bleeding or getting or spreading an infection until the biopsy sites have healed. It is especially important that you not have vaginal sex because you may be at higher risk for acquiring HIV after a biopsy. If you choose to have vaginal sex, it is especially important that a condom is used from start to finish.

Vaginal swabs

You may experience pain or discomfort from the vaginal swab. In some cases, this may cause some bleeding.

POTENTIAL BENEFITS:

There are no direct benefits to you from participating in the Tissue Subset portion of this study. However, you and others could benefit in the future from this research. You will also be treated for any sexually transmitted infections if you have them.

CONFIDENTIALITY:

To keep your information private, your samples will be labeled with a code that can only be traced back to your study clinic. Your name, where you live, and other personal information will be protected by the study clinic. The results of any tests done on these samples will not be included in your health records. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. Any publication of this study will not use your name or identify you personally. However, your records may be reviewed by:

- the United States Food and Drug Administration (FDA)
- the United States National Institutes of Health (NIH)
- the United States Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- [insert names of applicable IRBs]
- [insert applicable local authorities]
- study staff
- study monitors
- the companies that makes the study drugs (Gilead Sciences, Inc. and ViiV Healthcare)

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the U.S. Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

PROBLEMS OR QUESTIONS:

If you have questions about the study, or if you have a research-related injury, you should contact:

[site insert name of the investigator or other study staff]

[site insert telephone number and physical address of above]

For questions about your rights related to the study, contact:

[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]

[site insert telephone number and physical address of above]

SIGNATURE PAGE TISSUE SUBSET (VAGINAL COMPONENT)

**A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC),
Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate
(MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) For Pre-Exposure
Prophylaxis (PrEP) To Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and
in At-Risk Women, Version 3.0
(HPTN 069)**

CONSENT FOR TISSUE SUBSET (VAGINAL COMPONENT)

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 join the study, please sign your name or make your mark below.

It should be noted that all relevant information (e.g., compensation and treatment of injury, involuntary withdrawal, cost to subjects, new findings) from the Main study consent still applies to this consent form.

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness Name (print)
(As appropriate)

Witness Signature and Date