HPTN 073
Pre-Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three U.S. Cities

A Study of the HIV Prevention Trials Network

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute on Drug Abuse
US National Institutes of Health

Co-Sponsored by:
Gilead Sciences, Inc.

Protocol Chair:
Darrell P. Wheeler, PhD, MPH
Dean & Professor
Graduate School of Social Work
Loyola University
Chicago, IL

Protocol Co-Chair:
Sheldon D. Fields PhD, ARNP,
FNP-BC, AACRN, DPNAP, FAANP
Associate Professor and Assistant Dean of Clinical
Affairs and Health Policy College of Nursing and
Health Sciences
Florida International University
Miami, FL

Final Version 1.0
21 February 2013
DAIDS Document ID#11894
Non-IND Study

HPTN 073
Pre-Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three U.S. Cities
TABLE OF CONTENTS

HPTN 073
Pre-Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three U.S. Cities
LIST OF ABBREVIATIONS AND ACRONYMS

ACASI	Audio Computer Assisted Self Interview
ACTG	AIDS Clinical Trials Group
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
APTIMA	Amplified Probe by Transcription Mediated Amplification
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate transaminase
BGRB	Black Gay Research Group
BMSM	Black Men who have Sex with Men
BUN	Blood Urea Nitrogen
C4	Client Centered Care Coordination
CAB	Community Advisory Board
CAHPS	Consumer Assessment of Healthcare Providers and Systems
CBA	Capacity Building Assistance
CBC	Complete Blood Count
CBO	Community Based Organization
CCMT	Care Coordination Measurement Tool
CDC	Centers for Disease Control and Prevention
CFAR	Center for AIDS Research
CI	Confidence Interval
CLIA	Continuous Laboratory Improvement Act
CORE	(HPTN) Coordinating and Operations Center
CPCQ	Client Perception of Coordination Questionnaire
CPG	Community Planning Group
CPK	Creatine phosphokinase
CPQA	Clinical Pharmacology Quality Assurance
CQR	Consensual Qualitative Research Method
CRCS	Comprehensive Risk Counseling and Services
CRPMC	Clinical Research Products Management Center
CRF	Case Report Form
CRS	Clinical Research Site
CT	Chlamydia
CTM	Care Transition Measure
CTRC	Cancer Therapy Research Center
CTU	Clinical Trials Unit
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS
DBS	Dried Blood Spot
DEBI	Diffusion of Evidence-Based Interventions

DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics committee
EQA	External Quality Assurance
FDA	(United States) Food and Drug Administration
FTC	Emtricitabine
FTC/TDF	Emtricitabine/ Tenofovir Disoproxil Fumarate
FTC-TP	Emtricitabine Triphosphate
GC	Gonorrhea
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GW	George Washington University
HANC	HIV/AIDS Network Coordination
HBsAg	Hepatitis B Surface Antigen
HBCoreAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBV	Hepatitis B Virus
HCCQ	Health Care Climate Questionnaire
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
ICF	Informed Consent Form
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IoR	Investigator of Record
IQA	Immunology Quality Assurance
IRB	Institutional Review Board
LDMS	Laboratory Data Management System
LL	Local Laboratory
LTFP	Loss to Follow-up
MD	Medical Doctor
MSM	Men who have Sex with Men
NAAT	Nucleic Acid Amplification Test
NHBS	National HIV Behavioral Surveillance
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIDA	National Institutes on Drug Abuse
N MED ASSIST	National Institute on Drug Abuse Medical Alcohol, Smoking and Substance Involvement Screening Test
NIH	(United States) National Institutes of Health
NL	(HPTN) Network Laboratory
NP	Nurse Practitioner
OHRP	Office of Human Research Protection
PA	Physician Assistant
PBMC	Peripheral Blood Mononuclear Cells
PEP	Post Exposure Prophylaxis
PHC	Public Health Center
PLHIV	People Living with HIV

PrEP	Pre-Exposure Prophylaxis
PRO	Protocol Registration Office
PSRC	Prevention Science Review Committee
PSRT	Protocol Safety Review Team
PTC	Prevention Training Center
QA/QC	Quality Assurance/ Quality Control
RE	Regulatory Entity
RN	Registered Nurse
RNA	Ribonucleic Acid
ROC	Regulatory Operations Center
RSC	Regulatory Support Center
SA	Substance Abuse
SAE	Serious Adverse Event
SCHARP	Statistical Center for HIV/AIDS Research & Prevention
SDMC	(HPTN) Statistical and Data Management Center
SDT	Self-Determination Theory
SMC	Study Monitoring Committee
SOP	Standard Operating Procedure
SSP	Study Specific Procedure
STD	Sexually Transmitted Disease
STI	Sexually transmitted infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
SW	Social Worker
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TFV	Tenofovir
TFV-DP	Tenophovir Diphosphate
TSRQ	Treatment Self-Regulation Questionnaire
VQA	Virology Quality Assurance
UCLA	University of California Los Angeles Vine Street
ULN	Upper limit of normal
UNC	University of North Carolina at Chapel Hill (UNC)
U.S.	United States

TERMINOLOGY FOR TENOFOVIR, EMTRICITABINE, AND THEIR DERIVATIVES

Abbreviation	Compound name	Comments
TDF	Tenofovir disoproxil fumarate	This is the inactive, oral formulation of tenofovir (TFV, trade name: Viread®). The ester form enhances oral absorption and bioavailability. TDF is rapidly metabolized after dosing to the de-esterified pro-drug, which is also inactive.
TFV	Tenofovir	This is the inactive, de-esterified form of TDF. This is the form of the drug that is measured in serum, blood, other body fluids, and non-cellular tissue samples.
TFV-DP	Tenofovir diphosphate	This is the active, phosphorylated form of TFV that is generated in cells. This is the form of the drug that is measured in cells (*e.g.*, peripheral blood mononuclear cells, 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	FTC is an inactive pro-drug that is activated in cells by phosphorylation. This is the form of the drug that is measured in serum, blood, other body fluids, and non-cellular tissue samples.
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).
Truvada®	FTC/TDF	This is the trade name of a co-formulated drug produced by Gilead Sciences, Inc. Each tabletcontains 300 mg of TDF and 200 mg of FTC.

HPTN 073
Pre-Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three U.S. Cities
PROTOCOL TEAM ROSTER

Protocol Chair Darrell P. Wheeler, PhD, MPH Dean & Professor Graduate School of Social Work Loyola University Chicago 820 N. Michigan Avenue Chicago, IL 60611 Phone: (312) 915-7024 Email: dwheeler@luc.edu	**Protocol Co-Chair** Sheldon D. Fields PhD, ARNP, FNP-BC, AACRN, DPNAP, FAANP Associate Professor and Assistant Dean of Clinical Affairs and Health Policy College of Nursing and Health Sciences Florida International University 11200 SW 8th Street. MMC, AHC3 Room 524 Miami, FL 33199 Phone: (305) 348-6992 Email: sdfields@fiu.edu
David Borasky, MPH, CIP Deputy Director, Office of Human Research Ethics Medical School Bldg 52 CB# 7097 University of North Carolina at Chapel Hill Chapel Hill, NC 27599-7097 Phone: (919) 966-1344 Email: dborasky@email.unc.edu	Ying Qing Chen, PhD Full Member & Professor SCHARP/VIDD Fred Hutchinson Cancer Research Center 1100 Fairview Ave N, M2-C200 Seattle, WA 98109 Phone: (206) 667-7051 Email: yqchen@fhcrc.org
William Clarke, PhD Johns Hopkins School of Medicine Department of Pathology 401 North Broadway, Weinberg 2327 Baltimore, MD 21231-2410 USA Phone: (410) 502-7692 Email: wclarke@jhmi.edu	Vanessa Elharrar, MD, MPH Medical Officer Prevention Science Program/DAIDS/NIAID/NIH 6700-B Rockledge Drive, 5th Fl. Rm. 5249 Bethesda, MD 20892 Phone: (301) 827-0845 Email:elharrarva@niaid.nih.gov
Lynda Emel, PhD Research Program Manager SCHARP/FHCRC 1100 Fairview Avenue North E3-129 PO Box 19024 Seattle, WA 09109 U.S.A Phone: (206) 667-5803 Email: lemel@scharp.org	Rebecca Guzmán, CCRP Senior Clinical Research Associate Gilead Sciences, Inc. 333 Lakeside Dr., Bldg. 300 Foster City, CA 94404 Phone: (650) 524-3953 Email: rebecca.guzman@gilead.com

Craig Hendrix, MD Johns Hopkins University 600 North Wolfe Street Harvey 502 Baltimore, MD 21287, U.S.A Phone: (410) 955-9707 Email: cwhendrix@jhmi.edu	Lisa Hightow-Weidman, MD, MPH Associate Professor University of North Carolina at Chapel Hill Campus Box 7030 Chapel Hill, NC 27599 Phone: (919) 843-0033 Email: lisa_hightow@med.unc.edu
Damon L. Humes, MHS Legacy Project Director Office of HIV/AIDS Network Coordination Fred Hutchinson Cancer Research Center 1100 Fairview Ave. N., LE-500 Seattle, WA 98109-1024 Voice: 206-667-7139 Mobile: 215-431-1790 Fax: 206-667-6366 Email: dlhumes@fhcrc.org	Beryl A. Koblin, PhD Head, Laboratory of Infectious Disease Prevention Member, Lindsley F. Kimball Research Institute New York Blood Center 310 E.67th Street New York, NY 10065 Phone: (212) 570-3105 Email: bkoblin@nybloodcenter.org
LeTanya Johnson-Lewis, BS HPTN NL QC Coordinator Johns Hopkins University School of Medicine 600 North Wolfe Street Pathology 311C Baltimore, MD 21287, USA Phone: (410) 614-0638 Email: ljohns18@jhmi.edu	Jonathan Paul Lucas, MPH FHI360 Community Program Manager 2224 East NC Hwy 54 Durham, North Carolina 27713 Phone: (919) 544-7040 x11458 Email: jlucas@fhi360.org
Manya Magnus, PhD, MPH Associate Professor Department of Epidemiology and Biostatistics School of Public Health and Health Services George Washington University 2100-W Pennsylvania Avenue, NW, 8th floor Washington, DC 20037 Phone: (202) 994 3024 Email: manyadm@gwu.edu	Cheryl J. Marcus, BA, BSN Clinical Research Director UNC AIDS Clinical Trials Unit 130 Mason Farm Road 2105 Bioinformatics Building Chapel Hill, NC 27514 Phone: (919) 843-8761 Email: cjm@med.unc.edu
Kenneth Mayer, MD Infectious Disease Attending and Director of HIV Prevention Research Beth Israel Deaconess Medical Center Visiting Professor of Medicine Harvard Medical School Medical Research Director The Fenway Institute Fenway Health Boston, Mass 02215 Phone: (401) 793-4711 Email: Khmayer@gmail.com	Anthony Mwatha, MS SCHARP-FHCRC 1100 Fairview Ave. North, M2-C200 PO Box 19204 Seattle WA 98109, USA Phone: (206) 67-7123 Email: mwatha@scharp.org

LaRon E. Nelson, PhD, RN, NP Assistant Dean for Global & Community Affairs Assistant Professor of Nursing and Pharmacy University of South Florida, College of Nursing 12901 Bruce B. Downs Blvd., MDC 22 Tampa, Florida 33612 Phone: (813) 974-3351 Email: lnelson7@health.usf.edu	Alena V. Pechonkina, MD Clinical Program Manager Gilead Sciences, Inc. Phone: (650) 372-4462 Email: alena.pechonkina@gilead.com
Estelle M. Piwowar-Manning, M.T. Johns Hopkins University Hospital Department of Pathology Pathology Room 313 600 North Wolfe Street Baltimore MD 21287 Phone: (410) 614-6736 Email: epiwowa@jhmi.edu	Keith Rawlings, MD Director, Medical Affairs Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 Phone: (650) 372-4463 Email: Keith.Rawlings@gilead.com
Rotrease Regan, PhD, MPH, RN Project Director Center for Behavioral and Addiction Medicine Department of Family Medicine David Geffen School of Medicine at UCLA UCLA Vine Street Clinic 910 Vine Street Los Angeles, CA 90038 Phone: (323) 461-3106 Email: rregan@mednet.ucla.edu	James F. Rooney, M.D. Vice President Medical Affairs Gilead Sciences 333 Lakeside Drive Foster City, California 94404 Phone: (650) 522-5708 Email: jim.rooney@gilead.com
Scott Mitchell Rose, BS FHI360 Sr. CRM 2224 East NC Hwy 54 Durham, NC 27713 Phone: (919) 405-1447 Email: srose@fhi360.org	Katherine Shin, PharmD Pharmaceutical Affairs Branch DAIDS,NIAID.NIH 6700-B Rockledge Drive Room 4227 Bethesda, MD 20892-7626 Phone: (301) 594-1517 Email: kashin@niaid.nih.gov

Steve Shoptaw, PhD Professor & Vice Chair Academic Affairs, Dept. of Family Medicine at UCLA 10880 Wilshire Blvd, Suite 1800 Los Angeles, CA 90095-7087 Phone: (310) 794-6206 Email: sshoptaw@mednet.ucla.edu	Ron Stall, Ph.D., M.P.H. Professor Dept. of Behavioral and Community Health Sciences Graduate School of Public Health University of Pittsburgh Pittsburgh PA 15261 Phone: (412) 624-7933 Email: rstall@pitt.edu
Gregory D. Victorianne, BA Research / Administrative Coordinator Center for Behavioral & Addiction Medicine Department of Family Medicine at UCLA Administrative Office 10880 Wilshire Blvd., Suite 1800 Box 957087 Los Angeles, CA 90095-7087 Phone: (310) 794 0619 ext. 240 Email: GVictorianne@mednet.ucla.edu	Steven Wakefield, BS S. Wakefield, Director External Relations HIV Vaccine Trials Network Fred Hutchinson Cancer Research Center 1100 Fairview Avenue North, LE-500 Seattle, WA 98109-1024 Phone: (206) 667-6705 Email: wakefield@hvtn.org
Phaedrea Watkins FHI360 CRM 2224 East NC Hwy 54 Durham, NC 27713 Phone: (919) 544-7040 Email: pwatkins@fhi360.org	Christopher Chauncey Watson, BS Clinical Research Site Coordinator George Washington Univ. CRS 2100-W Pennsylvania Ave, NW Suite 800 Washington, DC 20037 Phone: (202) 994-3340 Email: cclwat@gwu.edu
John K. Williams, M.D. Assistant Professor UCLA, Department of Psychiatry & Biobehavioral Sciences 760 Westwood Plaza, 38-260 Los Angeles, CA 90024-1759 Phone: (310) 825-8810 Email: Keoniwmd@aol.com	Leo Wilton, PhD Associate Professor Binghamton University College of Community and Public Affairs (CCPA) Department of Human Development P.O. Box 6000 Binghamton, New York 13902 Phone: (607) 777-9215 Email: lwilton@binghamton.edu
Sarah Artis FHI360 Sr. Administrative Assistant 2224 E NC Hwy 54 Durham, NC 27713 Phone: (919)544-7040 ext. 11548 Email: sartis@fhi360.org	

HPTN 073
Pre-Exposure Prophylaxis (PrEP) Adherence and Initiation among Black Men who have Sex with Men (BMSM) in Three U.S. Cities
Final Version 1.0/ 21 February 2013

A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:
Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute on Drug Abuse
US National Institutes of Health

Co-Sponsored by:
Gilead Sciences, Inc.

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I agree to maintain all study documentation for a minimum of three years after submission of the site's final Financial Status Report to the Division of AIDS (DAIDS), unless otherwise specified by DAIDS or the HIV Prevention Trials Network (HPTN) Coordinating and Operations Center. Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be made available by the investigators to the HPTN Manuscript Review Committee and DAIDS for review prior to submission.

I have read and understand the information in this protocol 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

Pre-Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three U.S. Cities

SCHEMA

Purpose:	To assess the initiation, acceptability, safety, and feasibility of PrEP for Black men who have sex with men (BMSM) in three U.S. cities utilizing client-centered care coordination (C4) models.
Design:	An open label demonstration study with PrEP + C4 model. A subset of participants will also be recruited to participate in qualitative interviews about facilitators and barriers regarding PrEP.
Population:	HIV-uninfected BMSM at risk for HIV infection in three U.S. cities. Enrollment will include those aged 18 and over with efforts at each site to attempt to recruit an equal number of BMSM under age 25 and 25 and over.
Study Size:	A total of 225 participants with 75 participants at each of three sites.
Study Regimen:	All participants will be offered once daily oral emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (FTC/TDF) combined with C4.
Study Duration:	30 months including closeout activities. Recruitment is anticipated to take place over a 12-month period. Each participant will be followed for a total of 12 months. Six additional months are included for data clean-up and closeout.
Primary Objectives:	• To assess the initiation and correlates of daily PrEP use by sociodemographics, including age, education, and risk practices • To assess PrEP adherence via self-report (ACASI) and antiretroviral drug detection
Secondary Objectives:	• To describe side effects, toxicities, risk compensation, and STIs among participants who initiate PrEP • To describe patterns and attributes of PrEP initiation and adherence among participants (e.g., C4, substance use, sociocultural factors and incarceration) • To measure changes in sexual risk taking behavior among study participants • To describe reasons BMSM choose to initiate or decline PrEP • To describe the number of HIV seroconversions, and to analyze viral characteristics (e.g., drug resistance) and the host response to infection in participants who become HIV-infected while on PrEP To characterize the participant perception of care and referral plans
Exploratory Objectives:	• To evaluate the concordance of self-report (ACASI) to antiretroviral detection for evaluation of PrEP adherence • To describe space and staff needs for administering PrEP

Study Sites:

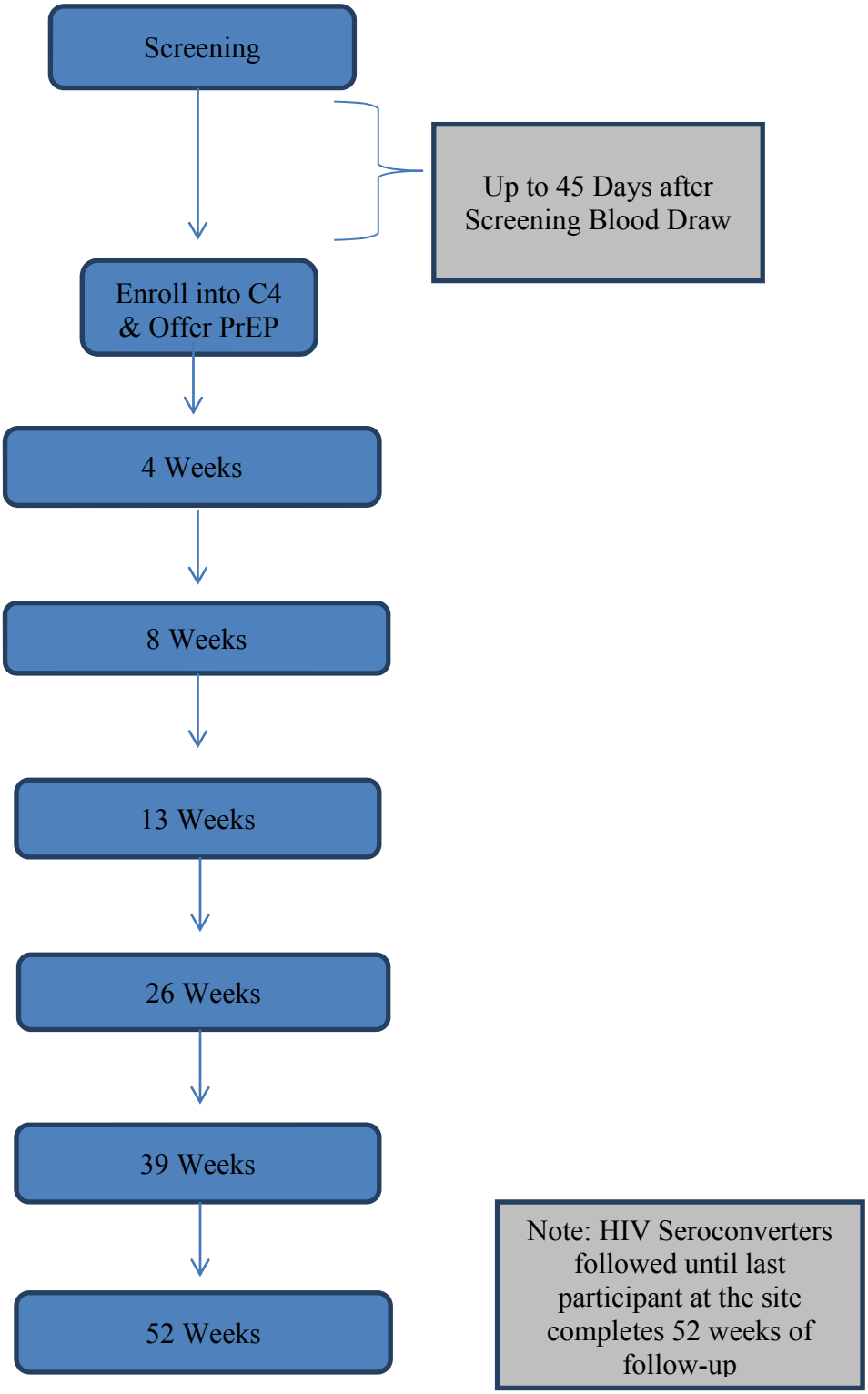
- University of California Los Angeles (UCLA) Vine Street
- George Washington University (GW)
- University of North Carolina at Chapel Hill (UNC)

Each study site consists of an HPTN Clinical Research Site (CRS) paired with one or more local healthcare facilities.

HPTN 073

Pre-Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three U.S. Cities

OVERVIEW OF STUDY DESIGN



1.0 INTRODUCTION

1.1 Background and Prior Research

The United States (U.S.) Centers for Disease Control and Prevention (CDC) statistics from August 2011 indicate that male-to-male sexual behavior is associated with the largest number of new HIV infections in the U.S. Men who have sex with men (MSM) represented 61% of newly diagnosed people living with HIV (PLHIV) in 2009, a proportion that has continued to climb in recent years. The recent iPrEx study demonstrated the first biomedical intervention using oral antiretroviral chemoprophylaxis to significantly decrease HIV incidence among MSM[1]. While such pre-exposure prophylaxis (PrEP) maybe the most promising new tool to address the domestic MSM epidemic, it may not be appropriate for all MSM in the U.S., as many are not at increased risk for HIV acquisition and such interventions are only cost saving if offered to those at greatest risk[2]. To keep logistics and costs manageable, it is more reasonable to focus on those MSM who are most vulnerable to HIV infection. While analyses for HPTN 061 data have not been completed the incidence data analysis reveals a 2.8 per 100 person-years of follow-up rate overall and 5.9 per 100 person-years of follow-up for young men (less than 30 years). In addition, significant findings suggesting high rates of STIs are correlated with new HIV diagnoses and risk of new HIV infection. As well, incarceration, unemployment and poor education are correlated with new HIV diagnoses. These findings point to the need to understand biological, behavioral and contextual factors that could impede up-take and/or adherence with PrEP.

Among ethnic and racial subgroups of MSM in the U.S., black men who have sex with men (BMSM) are at higher risk. Although BMSM comprise less than 0.4% of the total U.S. population, they accounted for more than 20% of all new infections in 2009. Younger BMSM specifically are at highest risk, experiencing a 48% increase in HIV incidence between 2006 and 2009. Most new HIV infections among BMSM are occurring among men under age 30. Among MSM age 13-24, BMSM accounted for 63% of HIV infections in 2009 while white MSM comprised only 18% of new infections and young Hispanic MSM represented 16% [3].

As stated above, the iPrEx study demonstrates the promise of PrEP in the prevention of new HIV infections among MSM. The daily use of oral co-formulated emtricitabine (FTC 200 mg) and tenofovir disoproxil fumarate (TDF 300 mg) was found to decrease HIV acquisition with acceptable safety and tolerability characteristics in an international (83% South American)[1] cohort of 2,499 HIV-uninfected MSM who received enhanced prevention interventions, including monthly counseling and biannual STI screening[1].

1.2 Rationale

Although they represent less than 1% of the population, BMSM account for 28% of all new HIV infections, which is a rate comparable to those found in sub-Saharan African countries which have been the epicenter of the global epidemic.[4] Despite their disproportionate representation in HIV and STI prevalence and incidence, BMSM have been underrepresented in HIV treatment and prevention clinical trials. Indeed fewer than 50 BMSM participated in the iPrEx study at the two U.S. sites in San Francisco and Boston[5]. To determine the potential short-and long-term effectiveness of PrEP in this population, one must first understand which at-risk BMSM are amenable to using PrEP, and whether

their adherence and side effect profiles differ from MSM of other racial and ethnic backgrounds. In this study, HIV-uninfected BMSM will be recruited and counseled on risk reduction practices including the efficacy of FTC/TDF for chemoprophylaxis and offered an open-label regimen (always with the option to accept or not) of once daily FTC/TDF, will receive client-centered care coordination (C4), and will be monitored at regular study visits (at Weeks 4, 8, 13, 26, 39 and 52).

BMSM will be recruited by teams that successfully enrolled BMSM into HPTN 061 at two sites and in one additional site that has a successful track record of enrolling BMSM into other primary prevention studies (a total of three U.S. sites). In this study, recruitment and follow-up may take place at local healthcare facilities where BMSM access clinical services and in collaboration with local healthcare providers. We anticipate that this study may include some former HPTN 061 participants who remained HIV-uninfected, but are still at increased risk for HIV acquisition. The majority of enrollees will not have been previously enrolled in HPTN 061. The recruitment strategy will be structured such that approximately 50% of men enrolled at each site are under 25 years of age, given the increased HIV incidence in this subpopulation.

1.2.1 Client-Centered Care Coordination

Client-centered care coordination (C4) is the longitudinal management of client-identified health and psychosocial needs by an interdisciplinary team. The C4 intervention takes into account the unique experience of BMSM in the U.S. with regard to biomedical interventions, psychosocial issues and barriers to accessing health care. The selection of this approach for the domestic delivery of PrEP with BMSM is informed by research experiences with 1500+ BMSM in HPTN 061; extensive literature supporting the efficacy and cost-effectiveness of interdisciplinary team-based clinical care models; and years of clinical practice experience providing expert medical, nursing, social work and psychological care and treatment for BMSM[6-13].

The major strength of C4 is the ability of the health care team to directly manage clinical issues, as well as provide guidance to participants experiencing complex health and psychosocial issues that may impact PrEP adherence[6]. While most of a client's care can be handled by a registered nurse (RN) working in collaboration with a social worker (SW), the team may also include a physician (Medical Doctor or MD), Physician Assistant (PA) or Nurse Practitioner (NP) with the capacity to prescribe and provide clinical oversight and drug monitoring[14,15]. This interdisciplinary team will have the capacity to conduct as-needed coordination and linkage to psychosocial services in an environment where client-centeredness is standard for approaches to counseling and plan development. This model is built on the practices and personnel typically in place within many local health departments and community health centers, which is where this study will be conducted.

The three core elements of the C4 model are outlined below:

Element 1: Care Coordination. This involves coordinating the care of what would typically be considered a "case." A case is defined as a constellation of factors that have an intersecting impact on the risk for, experience of, complexity of, and/or recovery from, an illness. This differs from the disease management model that focuses exclusively on interventions that directly impact the targeted illness phenomenon (e.g., HIV prevention) without attention to ancillary issues (e.g., STI screening and treatment) that influence treatment outcomes. Thus care coordination for a "case" with regard to PrEP would involve addressing proximal issues that impact the success of PrEP adherence such as addressing co-morbidities (e.g., TB, diabetes), or psychosocial issues that may impact adherence (e.g.,

substance use, housing/shelter, intimate partner violence). We will use Comprehensive Risk Counseling and Services (CRCS) as the care coordination base of C4. CRCS is a CDC-endorsed public health strategy that is focused on goal promoting the adoption and maintenance of HIV/STI risk-reduction behaviors by clients who have multiple, complex problems and risk-reduction needs [16,17]. CRCS is consistent with client-centered care coordination as it provides individualized prevention counseling, support, and service coordination, including working closely with providers to assist clients whose psychosocial needs are a barrier to their risk-reduction goals (e.g., linkage to mental health or substance abuse services). Moreover, CRCS is a component of the CDC's Diffusion of Evidence-Based Interventions (DEBI) program and thus would be available for nation-wide dissemination and implementation, post-study.

In situations where the client has an established medical home outside of the CRS, their care will also be coordinated with the primary care provider in order to facilitate continuity of care. This is accomplished through a two-way exchange of clinical information (verbally or via medical records) necessary to avoid duplication of services and to maximize congruency between plans of care that may be developed by different providers and impact PrEP adherence [18]. Care coordination can be handled by an RN, PA or other clinical staff working in collaboration with a social worker, which will replicate the efficient use of resources as PrEP is offered and administered in a typical, non-study environment. A manual will be created for all sites to follow when introducing PrEP to participants based on safety and efficacy language found in the Informed Consent Form (ICF) under "Study Purpose". The CRCS standard operating procedures will be tailored to fit within the context of each site.

Element 2: Client-Centered Approach to Care. This is an approach in which each client's unique biological, social, and interpersonal realities are taken into consideration with the goal of optimizing retention and adherence. Client centeredness is critical for the longitudinal management and retention in care of clients with pressing health and social needs. The C4 model itself is centered on BMSM to the extent that its conceptualization was the product of the evidence generated from BMSM in HPTN 061, and takes into account the complex needs of the men in that study. C4 also utilizes self-determination theory (SDT) to guide how "client-centered" is understood and operationalized within care coordination activities. Self-determination theory is anchored by three core components: (1) autonomy support-provision of evidence based health guidance and supporting the client-endorsement of the plan they believe best meets their needs and fits within their life circumstance; (2) competence support-expression of belief in the client's ability to implement his self-endorsed plan and provision of guidance for acquiring the necessary skills and resources for successful implementation; and (3) relational support-expression/demonstration of genuine care and concern for the client's successful implementation of the plan (e.g., follow-up phone/text check-ins). These three components are theorized to facilitate the adoption and maintenance of health behaviors. This can be applied across all the health behavior target domains in the study, including PrEP adherence, sexual risk reduction, and follow-through on referrals.

Client centeredness has not been a central part of public health clinic (PHC) STD program practice because, until now, such practices have not typically been involved in *longitudinal* management of clients (i.e., STI clients are managed until cure and HIV-infected clients are triaged to HIV primary care). These clinics have relied on the efficiencies offered by standardized medical directives for processing patients through clinical programs. The introduction of a new biomedical strategy (PrEP) and the targeting of a population with a high-concentration of unmet needs (BMSM) over time require that current models of practice be appropriately tailored to handle the associated complexities.

FTC/TDF for chemoprophylaxis will be discussed between participants and appropriate staff members at each study visit with the option to start/continue, stop, or abstain from usage.

Element 3: Provider for Clinical Oversight. The C4 model requires an added focus on clinical oversight for two reasons. First, the use of antiretroviral medication for PrEP requires the attention of a physician and/or nurse practitioner for study drug prescription, monitoring and management. Second, evidence from HPTN 061 indicated that the BMSM in the study had high priority health needs such as mental traumatic stress and other co-morbidities (i.e., diabetes, hypertension) that would need to be managed by a health provider with a clinical scope broader and, more advanced than that of an RN or SW.

Table 1: Provider for Clinical Oversight by Function

Service	Provider(s)
Clinical assessment of PrEP suitability	RN, PA or NP
ARV PrEP prescription	MD, PA or NP
ARV participant specific study product given to participant	RN, PA, NP or Pharmacist
Preparation and dispensing of study product	Pharmacist
PrEP health education	RN, PA or NP
Clinical monitoring and medical oversight	MD, RN, PA or NP
Individual needs assessments (ARV, psychosocial)	RN, PA, NP, SW or other trained staff
Autonomy supportive counseling	RN, PA, NP, SW or other trained staff
Substance abuse screening and appropriate referral	RN, PA, NP, SW or other trained staff
Coordinated linkage to psychosocial services and follow-up	RN, PA, NP, SW or other trained staff
Interim phone based adherence support	RN, PA, NP, SW or other trained staff
Interdisciplinary treatment planning	MD/NP, RN, SW

Key:
PrEP: Pre-Exposure Prophylaxis
ARV: Anti-Retroviral
MD: Medical Doctor
NP: Nurse Practitioner
PA: Physician's Assistant
RN: Registered Nurse

SW: Social Worker

Note: Each site will develop its' own C4 strategy in their site specific SOPs. See schedule of events for frequency.

C4 Rationale: C4 is not a program or a standard set of services; rather, it is a clinical model within which the resources and expertise of the interdisciplinary healthcare team can be mobilized based on the needs of the client. Attention will be given to providing adequate training and technical assistance to support the sites adoption and fidelity to the C4 approach to PrEP management for BMSM. In the early stages of its development, case management models focused on addressing disease-specific needs of participants. Care coordination is an innovation that evolved from case management to include understanding client needs in context. This understanding can facilitate interdisciplinary coordination with in-house clinical and psychosocial expertise as well as coordination with services available within the community, to better address the complexity of client needs[19]. Studies have shown that interdisciplinary team case-management and care-coordination models are effective in promoting adherence to antiretroviral regimens,[7] optimizing management of chronic health conditions[8-10] and sustaining ongoing participation in health programs[20]. The conceptualization of C4 draws on models that have been shown to be effective at reducing HIV sexual risk behaviors among individuals who experience complex psychosocial realities in their daily lives related to structural barriers (e.g., poverty, incarceration, substance use, etc.) [21,22]. Many men in the HPTN 061 study experienced these psychosocial realities, and we anticipate that many men who enroll in this study will have similar experiences. Given the evidence of successful use of these approaches with other populations and for a variety of health conditions, we believe that interdisciplinary, team-managed, client-centered care coordination is a highly promising practice model for addressing HIV prevention within the constellation of health and wellness needs of BMSM[23-25].

1.2.2 C4 Training and Technical Assistance

Comprehensive Risk Counseling and Services (CRCS)
C4 utilizes the public health strategy CRCS as the base of its care coordination model. Training will be provided by the CDC Behavioral Intervention Prevention Training Center (PTC) that is responsible for diffusing evidence-based intervention in the geographic region where the study site is located (Los Angeles Site=Oakland PTC; North Carolina Site=Dallas PTC; Washington DC Site=Rochester PTC). CRCS training for personnel at the three sites will be arranged with National Network of Prevention Training Centers. Sites can request ongoing technical assistance for CRCS from their regional capacity-building assistance (CBA) organizations.

Autonomy Supportive Approaches to Clinical Care
C4 incorporates self-determination theory (SDT) to guide how "client-centered" is understood and operationalized within care coordination activities. The central message of SDT is that support for the client's autonomy is essential for sustained adoption of a target health behavior. Autonomy support is experienced both at the clinic level (e.g., staff/provider's general approach with participants) and at the clinical encounter level (e.g., provider/counselor approach to addressing adherence, sexual risk reduction, or other health behavior targets). Healthcare practitioners that have experience with SDT in clinical practice and research contexts will conduct training.

- **Self-Determination Theory: Bridging Theory and Practice**

All personnel will receive on-site training on self-determination theory. The training will be provided to all site staff that will have direct contact with study subjects. This is important given that C4 is a structural intervention and our conception that client-centeredness is experienced at the "site" level as well as the clinical encounter level. Training will include case-based scenarios designed to demonstrate how SDT principles can be operationalized in staff/provider interactions with participants.

- **Autonomy Supportive Counseling**
  Those personnel who will provide any counseling to study subjects will receive training on counseling using the SDT framework. The training will include didactic modules designed to introduce trainees to SDT and the concept of autonomy support. Training will also include a mix of skills-building exercises designed to offer practice-based experiences in using SDT for different counseling scenarios. Emphasis will be placed on applying SDT in explaining PrEP, in counseling for adherence to PrEP, consistent use of condoms and follow-through on referrals.

Care Coordination Measurement Tool (CCMT) Data Collection Training

Training for CCMT data collection will follow the plan outlined in the study by Antonelli & Antonelli[26]. Training will consist of a 2-hour orientation session that will be attended by all personnel who will be required to collect data on their care coordination activities. The data collectors will be presented with case studies that represent likely experiences that may occur with participants who enroll in the PrEP program. These case studies will be analyzed and scored. Trainees will be provided with materials necessary to complete the CCMT including a scoring manual and printed data collection instructions. A CRS evaluation liaison will hold weekly visits with each site—up until the first 10 patients complete their first quarterly visit (Week 13)—to review and assess CCMT forms for completion, consistency across providers, compliance with the coding procedures, and to address any questions that may arise in the initial use of the tool. Ongoing technical assistance will be provided via a CRS evaluation liaison at each site.

1.2.3 PrEP Education

PrEP Education will be provided at each study visit to participants by appropriate staff members with the option to start/continue, stop, or abstain from usage. As stated in Section 1.2.1, a manual will be created for all sites to follow when introducing PrEP to participants based on safety and efficacy language found in the ICF under "Study Purpose".

1.2.4 Participating Sites

The study is designed to evaluate PrEP initiation and adherence in the population at greatest risk for HIV acquisition in the U.S., BMSM. We will achieve efficiencies by situating the C4 clinical model within real-world clinical settings and draw on the expertise of Clinical Research Sites (CRS) that have already demonstrated expertise in working with BMSM at high-risk for HIV. Sites located in Los Angeles, Washington, D.C., and Chapel Hill, North Carolina were chosen due to their experience and working relationships with community health centers and other community-based organizations that will assist with development and implementation of the protocol. These collaborative community partners include private physicians, community health centers, STD clinics, HIV clinics, and other settings as appropriate, based on the needs of BMSM in each location. Study conduct at these locations helps enhance the "external validity" of the demonstration project, facilitates the conduct of the coordinated care ("C4") approach, provides access post-study access to care and services, and will

increase expertise and capacity for future PrEP implementation in these sites. Each site has a track record of enrolling BMSM into prior prevention studies.

1.2.5 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 discontinue study medication and will be carefully characterized with regard to their HIV RNA level, CD4 cell count and set points over time, as well as antiretroviral drug resistance, and other factors.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

- To assess the initiation and correlates of daily PrEP use by sociodemographics, including age, education, and risk practices
- To assess PrEP adherence via self-report (ACASI) and antiretroviral drug detection

2.2 Secondary Objectives

- To describe side effects, toxicities, risk compensation, and STIs among participants who initiate PrEP
- To describe patterns and attributes of PrEP initiation and adherence among participants (e.g., C4, substance use, sociocultural factors and incarceration)
- To measure changes in sexual risk taking behavior among study participants
- To describe reasons BMSM choose to initiate or decline PrEP
- To describe the number of HIV seroconversions, and to analyze viral characteristics (e.g., drug resistance) and the host response to infection in participants who become HIV-infected while on PrEP
- To characterize the participant perception of care and referral plans

2.3 Exploratory Objectives

- To evaluate the concordance of self-report (ACASI) to antiretroviral detection for evaluation of PrEP adherence
- To describe space and staff needs for administering PrEP

2.4 Study Design (Quantitative Component)

The study is an open label demonstration project at three U.S. sites partnering with local healthcare facilities in order to utilize PrEP + C4. All BMSM will be offered PrEP and client centered care coordination (C4) throughout their planned 52-week duration in the study. Participants who acquire HIV infection during the study will discontinue dosing, will be actively linked to referral for HIV treatment and care, and will be followed until study closure (refer to protocol sections 5.11 and 6.8).

2.5 Study Design (Qualitative Component)

The primary objective of the qualitative component for HPTN 073 is to provide a contextual understanding of the barriers and facilitators in the initiation, acceptability, and adherence to PrEP for BMSM. The qualitative data will provide relevant findings regarding the men's overall impressions and experiences related to their study participation, including motivations for participating in the study, perceptions about PrEP, reasons that Black MSM choose to initiate or decline PrEP, and describing the most helpful and least helpful components of study/service uptake for PrEP provided in HPTN 073 (e.g., services provided by HPTN 073 such as C4). The qualitative component will also describe the individual, cultural, institutional, and geographic-specific barriers and facilitators that influence BMSM initiation, utilization and adherence to PrEP, including those critical factors that influence study participation and up-take of PrEP by Black MSM (e.g., socio-economic indicators, culturally specific psychosocial stressors related to stigma). Therefore, HPTN 073 will incorporate a multi-method qualitative methodological approach as a core component of the study design and collect individual interviews from a subset of participants and focus groups from the study's frontline staff from each of the three study sites.

3.0 STUDY POPULATION

The study will enroll 225 eligible HIV-uninfected BMSM at risk of HIV infection: 75 in Los Angeles; 75 in Washington, DC; and 75 in Chapel Hill, North Carolina. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. They will be recruited, screened and enrolled as described in Section 3.3. Issues related to participant retention and withdrawals from the study are described in Sections 3.4 and 3.5, respectively.

3.1 Inclusion Criteria

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

- 18 years of age or older
- No prior HIV diagnosis (self-report)
- Male at birth
- High risk for acquiring HIV infection including any one of the following in the previous 6 months:
    - Unprotected sex during receptive or insertive anal intercourse with a male partner
    - Any protected or unprotected:
        i. Receptive or insertive anal intercourse with more than three male sex partners
        ii. Exchange of money, gifts, shelter or drugs for receptive or insertive anal sex with a male partner
        iii. Receptive or insertive anal sex while under the influence of drugs or alcohol (i.e., high or drunk within two hours of the sex act) according to self-report"
    - STI diagnosis (i.e., syphilis, gonorrhea and chlamydia) by self-report
- Willing to provide locator information in accordance with the Study Specific Procedures (SSP) Manual
- Urine dipstick negative or trace for protein and glucose
- Hemoglobin > 11 g/dL, absolute neutrophil count > 750 cells/mm^3, and platelet count ≥ 100,000/mm^3
- Serum creatinine < upper limit of normal (ULN) and calculated creatinine clearance of at least 60 mL/min by the Cockcroft-Gault formula where:

    - eCcr in mL/min = [(140 – age in years) x (actual body weight in kg)] / (72 x serum creatinine in mg/dL) Alanine aminotransferase (AST) and aspartate aminotransferase (ALT) < 3 times the upper limit of normal (ULN)
- Total bilirubin < 2.5 ULN
- Hepatitis B surface antigen (HBsAg) negative

3.2 Exclusion Criteria

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

- Any reactive or positive HIV test at Screening, even if subsequent testing indicates that the person is HIV-uninfected
- Transgender
- Active or chronic hepatitis B infection (as evidenced by HBsAg, HbsAb, and HbcAb testing)
- Planning to move out of the area or to travel for more than 3 months during the study follow-up period
- Unwilling to adhere to study procedures
- Current participation in any research study via self-report (however, strictly non-HIV centered observational studies are not exclusionary)
- Previous participation in an HIV vaccine study is exclusionary unless documented evidence of enrollment into a placebo arm
- Use of ARV drugs (PrEP or PEP) in the last 60 days
- 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: interleukin therapy, medications with significant nephrotoxic potential (including but not limited to amphotericin B, aminoglycosides, cidofovir, foscarnet and systemic chemotherapy), and medications that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid) - (provided by self-report, or obtained from medical history or medical records)
- Any condition, that in the opinion of study staff, would make participation in the study unsafe, or interfere with achieving the study objective

Note: A maximum of 45 days are allowed between enrollment and the time of the first screening laboratory draw.

3.2.1 Vulnerable Populations

Persons under 18 years of age will not be included as the effects of ARV therapy on physical development and other growth parameters (e.g., effects on bone growth and bone mineral density) in HIV-uninfected children and minors have not been fully evaluated, and exploration of these safety issues is beyond the scope of this project.

Incarcerated persons will not be screened or enrolled into this study due to logistical, technical, and ethical reasons. Based on data collected in HPTN 061, a substantial proportion of participants are expected to become incarcerated over the duration of follow up. Incident incarcerations will be reported to each site's Institutional Review Board (IRB. Information known about the incarceration will be systematically collected on study case report forms (CRFs). Participants who are incarcerated

once they are enrolled in the study will not be followed while incarcerated, no data will be collected on them, and neither C4 nor PrEP provided. However, once released, participants will be followed, if they wish, from the time of release until the originally scheduled Week 52 visit.

As individuals who are incarcerated will not be available for study procedures, staff members typically learn of their incarceration via procedures implemented when unable to reach participants for a scheduled clinic visit. Each study site will develop their own SOPs for locating participants via friends, family, public electronic databases of incarcerated individuals.

Approximately 15-30 participants or 10% to 20% are anticipated to become incarcerated at some point during follow-up. This information is based on HPTN 061 recruitment and its' study population. Incarceration includes jail, prison, etc. which would prevent men from attending any study follow-up visits.

Any person who cannot provide informed consent will be excluded from participation in the project. Staff conducting screening will be trained to identify participants who cannot provide appropriate informed consent. If it is determined that the inability to provide informed consent is due to a temporary/situational factor (e.g., intoxication), these persons will be given the opportunity to reschedule their enrollment appointment as appropriate. All participants will be afforded the same protections.

3.3 Recruitment Process

Sites will be responsible for developing appropriate recruitment processes that are geared toward their respective local communities. Media advertisements, telephone scripts, fliers, and other locally acceptable methods for recruitment approved by each site's IRB may be used by recruiters at venues of socialization, open houses and public events.

3.4 Participant Retention

Each site will be responsible for developing plans for retention that reflect strategies necessary to achieve the required retention goal of 90% follow-up at the Week 52 visits. It is vital that each site recognize that BMSM represent a heterogeneous population requiring multiple methods to meet their needs, and also recognize the importance of interacting with the men in a culturally competent manner. It is also crucial that members of the study population be visible at all levels of the study teams. Study site staff are responsible for developing and implementing local standard operating procedures (SOPs) to target this goal and ensure that the target of 90% retention is met. 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
- Collection of detailed locator information at the screening visit, and active review and updating of this information at each subsequent visit
- Use of mapping techniques to establish the location of participant residences and other locator venues
- Use of appropriate and timely visit reminder mechanisms
- Immediate and multifaceted follow-up on missed visits

- Mobilization of trained outreach workers or "tracers" to complete in-person contact with participants at their homes, other community locations, and through friends and family
- Regular communication with the study community at large to increase awareness about HIV/AIDS, explain the purpose of HIV prevention research and communicate the importance of completing research study visits.

3.5 Participant Withdrawal

Regardless of the participant retention methods just described, 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 Chair, DAIDS Medical Officer, SDMC Protocol Statistician and CORE Protocol Specialist.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site IRBs/ECs terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (as described in Section 5.8) of participants who terminate from the study prior to Week 52, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4.0 STUDY PRODUCT CONSIDERATIONS

4.1 Study Product Formulation/Content/Storage

FTC/TDF is a fixed dose combination tablet containing 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF) in each tablet.

FTC/TDF (Truvada®) study tablets must be stored at 25°C, with excursions permitted to 15°C-30°C (59°F-86°F) (see USP Controlled Room Temperature). FTC/TDF tablets must be stored in the original container. Each container is packaged with a child-resistant screw cap and contains a silica gel to protect the product from humidity.

FTC/TDF 200mg/300 mg is available as Truvada®, a medication approved by the U.S. Food and Drug Administration (FDA) for treatment of HIV-1 infection and for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. Further information on Truvada® is available in the current package insert available at http://rsc.tech-res.com/safetyandpharmacovigilance.

4.2 Study Product Regimen, Administration, and Duration

Once enrolled, all participants who agree to initiate FTC/TDF study product will be directed to take one FTC/TDF 200mg/300mg (Truvada®) tablet orally once daily with or without food for up to 52 weeks.

The participant can decide to initiate FTC/TDF administration at any time after enrollment and week 48 of the study treatment period. Once initiated, the study participant may also decide to discontinue taking FTC/TDF study product at any time during the 52 week study treatment period. For

participants who decide to initiate PrEP at or after Week 48, partnerships will be established as applicable with community partners in order to provide adequate clinical care and follow-up.

4.3 Study Product Supply and Acquisition

Emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg study product tablets are manufactured and provided by Gilead Sciences, Inc. FTC/TDF 200mg/300 mg study product will be available through the National Institute of Allergy and Infectious Disease (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain FTC/TDF study product through the CRPMC by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks* and instructions in the SSP Manual.

4.4 Study Product Accountability

The site pharmacist must maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed to study participants. 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 manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

5.0 STUDY PROCEDURES

An overview of the study visit and procedures schedule is presented in Appendix I and has been written in concordance with current CDC interim guidelines for PrEP administration (http://www.cdc.gov/hiv/prep/pdf/PrEPfactsheet.pdf). In addition, all providers will be required to follow FDA requirements for the initiation of Truvada for PrEP. Presented below is additional information on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites will be provided in the study-specific procedures manual.

5.1 Screening

Sites will employ a standard approach to screening for study eligibility. The Screening visit will be jointly conducted by a research associate (or other designated evaluation team member) and a RN (or other designated clinical team member). Study staff will obtain written informed consent from each participant before any study procedures are initiated. Screening procedures may occur over one or more visits, but every effort should be made to complete procedures in a single visit, to minimize potential disruptions to participants' daily schedules. Staff members will assure participants that the detailed follow-up information will be deleted if they are not enrolled in the study. Participants may re-screen one time provided that they were not excluded because of previous participation in an HIV vaccine trial (unless there is documentation that they received only placebo), a reactive / positive HIV test, or a positive hepatitis B surface antigen test. Enrollment must be completed within 45 days of the Screening visit blood draw.
The SSP Manual provides additional information regarding the procedures outlined below, including laboratory procedures and requirements.

<u>Administrative and Behavioral Evaluations/ Procedures (evaluation team)</u>

- Informed consent including health record information from providers if applicable
- Locator information, including involvement with social media websites.

- HIV/STI behavioral counseling (pre- and post-test), including risk-reduction counseling
- PrEP discussion
- Offer condoms and other prevention resources

Note: Indication and Usage for Pre-exposure Prophylaxis will be reviewed with participants as part of a comprehensive package of risk reduction services. In general, sites must refer to the CDC interim guidelines for PrEP administration (http://www.cdc.gov/hiv/prep/pdf/PrEPfactsheet.pdf) and to the guidelines for PrEP Indication (https://www.truvadapreprems.com/#). More details will be provided in site specific SOPs.

.Clinical Evaluations/ Procedures (can be performed by licensed health provider)

- Complete medical history including but not limited to concomitant medications and socio-demographic information (e.g., age, education, race, ethnicity, income), sexual risk history and any known risks related to sexual partners, history of ARV use; surgical history; priority psychosocial needs assessment
- Symptom-driven physical exam
- N MED ASSIST
- Blood collection
- Rectal swab collection
- Urine collection
- Provide STI treatment if indicated (based on testing of samples collected at this visit)
- STI treatment, if indicated (based on testing of samples collected at Weeks 26 and 52)

Note: The N MED ASSIST or the NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test or NM ASSIST is a Web-based WHO validated interactive tool that guides clinicians through a short series of screening questions and, based on the patient's responses, generates a substance involvement score that suggests the level of intervention needed. The tool also provides links to resources for conducting a brief intervention and treatment referral, if warranted).

Laboratory Evaluations/ Procedures

- HIV testing per algorithm in the SSP Manual (note that participants who have a reactive or positive HIV test result are not eligible for enrollment, even if subsequent testing indicates that they do not have HIV infection)
- Hematology (CBC with differential)
- Renal function tests (BUN, creatinine)
- Calculated creatinine clearance
- Hepatic function tests (ALT/AST, bilirubin)
- Hepatitis B tests (HBsAg, HBsAb, HBCoreAb)
- Urine dipstick for protein and glucose
- STI testing: syphilis with treatment if applicable
- STI testing: Rectal swab and urine NAAT for gonorrhea (GC) and chlamydia (CT)
- Plasma storage for QC / Virology testing

Participants who do not have evidence of immunity to HBV will be referred for HBV vaccination. Screening must be discontinued if a participant is found to be ineligible. Participants may re-screen

one time provided that they were not excluded because of previous participation in an HIV vaccine trial (unless there is documentation that they received only placebo), a reactive / positive HIV test, or a positive hepatitis B surface antigen test. HIV/STI 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. Confirmatory testing for HIV infection will follow local guidelines. If HIV infection is confirmed, participants will receive counseling and be linked to HIV primary care. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed using an HIV RNA test if antibody-based HIV tests are non-reactive.

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. The participant will have 45 days from date of the first Screening blood draw to complete 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 (C4): Case Conference

Participants that enroll in the study will be managed using the C4 model described in section 1.2.1. General procedures will be outlined in sections 5.2 through 5.8. Detailed clinical/study visit procedures will be included in the SSP Manual.

During the time between the Screening visit and the Enrollment visit, the clinical care coordination team (RN, NP, PA, SW and MD), nurse practitioner or physician assistant, social worker, physician and other team members as designated by the site should meet to discuss a preliminary care plan for participants who have a scheduled enrollment visit. This plan should include a review of information obtained during the screening visit including: medical history, health record information, physical examination, laboratory results (e.g., GC and CT screens), N MED ASSIST, sexual risk assessments (including partners' risks), and priority psychosocial needs assessment.

The goal of the initial C4 case conference meeting is to develop a preliminary menu of options that may help to support the client's PrEP adherence. The preliminary menu will be developed by the care coordination team and may include, but is not limited to:

- Determining priority health issues that can be managed by the clinical team and those that require referral and coordination with an outside provider
- Identifying pharmacotherapeutics and other laboratory tests needed in order to manage priority health issues
- Discussion of substance abuse (SA) and preparing SA treatment referrals for ready initiation, if client is willing
- Using social/human service links to identify options for mitigating housing and food insecurity
- Identifying healthcare financing options (e.g., facilitated enrollment on public insurance, linkage with low/no-cost primary care provider when applicable)
- Pre-arranging mental health counseling sessions with social worker or other behavioral specialist
- Considering expedited partner-therapy and other partner services

The preliminary menu of options will be discussed with the client at the enrollment visit. The client will also be asked to identify adherence goal(s) and to generate other options that he believes will support his adherence goal(s). In collaboration with the clinical team (via the health provider present in the clinical encounter), the client will develop a plan that is centered on his needs. During periodic follow-up contacts and at each scheduled study visits, the client and provider will review how well the plan is working to meet the client's current needs and goals and revise/update as necessary. The HPTN 061 Resource Troubleshooting Guide will be a useful tool for the planning activities that occurs in the C4 case conference. The C4 case conference will be utilized for periodic review of the client's care plan and progress; however, a C4 team member can request case conference if they believe that more interdisciplinary review is needed to manage a particular scenario that emerges with a client.

5.2.1 Autonomy Support in Client Centered Care Coordination

Within the C4 model, the clinical team will work with participants to develop 30-day care plans (enrollment, Weeks 4 and 8), 90-day comprehensive care plans for the three quarterly visits (Weeks 13, 26 and 39) and a discharge/transition plan at the final study visit (Week 52). To ensure the successful implementation of client-centered care plans, it is essential to maintain an environment that supports participant autonomy. Autonomy support can be applied across all the health-behavior target domains in the study, including PrEP adherence and sexual risk reduction.

5.2.2 Autonomy Supportive Adherence Counseling when dispensing PrEP

Adherence counseling will be provided to all participants who initiate PrEP at each study visit starting at the enrollment visit, and each interim visit in which adherence is discussed. PrEP will be offered to each eligible participant at each study visit in a manner that is non-coercive. The counseling makes use of self-determination theory that is designed to facilitate the client's integration of PrEP usage into his health behavioral routines and support the client in making his own decisions regarding adherence[29,30]. Counseling will include the development of client-centered strategies to support the consistent daily adherence of PrEP and may be conducted by an appropriately trained team member according to local site guidelines. This counseling is delivered one-on-one with the client and provider during the study visit. The counseling will also include reminders not to share the medication and to contact project staff with questions about product use.

5.2.3 HIV/STI Behavioral Risk Reduction Counseling

Brief client-centered risk reduction counseling will be provided at each visit. The overall risk-reduction counseling package will include using a self-determination theory driven, evidence-based, client-centered counseling strategy[31,32]. Key to this counseling strategy is for the provider to support the participant's implementation of the self-endorsed, but collaboratively developed, risk-reduction plan. These counseling sessions will reinforce the role of consistent use of condoms in HIV/STI prevention, as well as other strategies such as routine screening and treatment for STIs, mutual monogamy and reduction in the number of sexual partners. The overall goal will be to supplement PrEP counseling by supporting participants to adopt or continue risk-reduction practices.

5.2.4 HIV/STI Treatment

Each site will treat or refer for treatment as needed as per local guidelines and capabilities. Every effort will be made to ensure successful completion of treatments for STDs/STIs. Site specific ICFs

and SOPs will have to be modified as needed when the time comes for follow-up of treatment at the Department of Health or other clinic of the participant's choosing.

5.3 Enrollment Visit

A participant is considered enrolled at the point in time that he begins enrollment visit procedures (confirmation of locator information during the enrollment visit).

Administrative and Behavioral Evaluations/ Procedures (clinical team)

- Verify locator information
- Behavioral and Psychosocial Risk Survey (ACASI)
- HIV/ STI behavioral risk-reduction counseling
- PrEP discussion
- Offer condoms and other prevention supplies

Note: Indication and Usage for Pre-exposure Prophylaxis will be reviewed with participants as part of a comprehensive package of risk reduction services. In general, sites must refer to the CDC interim guidelines for PrEP administration (http://www.cdc.gov/hiv/prep/pdf/PrEPfactsheet.pdf) and to the guidelines for PrEP Indication (https://www.truvadapreprems.com/#). A manual will be created for all sites to follow when introducing PrEP to participants based on safety and efficacy language found in the ICF under "Study Purpose".

If initiating PrEP:

- Assess participant's initial readiness for PrEP adherence (may be conducted at any time through Week 48)
- Study product supply
- Autonomy supportive adherence counseling
- PrEP adherence-goal setting
- PrEP Adherence Self-Regulation Questionnaire (participant self-administered)

- C4 including:
  - C4 Case Conference (by staff prior to enrollment)
  - Care Coordination Measurement Tool (recorded by providers)

Clinical Evaluations/ Procedures

- Interim medical history including concomitant medications
- Symptom-driven physical exam
- Hepatitis B vaccination, if appropriate
- Blood collection
- Urine collection

Laboratory Evaluations/ Procedures

- HIV testing per algorithm in the SSP Manual
- Urine dipstick for protein and glucose (if initial screening result is > trace for either protein or glucose)
- Plasma storage for Pharmacology testing*
- Urine storage for substance use testing

- Plasma storage for QC / Virology testing

*These samples may be tested as controls.

5.4 Weeks 4* and 8

Administrative and Behavioral Evaluations/ Procedures

- Review and update locator information
- Social Harms and AE Assessment
- HIV/STI behavioral counseling (pre- and post-test), including risk-reduction counseling
- PrEP discussion
- Offer condoms and other prevention supplies

  Note: Indication and Usage for Pre-exposure Prophylaxis will be reviewed with participants as part of a comprehensive package of risk reduction services. In general, sites must refer to the CDC interim guidelines for PrEP administration (http://www.cdc.gov/hiv/prep/pdf/PrEPfactsheet.pdf) and to the guidelines for PrEP Indication (https://www.truvadapreprems.com/#). A manual will be created for all sites to follow when introducing PrEP to participants based on safety and efficacy language found in the ICF under "Study Purpose".

  If initiating or on PrEP:
    - Assess participant's initial readiness for PrEP adherence (only if initiating)
    - Self-reported study product adherence assessment
    - Study product supply
    - Autonomy supportive adherence counseling
    - PrEP Adherence Self-Regulation Questionnaire (participant self-administered)
    - PrEP adherence goal setting

- C4 including:
    - Care Coordination Measurement Tool (recorded by providers)
    - Health Care Climate Questionnaire (participant self-administered)

Clinical Evaluations/ Procedures

- Interim medical history including concomitant medications
- Urine collection
- Blood collection

Laboratory Evaluations/ Procedures

- HIV testing per algorithm in the SSP Manual
- Renal function tests (BUN, creatinine at Week 4 only)
- Calculated creatinine clearance (Week 4 only)
- Plasma storage for Pharmacology testing (Week 8 only)**
- Lysed PBMC storage for Pharmacology testing (Week 8 only)**
- DBS storage for possible Pharmacology testing (Week 8 only)**
- Urine storage for substance use testing

- Plasma storage for QC / Virology testing

**Conduct a visit consisting of Week 4 procedures 4 weeks after initiating PrEP, or 4 weeks after a participant re-initiates PrEP.*

**Plasma and DBS samples will be processed and stored for all participants; testing may be limited to a subset of these samples. Lysed PBMC samples will be processed and stored only for participants who report that they used PrEP within 60 days of sample collection.

Note: Any participant who has not taken PrEP in the past 60 days and wishes to start PrEP at this visit must first be confirmed to be eligible according to the Screening Visit parameters.

5.5 Week 13

Administrative and Behavioral Evaluations/ Procedures

- Review and update locator information
- Social Harms and AE Assessment
- Behavioral and Psychosocial Risk Survey (ACASI)
- HIV/STI behavioral counseling (pre- and post-test), including risk-reduction counseling
- PrEP discussion
- Offer condoms and other prevention supplies

  Note: Indication and Usage for Pre-exposure Prophylaxis will be reviewed with participants as part of a comprehensive package of risk reduction services. In general, sites must refer to the CDC interim guidelines for PrEP administration (http://www.cdc.gov/hiv/prep/pdf/PrEPfactsheet.pdf) and to the guidelines for PrEP Indication (https://www.truvadapreprems.com/#). A manual will be created for all sites to follow when introducing PrEP to participants based on safety and efficacy language found in the ICF under "Study Purpose".

  If initiating or on PrEP:
    - Assess participant's initial readiness for PrEP adherence (only if initiating)
    - Self-reported study product adherence assessment
    - Study product supply
    - Autonomy supportive adherence counseling
    - PrEP Adherence Self-Regulation Questionnaire (participant self-administered)
    - PrEP adherence goal setting

- C4 including:
    - C4 Case Conference (by staff preferably prior to the Week 13 visit)
    - Health Care Climate Questionnaire (participant self-administered)
    - Client Perception of Coordination Questionnaire (participant self-administered)
    - Care Coordination Measurement Tool (recorded by providers)

Clinical Evaluations/ Procedures

- Interim medical history including concomitant medications
- Symptom-driven physical exam

- Blood collection
- Urine collection

Laboratory Evaluations/ Procedures
- HIV testing per algorithm in the SSP Manual
- Renal function tests (BUN, creatinine)
- Calculated creatinine clearance
- Urine dipstick for protein and glucose
- Urine storage for substance use testing
- Plasma storage for QC / Virology testing

Note: Any participant who has not taken PrEP in the past 60 days and wishes to start or restart PrEP at this visit must first be confirmed to be eligible according to the Screening Visit parameters. This does not have to be performed at a separate "interim" visit. Screening procedures can be repeated at any scheduled study visit if they needed to confirm eligibility for PrEP administration. All assessments to determine eligibility for PrEP initiation (including laboratory testing) must have been conducted within the previous 45 days.

5.6 Weeks 26, 39 and 52

Administrative and Behavioral Evaluations/ Procedures
- Review and update locator information
- Social Harms and AE Assessment
- Behavioral and Psychosocial Risk Survey (ACASI)
- Qualitative Interview (Week 52 only)
- Adherence goal setting (except Week 52)
- HIV/STI behavioral counseling (pre- and post-test), including risk-reduction counseling
- PrEP discussion
- Offer condoms and other prevention supplies
- Informed Consent for individual interview (Week 52 only)

Note: Indication and Usage for Pre-exposure Prophylaxis will be reviewed with participants as part of a comprehensive package of risk reduction services. In general, sites must refer to the CDC interim guidelines for PrEP administration (http://www.cdc.gov/hiv/prep/pdf/PrEPfactsheet.pdf) and to the guidelines for PrEP Indication (https://www.truvadapreprems.com/#). A manual will be created for all sites to follow when introducing PrEP to participants based on safety and efficacy language found in the ICF under "Study Purpose".

If initiating or on PrEP:
- Assess participant's initial readiness for PrEP adherence (only if initiating; initiation not allowed to start after Week 48)
- Self-reported study product adherence assessment
- Study product supply (except Week 52)
- Autonomy supportive adherence counseling (except Week 52)

- PrEP Adherence Self-Regulation Questionnaire (participant self-administered) (except week 52)

- C4 including:
  - C4 Case Conference (commencing discharge/transition planning for weeks 39 and 52)
  - Care Coordination Measurement Tool (recorded by providers)
  - Health Care Climate Questionnaire (participant self-administered)
  - Client Perception of Coordination Questionnaire (participant self-administered)
  - Care Transition Measure (Week 52 only or study exit)
  - Front Line Administrative Staff Satisfaction Survey (week 52 only or study exit)

Clinical Evaluations/Procedures

- Interim medical history including concomitant medications
- Symptom-driven physical exam
- Hepatitis vaccination or referral, if indicated
- Blood collection
- Urine collection
- Rectal swab collection (Weeks 26 and 52 only)
- N MED ASSIST (Week 52 only)
- Submit discharge summary to primary health provider, when applicable
- STI treatment, if indicated (based on testing of samples collected at Weeks 26 and 52)

Laboratory Evaluations/ Procedures

- HIV testing per algorithm in the SSP Manual
- Renal function tests (BUN, creatinine for those on PrEP within the past 60 days)*
- Calculated creatinine clearance (for those on PrEP within the past 60 days)*
- Urine dipstick for protein and glucose
- STI testing: syphilis (Weeks 26 and 52 only)
- STI testing: rectal and urine NAAT for GC and CT (Weeks 26 and 52 only)
- Hepatitis testing (HbsAg, HbSAb, HbcoreAb)**
- Plasma storage for Pharmacology testing (Weeks 26 and 52 only)***
- Lysed PBMC storage for Pharmacology testing (Weeks 26 and 52 only)***
- DBS storage for possible Pharmacology testing (Weeks 26 and 52 only)***
- Urine storage for QA of substance use testing
- Plasma storage for QC / Virology testing

**For participants who decide to initiate PrEP at or after Week 48, partnerships will be established as applicable with community partners in order to provide adequate clinical care and follow-up.*

***Hepatitis testing should be repeated at Week 52 for participants who were non-immune at the Screening visit, declined HBV vaccination, or were not diagnosed with HBV infection during the study.*

***Plasma and DBS samples will be processed and stored for all participants; testing may be limited to a subset of these samples. Lysed PBMC samples will be processed and stored only for participants who report that they used PrEP within 60 days of sample collection.

Note 1: Any participant who has not taken PrEP in the past 60 days and wishes to start or restart PrEP at Week 26, Week 39 or any other visit up to Week 48 must first be confirmed to be eligible according to the Screening Visit parameters. This does not have to be performed at a separate "interim" visit. Screening procedures can be repeated at any scheduled study visit if they needed to confirm eligibility for PrEP administration. All assessments to determine eligibility for PrEP initiation (including laboratory testing) must have been conducted within the previous 45 days.

Note 2: Staff Focus Groups will begin after all participants have completed the study.

5.7 Interim Visits

Interim visits may occur at any time during the project and may be conducted at the main clinic or at the affiliated sites. Interim visits may occur for one or more of the following reasons: 1) Medical reasons (e.g., a client may want to discuss barriers to adherence not related to side effects; client may require an interim visit related to a priority health issues; client may require STD/HIV screening); 2) Reasons related to an adverse event for example, intolerable side effects; 3) Desire to initiate PrEP (this may occur at any time up to the Week 52 visit); 4) Other reasons the participant may request. In general participants requesting interim visits should contact their assigned clinic/study nurse for triage. The nurse will make a recommendation to the client on whether an interim visit is indicated or whether an alternate plan is warranted.

When interim visits in response to participant reports of AEs are completed, the physician, physician's assistant or nurse practitioner member of the clinical team will clinically assess the reported event and provide appropriate medical care or make appropriate referrals. Participants with symptoms suggestive of acute HIV-infection syndrome will receive diagnostic testing to attempt to elucidate the cause of the syndrome, including HIV testing that includes testing for HIV RNA. Study medication will be stopped immediately if any HIV test is reactive or positive and plasma will be stored. All interim visits will be documented in the client's clinical/study records. All interim clinical visits identified in the health information exchange from client's primary or other health care provider (when applicable) will also be noted in the client's clinical/study records and on applicable CRFs.

5.8 Premature Study Discontinuation

Participants may voluntarily withdraw from the study for any reason at any time. Site Investigators of Record (IoRs) may, with the approval of the Protocol Chair and after consultation with the Division of AIDS (DAIDS) Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, and CORE Operations Center Protocol Specialist 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 Office of Human Research Protection [OHRP]), or site IRBs terminate the study prior to its planned end date. Site investigators are required to consult the Protocol Chair and Protocol Biostatistician prior to the termination of any study participant. Study staff will record the reason(s) for all withdrawals in participants' study records. The Week 52 visit schedule

should be followed when possible.

5.9 Participant Assessments Via Audio Computer-Assisted Self-Interview (ACASI)

Participants will undergo ACASI at enrollment and throughout study follow-up, to include sexual behavior, substance use proximal to sexual behavior and adherence.

Refer to the SSP Manual for further instructions.

5.10 Qualitative Interviews

5.10.1 Individual Semi-Structured Interviews with Participants

Each of the three study sites participating in HPTN 073 will conduct individual semi-structured interviews with approximately five participants that initiated PrEP at each site and approximately five men that did not initiate PrEP at each site. The objective of the individual interviews is to ascertain information about factors that serve as facilitators and barriers in the initiation, acceptability and adherence of PrEP. Consensual Qualitative Research methods[33] will be used to analyze the qualitative data. The objective of the individual interviews is to ascertain information about factors that serve as facilitators and barriers in the initiation, acceptability and adherence of PrEP. Interviews will be conducted among participants as they complete the Week 52 follow up visit. We will collect the data over approximately a 5 month period with approximately 2 participants per site (one that initiated PrEP and one that did not) per month starting when the first participant completes week 52. The sites will ask participants to complete the interview until the "slots" for that month have been filled.

Each interview will last approximately 60 to 90 minutes in length among participants who are recruited for and consent to this component of the study. A qualitative interview guide will be developed to address two primary domains (1) factors that facilitate the initiation, acceptability and adherence of PrEP and (2) factors that serve as barriers in the initiation, acceptability and adherence of PrEP.

The individual interviews will be conducted by trained study staff. Interviewers will probe for indicators of the two primary qualitative domains as well as for themes that emerge during the individual interviews. The interviews will be digitally audio-taped and transcribed verbatim for qualitative data analyses by a professional transcription service. Interviews will be conducted at a location identified by study staff to assure adequate privacy and confidentiality. Participants will be provided with a separate reimbursement for participation in the individual interview. All identifying information will be removed from the transcripts, and only the research team and the transcribers will have access to the audio interview data. Audio recordings of interviews will be destroyed within three years of study completion.

5.10.2 Focus Groups with Site Staff

Each of the three sites for HPTN 073 will conduct one focus group with the C4 team at the end of the study to elicit feedback on what resources they believe were necessary to optimally implement a C4-based PrEP program. This will include (1) resources that were available onsite (2) resources that were available in the community, (3) resources that were not available during the course of the study, and (4) discussion of how resources would have improved their ability to provide care. The C4 team will be consented for the focus group immediately prior to the conduct of the focus group and after all

participants have completed the study. A staff member will review the consent, or read it aloud with the entire group and then will answer any questions. During the consent procedure, staff will go over pertinent aspects of the focus group activity with participants, including ground rules, the structure of group discussion, potential risks, benefits, and compensation. The data from CCMT and focus groups will be triangulated to form a profile of the human and space resource needs across the three study sites.

5.11 Participants who have Suspected or Confirmed HIV at Screening or During the Study

In the case of suspected HIV infection at the Screening visit, HIV status will be confirmed using local HIV testing guidelines. Participants who have a reactive or positive HIV test at Screening are not eligible for enrollment, even if subsequent testing indicates that they are not HIV infected.

Participants who have a reactive HIV test result at a follow-up visit will be instructed to discontinue their study medication immediately and will be further evaluated following procedures 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, testing will be performed using an HIV RNA test if antibody-based HIV tests are non-reactive. Regardless of whether HIV RNA testing is used for diagnostic testing, HIV infection that is diagnosed after the Screening visit must be confirmed in all cases using samples collected on two different days.

Any participant who is found to have confirmed HIV infection after Enrollment will be followed at all scheduled visits and beyond as described in Appendices IA and IB. 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.

HIV-infected participants will also be able to continue with C4 visits to help ensure that all receive assistance in securing HIV medical care, retention in care over the year, and facilitation to take HIV medications, if these are prescribed as part of HIV medical care. Participants who acquire HIV infection during the study will be asked to provide releases of information that will allow study counselors to consult with providers of HIV medical care to coordinate case management, and to implement other strategies intended to help participants to be retained in medical care and to adhere to treatment regimens. These activities will be logged in C4 counselor charts.

Participants with suspected or confirmed HIV infection should follow the procedures outlined in Appendices IA and IB, and any instructions included in the SSP Manual.

In addition, if participants request post-exposure prophylaxis (PEP) for HIV exposure, they will be referred to their primary care provider for evaluation, when applicable. If participants start PEP, the Protocol Safety Review Team (PSRT) must be immediately consulted to discuss whether study medications should be discontinued.

5.12 Hepatitis B Virus

Testing for hepatitis B virus (HBV) infection and/ or immune status will be performed at screening (HBsAg, HBsAb, and HBCoreAb). Participants who have a positive HBsAg test will be excluded

from the study and will be referred to their primary provider for management when applicable. 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 the Screening visit, 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 testing (HBsAg, HBsAb, and HBCoreAb) will be performed at Week 52 for participants who did not have evidence of immunity at the Screening visit, declined HBV vaccination, and were not diagnosed with HBV infection during the study. If any participant has a positive HBsAg at Week 52, they will be referred for clinical care.

5.13 Sexually Transmitted Infections

In order to reduce disease risk and burden, sites will make every effort to provide on-site treatment for STIs detected during study participation. For sites that do not have the capacity or that cannot conduct on-site treatment for other reasons, participants who test positive for STIs will be referred for STI care either to local public health facilities that will treat the STI free of charge or, if participants have health insurance/medical care, to their primary care providers. In general, study product need not be held in the event of an STI requiring treatment, unless other product hold guidelines apply.

5.14 Measures of Client Centered Care Coordination

PrEP Adherence Self-Regulation Questionnaire (15-items)

We will use a modified version of the Treatment Self-Regulation Questionnaire (TSRQ) to assess participants' reasons for using PrEP if self-determined—whereby higher self-determination scores reflect greater internalization of the target behavior and increased likelihood of adherence[34]. The TSRQ uses a 7-point Likert scale and has been modified in previous studies to address adherence to antiretroviral medication[35] and other specific health behavior targets such as diet and exercise[31]. The TSRQ was shown to have adequate internal consistency with alphas ranging from (.85 to .93) across several studies.

Health Care Climate Questionnaire (15-items/ 5-item short form)

The HCCQ uses a 7-point Likert scale to assess the degree to which participants perceive their clinical team to be autonomy supportive [29]. Higher scores indicate greater perceived autonomy support. The HCCQ uses the concept of autonomy support, from self-determination theory, to characterize the client-centeredness of clinical environments, hypothesizing that autonomy-supportive (client-centered) clinical environments facilitate self-determined motivation for the adoption of target health behaviors[32,36]. The α coefficient for the internal consistently of the HCCQ is > 0.90.

Client Perception of Coordination Questionnaire (24-items)

We will use the CPCQ to measure the client's perspective whether the care they received over time was client-centered and coordinated between health care providers[37]. The CPCQ demonstrated good internal consistency (α= 0.92). CPCQ has six subscales with alphas ranging from 0.31 to 0.86. We will use the four subscales with good internal consistency and adapt them for structure of the C4 model: (1) acceptability of care coordination, (2) receipt of self-perceived needed care, (3) perception of clinical care provider, (4) perception of psychosocial care provider. This reduces the item count from 31 to 24. While the CPCQ is the longest measure within the C4 battery, it exhibited high completion rates (>95%) in the study in which it was developed[37].

Care Coordination Measurement Tool (CCMT).
We will measure the activities involved in providing client-centered care coordination for PrEP using a modified version of the CCMT. The CCMT was developed based on national expert panel recommendations for care coordination measurement[18]. Among the items captured on the CCMT include: (1) client complexity level, (2) focus of the encounter (e.g., clinical/medical, legal, mental health, referral management, social service), (3) type of coordination needed, (4) services/activities rendered, (5) time-spent on coordination activities, and (6) outcome of coordination. The CCMT is designed for use by all personnel involved in a particular client-centered care coordination evolution and has been successfully used in previous studies[26,38]. The CCMT will allow us to obtain robust characterizations of care-coordination encounters for use in addressing our secondary objectives.

Care Transition Measure (15-items/ 3-item short form)
The Care Transition Measure (CTM) uses 4-point Likert scale to assess quality of transition from hospital care to community-based care or home[39]. CTM will be adapted to assess client-centered transition from PrEP management in the C4 model to community-based clinical supervision of PrEP. The CTM demonstrated high-internal consistency and reliability, and adequate convergent validity with a validated measure[40] of client-perception of the quality of hospital discharge/transfer process. Spearman inter-item correlations were between 0.35 and 0.75 which indicate that the scales and conceptually similar but are not measuring identical constructs.

Front Line Administrative Staff Satisfaction Survey (2-items)
We will assess participants' experience of clerical and receptionist staff using 2-items subscale extracted from the Adult Specialty Care Questionnaire 1.0 of the AHRQ Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey. The CAHPS and its component subscales demonstrated good reliability and validity[41]. This brief measure asks participants to indicate how often over the past 12-months that clerical staff "were as helpful as you thought they should be" and "treated you with courtesy and respect" measured on a Likert-type scale from 1="never" to 4="always."

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

Close cooperation between the Protocol Chair(s), study site Investigator(s), NIAID Medical/Program Officer, CORE Protocol Coordinator, SDMC Biostatistician, SDMC Clinical Affairs Staff, 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 and management of AEs in conjunction with IoRs. Sites are required to have detailed SOPs describing methods for AE reporting and toxicity management to ensure that AEs are reported and managed in accordance with the protocol and for alerting the PSRT if unexpected concerns arise.

A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, site clinicians, and the SDMC Clinical Affairs Safety Associate will serve as the PSRT which will be

chaired on a rotating basis by qualified members.. The HPTN SDMC will prepare routine safety data reports for review by the PSRT. The PSRT 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 SDMC in advance of study implementation. In addition, for trials such as this with no DSMB oversight, the HPTN Study Monitoring Committee (SMC) may also review safety data, either in aggregate or by PrEP uses.

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 led by the SDMC Clinical Affairs staff (SMC reviews), the PSRT and study sponsors. The SMC will meet at least annually 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.

As stated above, 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 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 an unacceptable type and/or frequency of AEs has been observed.

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 the study be stopped. If at any time a decision is made to discontinue the study product in all participants, DAIDS will notify the site IoRs, who will notify the responsible IRBs expeditiously.

6.3 Adverse Event (AE) Reporting

Adverse events (AE) are defined as any untoward medical occurrence experienced by participants during the study, and may or may not have a causal relationship with the treatment. Information regarding all AEs regardless of seriousness or severity will be recorded in the participant's source files. Grade 3 and higher adverse events and all creatinine AEs will be recorded on study CRFs. All STIs will be recorded in CRFs. All SAEs must be reported on AE Log CRF. All AEs that result in a clinical hold or permanent discontinuation of study product are reported on AE Log CRF regardless of grade. Grade 3 and higher clinical AEs will be referred to a study clinician at the time of the visit. All critical laboratory values will be reported as applicable per site SOPs. Participants who are not

present at the study site at the time a laboratory AE requiring retesting or follow-up is identified will be followed as deemed clinically appropriate. With appropriate permission of the participant, and whenever possible, records from non-study medical providers related to untoward medical occurrences will be requested and required data elements will be recorded on study CRFs and/or in the participant's medical chart. All AEs regardless of severity will be followed clinically, until the AE resolves or stabilizes as per the appropriate toxicity algorithm. AEs will be assessed from the time of enrollment in this PrEP demonstration project.

6.4 Serious Adverse Events

Serious adverse events (SAEs) will be defined per CFR 312.32 guidelines, as AEs occurring at any dose that:

- Result in death;
- Are life-threatening adverse events;
- Require inpatient hospitalization or prolongation of existing hospitalization;
- Result in persistent or significant disability/incapacity; or
- Are congenital anomalies/birth defects.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or require medical or surgical intervention to prevent one of the outcomes listed above.

6.4.1 Grading System

All AEs will be graded using the DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification dated August 2009) and the DAIDS Addendum 2 - Male Genital Grading Table, which are available at http://rsc.tech-res.com/safetyandpharmacovigilance/. Grade 1 creatinine toxicity will be determined by either the DAIDS AE Grading Table OR Grade 1 as defined by creatinine > 1.5x the participant's baseline serum creatinine, whichever is higher."

6.4.2 Assessment of Relationship to Study Agent

The relationship of all AEs to FTC/TDF will be assessed per the package insert and investigator's brochure for FTC/TDF, and clinical judgment of the investigator. The relationship categories that will be used for this study are related and not related, as defined in the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010) which is available at http://rsc.tech-res.com/safetyandpharmacovigilance/.

6.5 Expedited Adverse Event Reporting

Requirements, definitions and methods for expedited reporting of AEs 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.

6.5.1 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.

6.5.2 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. The study agents for the purposes of SAE reporting are part of a fixed dose combination tablet: emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF).

The SAE reporting period for this study is per the DAIDS EAE manual and continues from enrollment of a trial participant to the end of trial follow-up for that participant. All reportable SAEs occurring during the study reporting period will be reported to the principal investigator and the DAIDS Regulatory Support Center (RSC) Safety Office in an expedited manner, within three reporting days of site awareness of the events (see definition in Appendix D of the DAIDS EAE Manual).

After the protocol-defined AE reporting period, only SUSARs as defined in Version 2.0 of the DAIDS EAE manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

Reporting requirements for the local IRBs will also be followed.

6.6 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result. For example, participants could be perceived as being HIV-infected or at high risk for HIV infection and be treated unfairly or have problems being accepted by their families and/or communities. Social harms that are judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to its individual requirements. Social harms will be collected and reported on CRFs during regular visits. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant. 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 CABs in exploring the social context surrounding instances of social harm, to minimize the potential occurrence of such harm.

6.7 Toxicity Management

The site investigator has the discretion to hold FTC/TDF at any time if s/he feels that continued medication use would be harmful to the participant or interfere with treatment deemed clinically

necessary according to the judgment of the investigator. Clinical or laboratory abnormalities that require follow up will be documented, and the research associate or clinician will contact the participant to schedule an interim visit for follow-up and/or repeat laboratory testing. All participants reporting an adverse event will be followed clinically until the occurrence resolves (returns to baseline grade, defined as grade at enrollment) or stabilizes or an effective referral to local health care providers is accomplished.

6.7.1 Discontinuation of Study Medication

Grades 1 or 2
Continue FTC/TDF at the discretion of the site investigator.

Grade 3
FTC/TDF may be continued at the discretion of the site investigator if a Grade 3 toxicity is considered to be unrelated to the study medication. Study medication will be temporarily withheld if Grade 3 toxicity is considered to be related to the study medication. After a Grade 3 toxicity returns to Grade 1, the participant can be reintroduced to medication after consultation with the site investigator, DAIDS Medical Officer, and other members of the PSRT. If a Grade 3 toxicity recurs and is considered to be related to study medication, FTC/TDF will be permanently discontinued.

Grade 4
For all Grade 4 laboratory-identified or clinical toxicities, FTC/TDF will be withheld unless it is determined to be not related. If a Grade 4 laboratory toxicity is not confirmed by repeat testing, it should be managed per algorithm for the new toxicity grade. Participants with Grade 4 AEs will be followed until the event resolves to baseline or stabilizes. Study drug may be restarted in the event of the resolution of a Grade 4 AE back to Grade 1, after consultation with the site investigator, DAIDS Medical Officer, and other members of the PSRT. If the toxicity recurs to Grade 3 or higher after FTC/TDF is restarted and is considered to be related to FTC/TDF, the study medication will be permanently discontinued.

6.7.2 Creatinine Elevations

For creatinine elevations >1.5-fold above baseline creatinine (at screening), serum creatinine will be repeated as soon as possible, preferably within 7 days. Participants who fail to have a confirmed test within two weeks of receiving the initial result should be permanently discontinued from use of the study drug and the PSRT should be notified. FTC/TDF will be held for confirmed creatinine elevations >1.5-fold above baseline until creatinine returns to <1.3-fold above baseline, at which point the participant may be re-challenged with FTC/TDF after consultation with the site investigator. Clinicians may re-test creatinine levels more often (i.e., weekly) should they choose; however, after the initial re-test approximately 7 days later, it is not required per protocol to re-test serum creatinine until the next scheduled study visit. If serum creatinine rises again to >1.5-fold above baseline when drug is restarted, the PSRT must be notified and FTC/TDF should be permanently discontinued and the participant will be monitored as deemed clinically appropriate in consultation with the PSRT until level returns to baseline (screening value) or stabilizes.

6.7.2.1 Creatinine Clearance

- Estimated CrCl< 60 mL/min

If the calculated creatinine clearance is <60mL/min, it should be confirmed ideally within approximately one week of the receipt of the results.
Discontinue study drug temporarily. Participants who fail to have a confirmed test within two weeks of receiving the initial result should be permanently discontinued from use of the study drug and the PSRT should be notified.

- Confirmed CrCl<60 mL/min
  If the calculated creatinine clearance is confirmed to be <60 mL/min, the study drug must be temporarily discontinued. As previously stated, participants who fail to have a confirmed test within two weeks of receiving the initial result should be permanently discontinued from use of the study drug and the PSRT should be notified. The participant will be monitored as deemed clinically necessary in consultation with the PSRT until level returns to baseline (screening value) or stabilizes.
  Temporarily discontinue study drug (unless the participant does not return for repeat testing within approximately two weeks).

- Re-testing result is ≥60 mL/min
  If re-testing yields a result ≥60 mL/min, the Investigator may re-start study drug use, and follow creatinine clearance over time as deemed clinically necessary.

6.8 HIV Seroconversion

Frequent testing for HIV acquisition during the study period will allow prompt cessation of study drug in an HIV-infected participant, minimizing the risk that resistant virus will emerge. Therefore, HIV testing will be performed at all scheduled study visits, including Screening, Enrollment, Weeks 4, 8, 13, 26, 39 and 52. If acute HIV infection is suspected, a HIV RNA test should be performed if antibody-based tests are non-reactive/negative. At the Screening visit, individuals will be deferred and referred for evaluation and care if they have any signs or symptoms consistent with acute (pre-seroconversion) HIV infection, or if they express a concern about recent HIV infection. Signs and symptoms consistent with acute HIV infection include fever (temperature >38° C), pharyngitis or a new rash. Evaluation of possible acute HIV infection prior to enrollment will be performed outside of the study, according to local 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 have further testing to confirm infection, as described in the SSP Manual.

Any enrolled participants who are confirmed to have acquired HIV infection during the study will permanently discontinue study product and will be followed at the regularly scheduled study visits. After Week 52, these participants will be followed every 12 weeks until the last study participant completes follow-up at the study site. Appendix 1B notes the additional laboratory tests to be completed at time of diagnosis and at subsequent study visits. in participants with confirmed HIV infection, all protocol procedures will be completed with the following exceptions:

- Study drug supply and associated counseling
- HIV testing
- Specimen collection related to drug tolerance (BUN/creatinine, creatinine clearance, urine protein and glucose) and/or adherence (plasma, lysed PBMC, and DBS for Pharmacology testing). Note

that plasma will still be stored for QC/Virology testing and urine will still be stored for substance use testing.

HIV-infected participants will be followed to contribute information regarding HIV outcomes after PrEP exposure, to maintain confidentiality, and to comply with expectations of communities. These participants will receive counseling and facilitated referrals for HIV treatment and care according to local guidelines. Records will be maintained to describe participants' progress in HIV care through the year as described below.

6.9 Concomitant Medications

With the exception of medications listed as prohibited (see below, this section), enrolled study participants may use concomitant medications during study participation. All concomitant medications, including prescribed and over-the-counter preparations, vitamins and nutritional supplements, recreational drugs and herbal preparations reported within 45 days prior to confirmation of eligibility for study enrollment and throughout the course of the study will be recorded on the CRF designated for that purpose. Medications used for the treatment of AEs that occur during study participation will also be recorded on applicable study CRFs. Participants who begin taking any medication during the trial that is listed as an exclusionary medication at Screening will temporarily discontinue study drug. Study drug may be resumed if no exclusionary medication has been taken in the last 4 weeks, if serum creatinine is within 1.3-fold above baseline, and if HIV testing is non-reactive/negative.

Should participants report use of any of the following medications, they will be required to discontinue use of study drug: interleukin therapy, medications with significant nephrotoxic potential (including but not limited to amphotericin B, aminoglycosides, cidofovir, foscarnet and systemic chemotherapy), and medications that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid).

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is an open-label, three-site, prospective, uncontrolled demonstration project that aims to assess the initiation, acceptability, safety, and feasibility of daily PrEP for BMSM in three U.S. cities utilizing C4 models. HIV-uninfected BMSM aged 18 and over and at risk for HIV infection will be recruited and enrolled. Each participant will be offered daily PrEP and followed up to 52 weeks. Participants will be followed at the specified study time points and will be evaluated for side effects, renal toxicity, adherence, risk behavior and HIV-seroconversion.

Primary Endpoints: The primary endpoints of this study are the initiation of and adherence to PrEP.

Initiation of PrEP

The timing of initiation of PrEP and correlates will be documented in either study CRFs or ACASI. A manual will be created for all sites to follow when introducing PrEP to participants based on safety and efficacy language found in the ICF under "Study Purpose".

Adherence to PrEP

Adherence will be assessed via self-report (ACASI), PBMCs and plasma concentration. Specifically, biological assessments of adherence will be objectively measured by obtaining plasma, and lysed PBMCs at specified study visits. Plasma will be assayed for TFV and FTC. PBMC will be assayed for TFV-DP and FTC-TP. Assay results will be compared to best available standards (e.g., results from directly observed dosing study results like STRAND or HPTN 066) to estimate level of adherence. Plasma and PBMC will be compared. A detailed analytical plan such as Bland-Altman plots and kappa statistics to measure concordance/discordance between different measures of PrEP adherence will be developed in a separate analysis plan.

Secondary Endpoints: The secondary endpoints of this study include the following:

Sexual risk-taking behavior

Sexual risk-taking behaviors will be measured by ACASI assessments performed at baseline and then at follow-up visits.

Reasons BMSM choose to initiate or refuse PrEP

Refusal rates will be measured by ACASI assessments conducted at enrollment and follow-up visits, which will be supplemented by acquiring information about core reasons for initiating or refusing PrEP, based on the individual interview qualitative data from participants.

Incident HIV-seroconversions and characteristics

HIV testing will be performed with confirmation if necessary at all study visits per procedures outlined in the SSP. HIV RNA and genotyping will be performed at the NL on samples confirmed to be HIV infected.

Adverse events

Measurement of AEs will be graded via the DAIDS Toxicity Grading System determined by review of reported adverse events (clinical and laboratory) during the study.

Sexually transmitted infections (STIs)

STIs will be measured at baseline, monthly for the first three months and then at quarterly visits. Tests will include rectal and urine GC/CT, and NAAT for syphilis and chlamydia.

Participant perception of care and referral plans

Participant Perception of care and referral will be assessed via interviewer-administered questionnaire at Weeks 13, 26, 39 and 52.

Exploratory endpoints:

Dried Blood Spots Assessment

To assess PrEP adherence via DBS assessment of study drug and anabolite concentrations for TFV, FTC, FTC-TP and TFV-DP using semi-quantitative methods, and to compare it with adherence measured by drug concentrations in plasma and PBMC. Semi-quantitative methods will be used given the lack of known precision of the current DBS analytical methods and present/not present interpretations may be needed. Use of DBS testing for off-study ARV drug use may also be explored.

ARV Testing using a Multi-drug Screening Assay
Stored plasma samples will also be tested using a high-throughput multi-drug ARV screening assay. Results from this assay will be compared to other Pharmacologic assessments of adherence, and to assess off study ARV drug use.

Cost Characterization
Since the intervention may provide good value for the money spent (e.g., the cost of a vaccine vs. the cost of treating those who are infected), cost characterization will be described regarding space and staff needs for administering PrEP.

7.2 Sample Size Consideration

A total sample size of 225 BMSM participants will be recruited into the study. Each participant will be enrolled to receive C4 and offered daily PrEP for at least 12 months.

According to the primary objective, two primary endpoints are considered: (1) PrEP initiation measured by the acceptance rate of the BMSM who are offered PrEP, and (2) PrEP adherence measured by the percentage of PrEP adherence among the BMSM who choose PrEP.

For the PrEP initiation endpoint, Table 3 lists the two-sided 95% confidence intervals for the true percentage of the PrEP acceptance rate for the BMSM who are offered PrEP. For example, if the observed PrEP acceptance rate is 50%, then there is 95% chance that the range of 44% - 57% will contain the true PrEP acceptance rate.

Table 2: 95% Confidence Intervals for the True PrEP Initiation Given by Possibly Observed PrEP Percentages

N	Observed PrEP Acceptance Rate	95% CI for True PrEP Acceptance Rate
225	33%	(27%, 39%)
	50%	(44%, 57%)
	67%	(61%, 73%)

For the PrEP adherence endpoint, Table 4 lists the two-sided 95% confidence intervals for the true percentage of the PrEP adherence rates for the BMSM who actually receive PrEP, assuming a 10% to 20% loss-to-follow-up (e.g. including those lost due to incarceration) during the 12-month period. For example, if the PrEP acceptance rate is 50% and an observed adherence rate is 67%, then there is 95% chance that the range 58%-76% will contain the true PrEP adherence rate.

Table 3: 95% Confidence Intervals for the True PrEP Adherence Rate Given by Possibly Observed PrEP Adherence Percentages

PrEP Acceptance Rate	PrEP Adherence Rate	95% CI for True PrEP Adherence Rate

		10% LTFP*	20%LTFP*
33% (low)	33%	(22%, 44%)	(21%, 45%)
	50%	(38%, 62%)	(37%, 63%)
	67%	(56%, 78%)	(55%,79%)
50% (moderate)	33%	(24%, 42%)	(23%, 43%)
	50%	(40%, 60%)	(39%, 60%)
	67%	(58%, 76%)	(57%,77%)
67% (optimistic)	33%	(25%, 41%)	(25%,41%)
	50%	(42%, 58%)	(41%,59%)
	67%	(59%, 75%)	(59%.75%)

*LTFP: Loss-to-Follow-up

7.3 Data Analysis

7.3.1 Primary Analyses

- To assess initiation and adherence of daily PrEP among BMSM who are offered PrEP. PrEP acceptability will be assessed by the acceptance/refusal rate of PrEP. PrEP initiation will be measured by time-to-PrEP initiation. The measure of initiation can be a participant's use of PrEP at any point in the study. Acceptance and refusal rates will be calculated, with 95% exact or normally approximated binomial confidence intervals. Acceptance and refusal rates will also be calculated by age, education, site, and risk practices. In addition, to identify correlates associated with refusal, we will use backward stepwise multivariate logistic regression models to examine statistically significant factors. Predictiveness of associated factors will be summarized by respected ROC curves. Kaplan-Meier plots will be used to characterize time to PrEP initiation, overall and by age, education, and risk group.

- To assess adherence and persistence to PrEP among participants in the demonstration project. PrEP persistence time is defined as the time from PrEP start to PrEP discontinuation. A PrEP discontinuation is considered to have occurred if a participant self-reported via ACASI to miss the PrEP doses for 30 or more consecutive days, for reasons other than a medication hold instituted by a clinician.. Kaplan-Meier plots will be used to characterize time to first discontinuation, as well as time to restarting PrEP among discontinuers, both overall and by age, education, and risk group. Among those continuing on treatment, we will consider the so-called medication possession ratio, defined as the number of tablets dispensed divided by the number of days between visits, a measure that performed best as an indicator of drug exposure in the iPrEx study. Adherence patterns of interest (e.g., intermittent use only before planned exposures) will also be assessed by self-report, and their prevalence characterized by reporting period. Tablet-taking practices will also be evaluated by drug detection rates in biological samples. Concordance between quantitative adherence measures based on self-report and pharmacological measures will be assessed using Bland-Altman plots; concordance of binary measures of drug detection will be assessed using the Kappa statistic. PrEP persistence times will be analyzed by multiplicative Andersen-Gill counting processes models.

7.3.2 Secondary Analyses

Analyses for secondary objectives will be mostly descriptive. Line listings as well as summary descriptive statistics including means, medians, and proportions with 95% exact or asymptotic confidence intervals as appropriate at each visit, will be used for the following secondary objectives. Specifically,

- Use GEE or random effects models to describe longitudinal patterns and their correlates of PrEP initiation and adherence among participants (e.g.: C4, substance use, sociodemographics, sociocultural factors, risk practices and incarceration)
- To describe side effects and toxicities of PrEP among participants in the PrEP demonstration project. AEs will be tabulated, overall and by grade. For any reasonably common AEs (> 20 events), exploratory analyses will be conducted to assess correlates of the AE, including demographics and duration and patterns of PrEP use, within the limits imposed by the small expected number of events.
- Describe and produce summary plots for longitudinal changes in sexual risk-taking behavior among study participants
- List and summarize reasons BMSM choose to initiate or decline PrEP
- List and summarize HIV seroconversions and characteristics of the infection(s) (e.g., viral set point, drug resistance patterns) in participants who initiated PrEP
- Use Kappa-statistics to assess agreement of adherence under different measures.

7.3.3 Qualitative Data Analyses

Qualitative data analyses will be conducted on an ongoing basis in collaboration with data collection. Thematic coding will be used to analyze the data from the individual interviews based on a grounded theory approach. The Consensual Qualitative Research Method (CQR) will be used by the study team to analyze the data. The CQR method provides a reliable, systematic, and rigorous method in conducting qualitative data analyses - recognizing the importance of context, incorporating an inductive analytic process, using a team and making decisions by consensus, using auditors, and verifying results by systematically checking against the raw data. The key elements of conducting qualitative data analyses using the CQR method include: (1) develop and code domains, (2) construct core ideas, and (3) develop categories to describe consistencies across cases (cross analysis).

8.0 HUMAN SUBJECTS CONSIDERATIONS

This protocol and the template informed consent form(s) contained in Appendix II and any subsequent modifications will be reviewed and approved by the HPTN SRC and DAIDS Prevention Science Review Committee (PSRC) 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 will also 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 may 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 reviews to the DAIDS Protocol Registration Office, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

8.1 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 template in Appendix II 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.

Literate participants will document their provision of informed consent by signing their informed consent forms. Any other local IRB requirements for obtaining informed consent from non-literate persons will also be followed.

Participants will be informed that they can decline to participate without any change in their relationship with their local Department of Public Health or STD clinic. They will also be informed that they can quit the study at any time.

8.2 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.

8.3 Confidentiality

All study-related information will be stored securely at the study site and/ or collaborative partner. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, and study data-collection, process and administrative forms will be identified by a coded number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored with restricted access according to local SOPs. All local databases will be secured with password-protected access systems.

Participant 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., representatives of the HPTN CORE, SDMC, and/or NL, 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.

8.4 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.

8.5 Study Discontinuation

The study may be discontinued at any time by NIAID, NIDA, the HPTN or Gilead Sciences, Inc., other government or regulatory authorities (e.g.,OHRP), or site IRBs.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

As described in Section 5, specimens will be processed at the local site laboratories (LL) with tests that include HIV testing (e.g., HIV screening tests, HIV confirmatory tests; HIV RNA tests); hepatitis testing (HBsAg, HBsAb, HBCoreAb, anti-HCV Ab), CBC with differential, chemistry tests (BUN, creatinine, calculated creatinine clearance, hepatic function tests [ALT and AST, total bilirubin], STI tests (syphilis testing following local standards, urine for NAAT for GC/CT, rectal swabs for NAAT for GC/CT [rectal NAAT for GC/CT can also be done at the HPTN Network Lab if this testing is not available at the study site]), urine dipstick for protein and glucose. Specimens will also be collected and processed for Pharmacology testing (plasma, lysed PBMCs, DBS). Urine will be collected to test for substances of abuse.

Additional assessments will be performed for participants who acquire HIV infection during the study (see Appendix 1B), including CD4 cell count, HIV viral load, and HIV genotyping; additional specimens will also be collected for storage and analysis at the HTPN NL in these participants.

Testing will be performed in CLIA certified laboratories and/or CLIA waived locations, as appropriate. Laboratories must demonstrate successful participation in relevant External Quality Assurance (EQA) programs.

Participation in the Immunology Quality Assurance (IQA) and/or Virology Quality Assurance (VQA) programs is preferred, but is not required. Laboratories must demonstrate successful participation in the relevant EQA programs.

Each study site will adhere to standards of good clinical laboratory practice, and local standard operating procedures for specimen management including proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the SSP Manual.

9.2 Network Laboratory Specimens

As described in Section 5, specimens will be collected for testing at the HPTN Network Laboratory (NL):

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, suspected acute HIV infection).

Samples from participants who become HIV-infected during the study will be shipped to the HPTN NL for analysis for research purposes. This analysis may include HIV genotyping, HIV phenotyping, HIV subtyping, minority variants assays, or other tests to characterize HIV viruses and/or the host response to HIV infection. Results from individual participants obtained from this testing will not be returned to study sites or study participants.

9.2.2 Pharmacology

Analysis of ARV drug levels will provide an objective estimate of average adherence over a time period that varies with the matrix assessed. Plasma and lysed PBMC samples will be prepared in the LL and shipped to HPTN NL for Pharmacology studies. Specific information regarding sample preparation will be detailed in the SSP Manual. The levels of TFV and FTC in plasma and FTC-TP and TFV-DP in lysed PBMCs will be monitored at Weeks 8, 26 and 52. The specimens will be analyzed in batches at the end of the study, and will not be used for adherence counseling during this study. These assessments will be performed using assays that are approved and monitored through periodic proficiency testing (where available) by the Clinical Pharmacology Quality Assurance Committee (CPQA).

DBS samples will also be collected for assessment of RBC-associated study drug concentrations. Adherence to study drugs and off-study ARV drug use will also be assessed using a high-throughput multi-drug ARV screening assay.

9.2.3 STI Testing

NAAT of rectal swab specimens for GC/CT will be performed at the HPTN NL if these assays are not available at study sites.

9.2.4 Retrospective analysis of substances of abuse

Stored urine specimens will be tested for the presence of substances of abuse (SOA). This analysis will be performed retrospectively using batched samples. Data from individual study participants will not be returned to study sites or study participants.

9.3 Quality Control and Quality Assurance Procedures

The clinical sites will document that their clinical laboratories are certified under the Continuous Laboratory Improvement Act of 1988 (CLIA) and/or participate in DAIDS-sponsored EQA programs. HPTN NL staff will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control (QC) procedures, including proper maintenance of laboratory testing equipment and use of appropriate reagents. HPTN NL staff will follow up directly with site staff to resolve any QC or quality assurance (QA) problems identified through proficiency testing and/or on-site assessments. Throughout the course of the study, the HPTN NL will select a random sample of stored specimens to test for QA purposes. HPTN NL staff will follow-up directly with site staff to resolve any QA problems identified through this process.

9.3.1 QC for HIV diagnostic testing

The HPTN NL will perform HIV diagnostic testing for QC.

Before performing HIV diagnostic testing, all sites must validate their testing algorithm, and the validation study must be approved by the HPTN NL. Local laboratories will perform testing for HIV diagnosis at Screening, Enrollment and other scheduled visits. Algorithms for HIV diagnostic testing will be provided in the SSP Manual.

The HPTN NL must approve the testing algorithm at each site prior to study activation and/or when a site needs to change a kit or test method. Participants who have any reactive or positive HIV test result at the Screening visit are not eligible for study enrollment, even if subsequent testing indicates that they are not HIV infected. If a participant has a reactive screening test at Enrollment, HIV infection status will be confirmed using local HIV testing guidelines. Participants who have a reactive HIV test result at any other study visit will have further testing performed following procedures 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, testing will be performed using an HIV RNA test. Regardless of whether HIV RNA testing is used for diagnostic testing, HIV infection must be confirmed in all cases using two independent samples.

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. Viral load testing will be performed in HIV-infected participants at the visit when HIV infection is confirmed, and at subsequent study visits, as described in Appendix 1B. Note that this is distinct from use of qualitative HIV RNA testing performed to determine HIV infection status (see above). Sites must use a CLIA-certified laboratory that participates in an EQA program; VQA program participation is recommended.

9.3.3 QC for CD4 cell count determination

For participants who become HIV-infected during the study, CD4 cell count testing will be performed at the time when HIV infection is confirmed and at subsequent study visits, as described in Appendix 1B. Sites must use a CLIA-certified laboratory that participates in an EQA program; IQA program participation is recommended.

9.4 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 U.S. CDC. All infectious specimens will be transported in accordance with U.S. regulations [42 Code of Federal Regulations (CFR) 72].

9.5 Sample storage

Selected samples from HIV seroconverters and other participants will be shipped to the HPTN NL. At the discretion of the HPTN NL, samples may be transferred to a DAIDS-approved repository. Other specimens will be stored at study sites and shipped to the HPTN NL upon request.

Study site staff will store all plasma, lysed PBMC, urine, and DBS samples collected in this study until all protocol-related testing has been completed, including QC testing and other testing performed at or coordinated by the HPTN NL. The study site will be informed by the SDMC when shipments to the NL are required and will be instructed which samples to ship. In addition, study participants will be asked to provide written informed consent for their blood and urine specimens to be stored after the end of the study for possible future 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.

10.0 ADMINISTRATIVE PROCEDURES

10.1 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local IRB/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Services Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) *WILL* be reviewed and approved by the DAIDS PRO and 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.

10.1.1 Protocol Amendments

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

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

10.2 Study Activation

Pending successful protocol registration and submission of all required documents, CORE staff will "activate" the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

10.3 Study Coordination

Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement executed by DAIDS and Gilead Sciences, Inc.

Study implementation will be directed by this protocol as well as the SSP manual. The SSP manual - which will contain reference copies of the *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* as well as the DAIDS Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, dates January 2010 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 CRFs and other study instruments will be developed by the protocol team and HPTN SDMC. Data will be transferred to the HPTN SDMC for data entry, cleaning, reporting and analysis. Quality control reports and queries will be generated and distributed to the study sites on a routine schedule 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 by the HPTN Study Monitoring Committee. The Protocol Chair, DAIDS Medical Officer, Protocol Biostatistician, SDMC Project Manager and CORE 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., ICFs, clinic and laboratory records, other source documents, CRFs), 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, SDMC, NL, NIAID, Gilead Sciences, Inc., and U.S. government and regulatory authorities. A site-visit log will be maintained at the 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)/EC(s) and the DAIDS Regulatory Support Center (RSC) prior to implementing the amendment.

10.6 Investigator's Records

The study site investigator will maintain and store in a secure manner, complete, accurate and current study records throughout the study. The investigator will retain all study records for at least three years after submission of the CTU's final Financial Status Report to DAIDS, which is due within 90 days after the end of the CTU's cooperative agreement with DAIDS, unless otherwise specified by DAIDS or the HPTN CORE. 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 for and/or enrolled in the study — including informed consent forms, locator forms, CRFs, 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 the HPTN Manual of Operations and policies. Any presentation, abstract or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, DAIDS and Gilead Sciences, Inc. for review prior to submission.

11.0 APPENDIX IA - SCHEDULE OF EVALUATIONS AND PROCEDURES

	Screening (up to Day -45)	Enrollment	Weeks 4[1] and 8	Week 13	Quarterly (Weeks 26, 39 and 52)
Administrative and Behavioral Evaluations/Procedures					
Informed Consent	x				X[2]
Locator information	x	x	x	x	x
Demographic information	x				
Social harms and AE assessment			x	x	x
Behavioral risk assessment (ACASI)		x		x	x
PrEP Discussion	x	x	x	x	x
C4 Case Conference		x		x	x
HIV/STI risk reduction counseling	x	x	x	x	x
Self-reported study product adherence assessment			x	x	x
Initial PrEP adherence readiness assessment[3]		x			
Study product supply[4]		x	x	x	x[5]
Autonomy Supportive Adherence Counseling		x	x	x	x[5]
PrEP Adherence Self-Regulation Questionnaire		x	x	x	x[5]
Client-Centered Care Coordination (C4)		x	x	x	x
Health Care Climate Questionnaire			x	x	x
Care Coordination Measurement Tool (provider administered)		x	x	x	x
Participant Perception of Coordination Questionnaire (self-administered)				x	x
Care Transition Measure					x[6]
PrEP Adherence Goal Setting		x	x	x	x[5]
Front Line Admin Staff Satisfaction					x[6]
Offer condoms and other prevention supplies	x	x	x	x	x
Individual Interview for selected participants					x[6]
Staff Focus Group (after all participants complete study)					x
Clinical Evaluations/Procedures					
Complete medical history including medications	x				
Interim medical history including concomitant meds		x	x	x	x
Symptom-Driven Physical Examination	x	x		x	x
Blood collection	x	x	x	x	x
Urine collection	x	x	x	x	x
Rectal swab collection	x				x[7]
NM ASSIST	x				x[6]
Discharge summary to primary provider if applicable at Week 52 or premature discontinuation					x
Hepatitis vaccination or referral, if indicated		x[8]			x[8]
STI treatment if applicable: syphilis	x				x[7]
STI treatment if applicable: gonorrhea and chlamydia	x				x[7]

Laboratory Evaluations/Procedures					
HIV diagnostic testing[9]	x	x	x	x	x
Hematology (CBC with differential)	x[10]				

Renal function tests (BUN, creatinine)	x		x[11]	x	x[12]
Calculated creatinine clearance	x		x[11]	x	x[12]
Hepatic function tests (ALT/AST, bilirubin)	x				
Hepatitis B status (HbsAg, HbsAb, HbcAb)	x				X[8]
Urine dipstick for protein and glucose	x	x[13]		x	x
STI testing: syphilis	x				X[7]
STI testing: rectal swab and urine NAAT for gonorrhea and chlamydia	x				X[7]
Plasma storage for Pharmacology testing[14]		x	x[15]		x[16]
Lysed PBMC storage for Pharmacology testing[14]			x[15]		x[16]
DBS storage for possible Pharmacology testing[14]			x[15]		x[16]
Urine storage for substance use testing		x	x	x	x
Plasma storage for QC and Virology testing	x	x	x	x	x

[1] Conduct a visit consisting of Week 4 procedures 4 weeks after initiating PrEP, or 4 weeks after a participant re-initiates PrEP.
[2] Individual Interview Informed Consent for selected participants at Week 52.
[3] May occur at any time through Week 48.
[4] Study drug supply and study drug counseling will begin when and if participants agree to begin PrEP.
[5] Weeks 26 and 39 only.
[6] At Week 52 only or on exit from study, if prior to Week 52.
[7] STI testing (syphilis, rectal swab and urine NAAT) are performed only at Screening and Weeks 26 and 52.
[8] For participants who do not have evidence of HBV immunity at Screening, a course of HBV vaccination will begin at Enrollment and continue until completed (some doses will be given at subsequent study visits). For participants who do not have evidence of HBV immunity at Enrollment, 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. In addition, for participants who do not have evidence of immunity at Enrollment, decline vaccination, and have not been diagnosed with HBV infection during the study, hepatitis testing (HbsAg, HbsAb, HbcAb) should be repeated at Week 52. If a participant acquires HBV infection during the study, stored samples may tested at the HPTN NL for HBV characterization and other HBV-related studies, including HBV resistance testing; these results will not be reported to study sites or participants.
[9] HIV diagnostic testing must be performed according to the algorithms provided in the SSP Manual. The HPTN NL should be consulted in any case where HIV infection status is unclear, one HIV test is reactive, HIV seroconversion is documented, or acute HIV infection is suspected. Additional assessments are required for participants with confirmed HIV infection (see Appendix 1B). 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.
[10] Repeat testing prior to initiating PrEP if participants decide to initatie PrEP post Enrollment.
[11] Renal function tests (BUN and creatinine) and creatinine clearance are not performed at Week 8.
[12] Renal function tests (BUN and creatinine) and creatinine clearance are only performed at Week 52 for participants who report that they have used PrEP in the previous 60 days.
[13] Repeat dipstick urine testing at enrollment if result from the Screening visit is > trace for either protein or glucose.
[14] Plasma and lysed PBMC will be collected for ARV drug testing. Plasma may also be tested using a high-throughput multi-drug ARV drug screen (qualitative testing). DBS will be collected for possible ARV drug testing, using assays that are in development. Plasma and DBS samples will be processed and stored for all participants; testing may be limited to a subset of these samples. Lysed PBMC samples will be processed and stored only for participants who report that they used PrEP within 60 days of sample collection.
[15] Week 8 only.
[16] Weeks 26 and 52 only.

NOTE 1: If any participant wishes to start or restart PrEP after enrollment, eligibility must be confirmed using all Screening criteria. If assessments performed at the Screening visit occurred more than 45 days earlier, all of these assessments, including laboratory tests, must be repeated (see Section 5).

NOTE 2: For participants who decide to initiate PrEP at or after Week 48, partnerships will be established as applicable with community partners in order to provide adequate clinical care and follow-up.

12.0 APPENDIX IB - ADDITIONAL PROCEDURES FOR PARTICIPANTS WITH CONFIRMED HIV INFECTION

	Time of diagnosis (confirmatory visit)	Weeks 4, 8, 13, 26, 39, and 52 (if after HIV diagnosis)	Every 12 weeks after Week 52[1]
Behavioral Risk Assessment (ACASI)	x	x[2]	x
CD4 cell count testing	x	x	x
HIV viral load testing	x	x	x
HIV genotyping[3]	x		
Additional plasma storage for HPTN NL testing[4,5]	x	x	x
Lysed PBMCs for Pharmacology testing[6]	x		

[1] Participants with confirmed HIV infection will continue in the study, off of study drug. Any participants who acquire HIV infection during the study will permanently discontinue study product and will be followed after Enrollment at regular visits until the last HIV-uninfected participant reaches Week 52 at that site.

[2] Excluding Weeks 4 and 8

[3] HIV genotyping will be performed in real-time at a laboratory that is used for clinical care at the study site; these results will be provided to the study site and participant. Additional resistance assessments/testing may be performed retrospectively using stored samples shipped to the HPTN NL; those results will not be reported back to study sites or participants.

[4] In addition to plasma stored at other scheduled visits, additional plasma aliquots must be stored at the time of HIV diagnosis (confirmatory visit) and other visits indicated in Appendix IB. Stored plasma samples from HIV seroconverters will be shipped to the HPTN NL; sites should store samples until they receive a request for shipping from the SDMC. These samples may be used for HIV diagnostic testing, QA testing, Pharmacology testing, resistance testing, and other testing (see footnote 5).

[5] Additional testing may be performed at the HPTN NL. At the discretion of the HPTN NL, this testing may be performed at another laboratory (e.g., at one of the study sites, at the U.S., CDC, or at another laboratory with special expertise). Results of this testing 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.

[6] If the time of HIV diagnosis (confirmatory visit) occurs at a visit where lysed PBMCs are not already being collected, they should also be collected at this visit for any participant who reports that he used PrEP within 60 days of the confirmatory visit.

13.0 APPENDIX II - SAMPLE INFORMED CONSENT FORMS

13.1 SAMPLE MAIN STUDY CONSENT FORM

Pre Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three US Cities
(HPTN 073)

Final Version 1.0
21 February 2013
DAIDS Document ID: 11894

Study Sponsors: NIH, Division of AIDS (DAIDS), U.S. National Institute of Allergy and Infectious Diseases (NIAID), and National Institute of Drug Abuse (NIDA). Study drug is provided by Gilead Sciences, Inc.

PRINCIPAL INVESTIGATOR: [Insert Name]
PHONE: [Insert Number]

INTRODUCTION
You are being asked to take part in a research study. This research study is for Black men who have sex with men who may be a risk for getting Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decide 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.

YOUR PARTICIPATION IS VOLUNTARY
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. That process is called informed consent.

This informed consent document gives information about the study that will be discussed with you. This consent form might contain some words that are not familiar to you. Please ask us to explain anything that you do not understand before you sign this form. 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.
- There may be no direct benefits for you if you participate in this study.
- There may be some risks with taking part 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 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.
- You might not be able to join this study if you are taking part in another study or were part of an HIV vaccine trial in the past. However, if you were in a vaccine trial in the past and can show proof that you did not receive the active vaccine, you will be allowed to take part in this study. If you are currently in an observational study that does not focus on HIV you may take part of this study, but we still ask you to let us know about other studies you are on in order to support you in meeting all study requirements.

PURPOSE OF THE STUDY

The main purpose of this study is to see how willing Black men who have sex with men are to take PrEP and how consistently they are able to take one tablet at approximately the same time during each day of the week, and what that experience is like for them. The study also hopes to describe various sexually transmitted infections (STIs) that participants may have and whether or not anyone who is enrolled in the study acquires HIV. Taking medications to prevent becoming HIV infected is sometimes called "pre-exposure prophylaxis" or "PrEP." The drug being used for PrEP in this study is called Truvada®. Truvada® is commonly used to treat HIV infection. Truvada® is a tablet that has two drugs in it. These drugs are called "emtricitabine" and "tenofovir". Truvada® is generally safe when used as treatment for HIV. Truvada® is not a cure for HIV or AIDS. When given together with other drugs, Truvada® may help to prevent or delay AIDS in people with HIV. On July 16, 2012, the United States Food and Drug Administration (FDA) approved oral PrEP using Truvada for prevention of HIV in adult men and women who are at risk of getting HIV through sex. The FDA recommended daily dosing based on published results from the iPrEx study and the Partner's PrEP study, which recommended daily use of the tablets. Actual use varied among participants. The optimal dosing regimen for PrEP has not been established. Whether Black men who have sex with men decide to take PrEP and whether they are adherent to a daily dosing strategy (taking one tablet at approximately the same time during each day of the week) is being evaluated in this study. **You do not have to accept PrEP (Truvada®) to be in this study, or you may decide to start taking or stop taking PrEP (Truvada®) at any time during this study.**

Providing MSM with Truvada for PrEP has been found to reduce the risk of HIV infection by approximately 44% effective. Other examinations of study data suggest that it can be as high as 92% effective when taken daily. How well PrEP does at preventing HIV depends a lot on people actually taking PrEP daily and when people take it less than that it is not as effective. Taking PrEP does not prevent pregnancy or other sexually transmitted infections. By way of comparison, condoms, when used consistently, are more than 95% effective in preventing HIV, syphilis, other sexually transmitted infections and can also prevent pregnancy.

One clear finding from these studies is that Truvada® can only provide protection if people take it consistently. It is important that all study participants try to take the tablets each day and preferably at the same time. If you cannot do this, you need to tell the study staff you are having difficulty taking the tablets. If you are having problems taking the tablets, or have concerns, or have decided not to take the tablets for personal reasons, please tell us. Telling us about your experience allows us to understand the most acceptable way to design and implement PrEP programs for Black men who have

sex with men. All participants in this study will be updated with any new information and findings that come out regarding PrEP studies. We encourage all participants to discuss any concerns about these studies, or the safety of Truvada®, with the study staff.

It is important to note that PrEP does not prevent sexually transmitted infections like syphilis, gonorrhea, or herpes. Using condoms for all intercourse is a good way to maintain your sexual health. Thus, it is important to continue using condoms from start to finish every time you have sex.

About 225 people will take part in this study at three different U.S. study sites. People in the study will be asked to take part in the study for a total of 52 weeks (approximately 1 year).

STUDY PROCEDURES

(Note to sites with participants from HPTN 061: We will transfer any applicable information (i.e. Demographics) from those study records to the records from this study.)

Screening visit: The first study visit is called the screening visit. The screening visit will take about *[insert local time]*. During this visit, we will ask you questions about your health, current medications and personal life to see if you are eligible to participate. You will be asked to provide your address and phone number(s). The staff will ask you for names of people who will always know how to find you and places where you can be found. If you use social media (Facebook, Twitter, etc.), we may ask whether we can contact you that way if we need to reach you. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff have important information for you. If we talk to people on this list, staff members introduce themselves as working on a health study in which the participant is enrolled. If we are unable to find you, we will also search publically available sources to find out if you are incarcerated (in jail or prison) or in the hospital. If you are not enrolled, this information will not be used for tracking you. It is for study purposes ONLY. (Site specific: You will also be asked for your Social Security Number, driver's license number and *xxxx identification number. Please remember that this information will only be used to locate you for the project sessions or interviews. This information will be used to look for you by searching public databases such as those for General Relief, Section 8 or the County Sheriff's Department. We will not share this information with anyone else. This information will be kept in a secure place. If you decide to provide your Social Security Number and/or driver's license number and/or your xxxx identification number you will be asked to sign a Release of Information form. Please remember that you can call the project office at any time to withdraw the use of your social security number, driver's license number or xxx identification number to locate you. You may call the project office at XXX-XXX-XXXX and verbally state that you wish to revoke access and use of your social security number or driver's license number or xxxx identification number. Your information will be immediately destroyed. We will not retain any electronic or hard copies of your release of information form or your social security number, driver's license number or xxxx identification number.)*

If you are not willing to give us this information, you should not agree to be in this study. We will ask you questions about your past medical history and what medications you are currently taking and provide you with a physical examination focused on any current health problems that you report.

You will be asked to complete an interview, using a computer, about your age and background, whether or not you have been recently incarcerated or are on parole, which drugs (legal and illegal) you take, and your sexual practices. This information does not include your name and will not be seen by study staff, police, or health departments. The information will be sent via a secure link to the main study database with only your Participant Identification Number with it. A counselor will talk to you about protecting yourself and your partner(s) from HIV and other diseases passed during sex (sexually transmitted infections, or "STIs"). We will offer you condoms and lubricant, and counsel you on how to use them safely. We will draw ~XX mL of blood (about X tablespoons). This blood will be tested for HIV, hepatitis B virus, and [insert other local testing as applicable]. Some of your blood will be stored in case it is needed later for tests related to this study. We will also ask you for a urine sample and take a rectal swab. Your blood, urine and rectal swab will be tested to assess your overall health, whether your liver and kidneys are working normally and whether you have any STIs that might need treatment. If your blood, urine or rectal swab shows that you have an STI, we will either treat you or refer you for treatment.

Study staff will inform you of the results of all tests we conducted. Some people may not be able to join the research study because of information they provide during the screening process or if it would not be safe for them to participate in the study. For example, if you are infected with HIV or active Hepatitis B, you will not be able to join. If any of your tests for HIV are initially positive, you will not be able to join, even if further testing shows that you do not have HIV infection. Please also tell us if you join another study after agreeing to take part in this one, as this may affect your health.

To protect your health, everyone who takes part in the study should be vaccinated for hepatitis B virus infection (unless you already have immunity to the disease). This is because the drugs used in Truvada® can also be used to treat hepatitis B virus and taking Truvada® now might result in less effective treatments for hepatitis B virus if you were ever infected. You will need to come back to get the results of the testing for hepatitis B virus. If you are not immune, you will be offered a vaccine against the hepatitis B virus. If you agree, we can give you the first vaccination or offer a referral. The hepatitis B follow-up visit will take about 30 minutes. You will receive the second vaccination or offer for referral about a month later and the third one about six months later. If you receive the vaccine at another location, you will need to bring in a copy of the medical record showing that you have been vaccinated. If you have active hepatitis B virus infection you cannot be in the study. If you later develop another form of hepatitis while in the study, you should let study staff know and stop taking the study drug. Study staff will examine you and most likely draw some blood to determine whether continued study participation is safe and in your best interests.

Enrollment visit: If you are eligible and agree to participate, you will be asked to come back to the clinic to start the study within 45 days of the time of your first laboratory blood draw at the Screening visit. This will be your Enrollment visit, which will take about [insert local time]. During this visit, we will ask you questions about any changes in your health and medications and give you a physical exam. Study staff will confirm your name and update your contact information and collect any updated medical history information.

We will again counsel you about HIV and STI infection, risks you may be taking, and how to avoid getting HIV or STIs. We will offer you condoms and lubricant and counsel you on how to use them safely. We will draw ~XX mL of blood (about X tablespoons) and your blood will be tested for HIV.

Some of your blood will be stored in case it is needed later for tests related to this study. These tests include testing to measure the levels of Truvada® or any other HIV treatment medications may be in your body and may not be done for a year or more after you have had your last study visit. The results will not be reported back to you or the study staff. Study staff will inform you of the results of all tests which affect your health while on study.

We will also collect a urine sample to test for your general health. Part of your urine sample will be stored and tested after your completion in the study for HIV medications or any legal or illegal drugs that you may be taking. These results will not be reported back to you, the police, health departments, or the study staff.

You do not have to accept PrEP (Truvada®) to be in this study. If you do decide to start taking PrEP, you will meet with staff to develop a plan to help you remember to take your Truvada® and be asked about your adherence and experiences taking Truvada®. Regardless of whether or not you are utilizing Truvada®, study staff will develop a plan of care and support that may include referral to health care services or people to help you with other needs you may have, such as mental health issues, housing, or drug or alcohol use. This plan will be centered on your needs. You will be given a supply of Truvada® to last until the Week 4 visit and counseled on how to take the tablets properly. It is important that you do not share your medications with anyone else, as it may harm them.

Weeks 4 and 8: Study visits for weeks 4 and 8 will last about [insert local time]. We will ask you questions about any changes in your health and medications. Study staff will confirm your name and update your contact information. We will ask you about anything that has happened as a result of your study participation.

A counselor will talk to you about protecting yourself and your partner(s) from HIV and other diseases passed during sex (sexually transmitted infections, or "STIs"). We will offer you condoms and lubricant and counsel you on how to use them safely. We will draw ~XX mL of blood (about X tablespoons) and your blood will be tested for HIV and [insert other local testing as applicable]. Some of your blood will be stored in case it is needed later for tests related to this study. These tests may include testing to measure the levels of Truvada® or any other HIV treatment medications may be in your body and may not be done for a year or more after you have had your last study visit. The results will not be reported back to you, the police, health departments, or the study staff. We will offer or refer you the last (third) round of the Hepatitis B vaccination if suitable.

If you do decide to start taking PrEP or have been taking PrEP, you will meet with staff to develop a plan to help you remember to take your Truvada® and be asked about your adherence and experiences taking Truvada®. Regardless of whether or not you are utilizing Truvada®, study staff will develop a plan of care and support that may include referral to health care services or people to help you with other needs you may have, such as mental health issues, housing, or drug or alcohol use. This plan will be centered on your needs. You will be given a supply of Truvada® to last until your next study visit (either Weeks 8 or Week 13) and counseled on how to take the tablets properly. It is important that you do not share your medications with anyone else, as it may have an effect on their health that is not being monitored.

We will also collect a sample of urine. Your urine and blood will be tested to assess your overall health

and whether your kidneys are working normally. Study staff will inform you of the results of all tests which affect your health. Part of your urine sample will be stored and tested after your completion in the study for any HIV medications or legal or illegal drugs that you take. These results will not be reported back to you, the police, health departments, or the study staff.

Week 13: The week 13 study visit will last about [insert local time here]. We will ask you questions about any changes in your health and medications. Study staff will confirm your name and update your contact information. We will conduct a physical examination focused on any current health problems that you report and ask you about anything that has happened as a result of your study participation. You will be asked to complete an interview, using a computer, about your age and background, whether or not you have been recently incarcerated or are on parole, which legal or illegal drugs you take, and your sexual practices. This information will not be available for review by study staff or health departments. The data will be uploaded and sent via a secure web link to the main study database with only your Participant Identification Number, not your name or other personal information.
A counselor will talk to you about protecting yourself and your partner(s) from HIV and other diseases passed during sex (sexually transmitted infections, or "STIs"). We will offer you condoms and lubricant and counsel you on how to use them safely. We will draw ~XX mL of blood (about X tablespoons) and your blood will be tested for HIV and [insert other local testing as applicable].
Some of your blood will be stored in case it is needed later for tests related to this study. These tests include testing to measure the levels of Truvada® or any other HIV treatment medications may be in your body and may not be done for a year or more after you have had your last study visit. The results will not be reported back to you or the study staff

We will also collect a sample of urine. Your urine and blood will be tested to assess your overall health and whether your kidneys are working normally. Study staff will inform you of the results of all tests which affect your health. Part of your urine sample will be stored and tested after your completion in the study for any HIV medications or legal or illegal drugs that you take. These results will not be reported back to you, the police, health departments, or the study staff.

If you do decide to start taking PrEP or have been taking PrEP, you will meet with staff to develop a plan to help you remember to take your Truvada® and be asked about your adherence and experiences taking Truvada®. Regardless of whether or not you are taking Truvada®, study staff will develop a plan of care and support that may include referral to health care services or people to help you with other needs you may have, such as mental health issues, housing, or drug or alcohol use. This plan will be centered on your needs. You will be given a supply of Truvada® to last until your next study visit (Week 26) and counseled on how to take the tablets properly. It is important that you do not share your medications with anyone else, as it may harm them.

Weeks 26, 39 and 52: Study visits at weeks 26, 39 and 52 will take about [insert local time]. During these visits, we will ask you questions about any changes in your health and medications. Study staff will confirm your name and update your contact information. We will conduct a physical examination focused on any current health problems that you report and ask you about anything that has happened as a result of your study participation. You will be asked to complete an interview, using a computer, about your age and background, whether or not you have been recently incarcerated or are on parole, which legal or illegal drugs you take, and your sexual practices. This information will not be available

for review by study staff or health departments. The data will be uploaded and sent via a secure web link to the main study database with only your Participant Identification Number.

We will again counsel you about HIV infection, risks you may be taking, and how to avoid getting HIV. We will offer you condoms and lubricant and counsel you on how to use them safely. We will draw ~XX mL of blood (about X tablespoons) and your blood will be tested for HIV, syphilis and [insert other local testing as applicable].

Some of your blood will be stored in case it is needed later for tests related to this study. These tests may include testing to measure the levels of Truvada® or any other HIV treatment medications may be in your body and may not be done for a year or more after you have had your last study visit. The results will not be reported back to you or the study staff.

We will collect a swab from your rectum and also collect a urine sample to test for two other infections passed during sex, Chlamydia and gonorrhea. Your urine and blood will also be tested to assess your overall health and whether your liver and kidneys are working normally. Study staff will inform you of the results of all tests which affect your health.

At the Week 52 visit, you will also be tested for hepatitis if you had no evidence of immunity to Hepatitis virus at the Screening visit, you chose not to have the Hepatitis vaccine, and you were not diagnosed with Hepatitis infection during the trial. If your results show that you have active Hepatitis infection, you will be referred for clinical care.

If you do decide to start taking PrEP at or prior to Week 48 or have been taking PrEP, you will meet with staff to develop a plan to help you remember to take your Truvada® and be asked about your adherence and experiences taking Truvada®. Regardless of whether or not you are utilizing Truvada®, study staff will develop a plan of care and support that may include referral to health care services or people to help you with other needs you may have, such as mental health issues, housing, or drug or alcohol use. This plan will be centered on your needs. You will be given a supply of Truvada® (except at Week 52) to last until your next study visit (Weeks 39 or 52) and counseled on how to take the tablets properly. It is important that you do not share your medications with anyone else, as it may have an effect on their health that is not being monitored. The tablets will no longer be available to you as part of the study to "start" after Week 48. This is in order to ensure that study staff have the proper amount of time to assess whether or not the tablets are safe for you to take. *(Insert as locally applicable) If you decide to start taking Truvada as PrEP at or after Week 48, we will coordinate your care with a local provider so that you can safely take the medication all the way until the end of the study (Week 52). If this happens for you, we will ask you to provide us your approval to access your medical records at the local provider through the end of Study Week 52 so that we can document your safety.*

At Week 52, you may be asked to participate in an interview with a member of the site staff regarding factors that helped or hindered you for starting (or not), liking and adhering to PrEP.
During Week 52 (or study exit) you will not receive additional adherence counseling or Truvada® tablets. We will provide you with a care transition plan and ask you questions related to your overall study participation.

We will also collect a sample of urine. Your urine and blood will be tested to assess your overall health and whether your liver and kidneys are working normally. Study staff will inform you of the results of all tests which affect your health. Part of your urine sample will be stored and tested after your completion in the study for any legal or illegal drugs that you take. These results will not be reported back to you, the police, health departments, or the study staff.

Note: For any study visit, staff may need to draw additional blood as part of evaluation of abnormal test results or to confirm test results.

What if your blood shows that you have HIV?
At every visit, we will give you the results of your HIV testing. If you have a test result at any study visit that indicates you may have been infected with HIV, we will arrange to confirm the test result and ask that you stop taking the study medication (Truvada®), but ask that you continue to come to the study clinic as scheduled. When you come back, the staff will discuss your test results with you. They will refer you for care if the tests confirm that you are infected. Sometimes an HIV test result is not clearly positive, but is also not negative. In that case (and also if your HIV test results are positive), we will collect some more blood (about xx mL) and test it again until we know for sure whether or not you are infected with HIV.

If the confirmatory tests show that you do have HIV infection, we will perform tests to see how well your body can fight off infections and measure the amount of virus in your blood. In this case, we will test your blood to see the effect taking Truvada® had on your HIV infection before you stopped. [Insert any additional local testing that may be performed and any local reporting requirements.] We will also refer you for HIV treatment and care and would like to continue following you to assess your health at the normally scheduled visits through Week 52 and beyond until all participants have completed 52 weeks of follow-up at this site. As part of your health monitoring we will draw additional blood (XX mL) in order to see whether your body is maintaining normal immune function as well as to look at the HIV virus itself. We may also look at your immune response to HIV infection. This may mean that we would like to monitor your health an additional year as long as you are willing and able. Additionally, we will perform genetic testing on the virus itself. We will NOT perform any genetic testing on you. The genetic testing of the virus will not be reported back to you or clinic staff.

Incarceration
If you are incarcerated (put in jail, prison, or correctional facility) at any time during the study, we will not attempt to conduct study follow-up while you are incarcerated. But we would like for you to inform us when you are released so that you can resume your study participation if you are still within your study period (52 weeks from enrollment). If, during the study, we are unable to contact you and don't know where you are, we would like to check publicly available databases to see if you might be incarcerated. These databases can also report when people are expected to be released, which helps us know when to contact them. You will be asked at the end of this consent to say whether or not you give us permission to check these databases to see if you have been incarcerated, and if so, when you will be released.

How Will Your Samples Be Used?
As part of the study we will collect rectal swabs and samples of your blood and urine. These samples will be used for a number of laboratory tests for your safety and measurements of study drug in your body. Samples of your blood and urine will be sent to designated laboratories in the U.S. for further testing related to potential or confirmed HIV infection, and the potential presence of HIV medications including Truvada® and legal or illegal drugs. There may be some leftover samples of blood and urine samples after all of the study-related testing has been completed. We would like to use these samples for future research studies to develop new HIV tests, HIV vaccines and treatments. If you agree to this use of your samples, we will ask you to check a box the end of this form.

If you do not agree to have your left over samples stored, you can still be in this study. If you agree to store your samples but change your mind later, you can contact study staff. We will then destroy your samples. If you agree, your left over samples will be stored indefinitely [insert local guidelines]. Any future use or the ability to store your samples longer needs to be reviewed and approved by the NIH and local authorities. If these studies involve other laboratories, we will need approval from your local authorities to store or transfer them elsewhere. Your left over samples will not be sold or used for commercial reasons.

RISKS AND/OR DISCOMFORTS

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.

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.

HIV Resistance
If you become infected with HIV, there is a risk that the HIV you have become infected with could become "resistant" to Truvada®. This may then mean that you may not be able to be treated with Truvada® nor the drugs which are combined together to make Truvada® (Tenofovir and Emtricitabine). Viral drug resistance to these drugs can also cause cross resistance (meaning your virus is also resistant to other drugs as well as the drugs in Truvada ®) to more commonly used drugs such as Lamivudine (3TC). Your doctor would need to prescribe different drugs which are used to treat HIV infection. These other drugs may have more side effects or may be less easy to take than a treatment that has Truvada®. Truvada® alone is never enough for treatment of HIV infection, so additional drugs are always needed for treatment. If you become infected, we will perform a blood test to see if there is any evidence of resistance to Truvada®.

Study Drug Side Effects
Truvada® may have side effects, some of which are listed below. Please note that this list does not include all the side effects seen with this drug. This list includes the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional Truvada® 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 in HIV negative people.
The following side effects have been associated with the use of Truvada®:

- Allergic reaction. Participants should report the following symptoms to the site medical doctor immediately should they arise:
    - Fever
    - Rash
    - Upset stomach
    - Vomiting,
    - Loose or watery stools
    - Abdominal pain
    - Achiness
    - Shortness of breath
    - A general feeling of illness
    - A potentially serious swelling of the face, lips, and/or tongue
- Runny nose
- Gas
- Itching
- Headache
- Dizziness
- Depression
- Increased cough
- Shortness of breath
- Generalized weakness or tiredness
- Abdominal pain
- Upset stomach (nausea) or vomiting
- Loose or watery stools

- Muscle pain and muscle weakness
- Inability to sleep, unusual dreams
- Skin darkening of the palms and/or soles
- 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
- Inflammation or swelling and possible damage to the pancreas and liver
- Increased triglycerides
- Increased creatine phosphokinase (CPK), which could mean muscle damage
- Worsening or new kidney damage or failure
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage

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 Truvada® is stopped.

Other Possible Risks
We do not know if there are other risks if you use herbal treatments or supplements while you are using Truvada®. 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.)]

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 or other harms may occur. Truvada® does not contain HIV and cannot cause HIV infection.

BENEFITS
We will test you for HIV infection 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, 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.

Please note that if you withdraw from the study prior to your scheduled Week 52 visit, we will ask you to have a final evaluation visit.

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, emtricitabine, tenofovir, and/or the combination tablet, Truvada (TDF+FTC), are all available by prescription from your healthcare provider to treat HIV infection and the FDA has recently approved Truvada (TDF +FTC) for the prevention of HIV.

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. 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 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. 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 National Institutes of Health (NIH)
- the United States Department of Heath and Human Services (DHHS), Office of Human Research Protection (OHRP)
  - [insert names of applicable IRBs]. An IRB ensures adherence to all federal, state, local and institutional regulations concerning the protection of human subjects in rresearch.
- study staff
- study monitors
- Gilead Sciences, Inc., the company that makes the study drugs

[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].

Pre Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three US Cities
(HPTN 073)

Final Version 1.0
21 February 2013
DAIDS Document ID: 11894

US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)
US National Institute for Drug Abuse (NIDA)

Sponsor: NIAID, NIH and NIDA

INFORMED CONSENT FORM

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

SIGNATURE PAGE
Samples Stored for Future Testing
Blood:

_____ My initials indicate that any leftover blood samples may be stored for future testing after study-related testing has been completed.

_____ I do not agree to allow left over blood samples to be saved for long-term storage and future testing after study-related testing has been completed.

_____ If I am incarcerated at any time during the trial, I agree to let study staff contact the local authorities to confirm my presence and release date in order to contact me for follow-up.

_____ If I am incarcerated at any time during the trial, I do not agree to let study staff contact the local authorities to confirm my presence and release date in order to contact me for follow-up.

Note: We ask that you contact site staff immediately upon your release if you have been incarcerated. This is so that we may follow-up on your health and coordinate any necessary care.

Urine

_____ My initials indicate that any leftover urine samples may be stored for future testing after study-related testing has been completed.

_____ I do not agree to allow left over urine samples to be saved for long term storage and future testing after study-related testing has been completed.

As discussed above, we would like to get your Social Security Number, driver's license number and xxxx identification number.

Please check the appropriate box below and initial:

Are you willing to provide us your Social Security Number which will help us to locate you?
Yes__ No ____

Are you willing to provide us your Driver's License number which will help us to locate you?
Yes__ No ____

Are you willing to provide us your state or other Identification number which will help us to locate you?
Yes__ No ____

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.

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

13.2 SAMPLE QUALITATIVE INDIVIDUAL INTERVIEW INFORMED CONSENT FOR SELECTED STUDY PARTICIPANTS

Pre Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three US Cities
(HPTN 073)

Final Version 1.0
21 February 2013
DAIDS Document ID: 11894

Study Sponsors: NIH, Division of AIDS (DAIDS), U.S. National Institute of Allergy and Infectious Diseases (NIAID), and National Institute of Drug Abuse (NIDA). Study drug is provided by Gilead Sciences, Inc.

PRINCIPAL INVESTIGATOR: [Insert Name]
PHONE: [Insert Number]

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

Introduction

You have been invited to have an individual interview with a study counselor to discuss your participation in the HPTN 073 study. We are interested in learning about your thoughts, opinions, and experiences with being a part of the study. We would like to talk with you about topics such as healthcare, HIV/STI testing, and your community. We also are interested in learning about your thoughts and opinions about PrEP, including your experiences if you are taking PrEP. PrEP means Pre Exposure Prophylaxis. People take PrEP or medications to help prevent them from becoming infected with HIV. We hope that the information learned from this study will help us to better understand the health needs of Black men who have sex with men (MSM).

What Will Happen During This Study?

If you decide to be in this study, you will be asked to have a 60 to 90 minute interview with a study counselor. The interview will be at a location identified by study staff to assure adequate privacy and confidentiality. The information that you share during the interview will be treated confidentially. There will be no cost to you for participation.

During the interview, you will talk with a study counselor about different questions like:

- Please tell me about your experiences with the study so far?
- What experiences have you had with HIV testing before joining the study?
- What do you think are the HIV prevention needs of Black men who have sex with men in your community?

The interview will be recorded to help us get the best understanding possible from the interview. This recording will be used to make a written transcript of the interview. The recording and transcript will only have a Participant ID number. Your name or any other identifying information about yourself that you mention during the interview will not be associated with your responses. All identifying information will be removed from the transcript. These recordings will be destroyed after all analysis is completed.

You will receive [insert local amount] for your time and effort with the interview.

Your participation in this interview is voluntary. You are not required to participate in this interview in order to remain in the rest of the study (HPTN 073). Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions.

Please also understand that you may stop your participation completely at any time. For example, if any of the questions make you upset either you or the interviewer may stop the interview at any time. You will also be provided with contact and referral information if any of the questions raise issues that you would like to talk about at a later time. You will not lose any of the regular benefits of your regular medical care at [study clinic].

[To be modified to reflect site practices: The interview will take place in a location that the study staff have determined will provide you with privacy and confidentiality such as the clinic, or other appropriate places. The study team will talk with you about this so you know where to go for the interview.

What Are the Potential Benefits?
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.

What Are the Possible Risks or Discomforts?
To minimize any discomfort and to protect your privacy, the interview will take place in a private area that will allow you to speak comfortably without being overheard. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time. The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

How Will Your Privacy Be Protected?
Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study.

All identifying information will be removed from the transcripts, and only the research team and the transcribers will have access to the audio interview data. Audio recordings of interviews will be destroyed within three years of study completion.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH), US NIMH) and their representatives, ***[insert name of site]*** IRB, study staff, study monitors and [insert applicable local regulatory authorities].

We cannot guarantee absolute confidentiality. 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. Any publication of this study will not use your name or identify you personally.

People who may review your records include: the ***[insert name of site]*** IRB, National Institutes of Health (NIH), study staff, study monitors, and drug companies supporting this study. Also, 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.

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.]

What Are Some Reasons Why You May Be Withdrawn From This Activity Without Your Consent?

You may be withdrawn from the study without your consent for the following reasons:

- The research study, or this part of the study, is stopped or cancelled before you participate.

- The study staff feels that completing the study or this part of the study would be harmful to you or others.

Persons to Contact for Problems or Questions

For questions about this study or a research-related injury, 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 as a research participant, contact:

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

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.

Pre Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three US Cities
(HPTN 073)

Final Version 1.0
21 February 2013
DAIDS Document ID: 11894

US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)
US National Institute for Drug Abuse (NIDA)

Sponsor: NIAID, NIH and NIDA

QUALITATIVE INDIVIDUAL INTERVIEW INFORMED CONSENT FOR SELECTED STUDY PARTICIPANTS

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

SIGNATURE PAGE

If you have either read or have heard the information in this consent form, if all of your questions have been answered and if you agree to take part in the Interview, please sign your name on the line below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date

13.3 SAMPLE FOCUS GROUP INFORMED CONSENT

Pre Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three US Cities
(HPTN 073)

Final Version 1.0
21 February 2013
DAIDS Document ID: 11894

US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)
US National Institute for Drug Abuse (NIDA)

Sponsor: NIAID, NIH and NIDA
FOCUS GROUP INFORMED CONSENT FORM– STUDY STAFF

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

Introduction
You have been invited to take part in a focus group with other C4 staff from HPTN 073. The focus group will be led by a trained and experienced group leader. We are interested in learning about your thoughts, opinions, and experiences with being a part of the study, including talking with you about the C4 model that is being used in the study. We hope that the information learned from this study will help us to better understand the health needs of Black men who have sex with men (MSM).

What Will Happen During This Study?
If you decide to be in this study, you will be asked to participate in a 60 to 90 minute focus group with a trained and experienced group leader. The focus group leader will be a member of the study team that you did not work with during the study. Each of the three sites for HPTN 073 will conduct one focus group with the C4 team at the end of the study to elicit feedback on what resources they believe were necessary to optimally implement a C4-based PrEP program. This will include (1) resources that were available onsite (2) resources that were available in the community, (3) resources that were not available during the course of the study, and (4) discussion of how resources would have improved their ability to provide care.

The focus group will be at a location identified by study staff to assure adequate privacy and confidentiality. The information that you share during the focus group will be treated confidentially. There will be no cost to you for participation.
The focus group will be recorded to help assure that we get the best understanding possible from each focus group. This recording will be used to make a written transcript of the interview. The recording and transcript will only have a Participant ID number. Your name or any other identifying information about yourself that you mention during the focus group will not be

associated with your responses. All identifying information will be removed from the transcript. These recordings will be destroyed after all analysis is completed.

Your participation in this focus group is voluntary. You are not required to participate in this focus group in order to remain employed for HPTN 073. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop your participation completely, at any time. If you choose not to participate in a focus group discussion or refuse to answer any of the questions, you will not lose any of the benefits of your regular employment.

[To be modified to reflect site practices: The focus group will take place in a location that the study staff have determined will provide you with privacy and confidentiality such as a room at the clinic, or other appropriate places. The study team will talk with you about this so you know where to go for the focus group.***]***

What Are the Potential Benefits?
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.

What Are the Possible Risks or Discomforts?
The questions we will ask you may make you feel uncomfortable. We hope that the focus group procedures described above will protect your confidentiality and minimize your discomfort when discussing sensitive topics. However, the greatest risk may involve your privacy and confidentiality. This is because confidentiality is limited in a focus group setting, since the other members of the focus groups are present during the discussion and we cannot guarantee that they will not discuss what you will say later. Additional steps that the study team has taken to protect your privacy are described below.

How Will Your Privacy Be Protected?
Every effort will be made to keep your personal information confidential. Your personal information (name, address, phone number) will be protected by the research clinic. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study. We encourage you to make up a name or use a nickname during this focus group.

Your records may be reviewed by the sponsor of the study (US National Institutes of Health (NIH), US NIMH) and their representatives, ***[insert name of site]*** IRB, study staff, study monitors and [insert applicable local regulatory authorities]..

We cannot guarantee absolute confidentiality. 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. Any publication of this study will not use your name or identify you personally.

People who may review your records include: the ***[insert name of site]*** IRB, National Institutes of Health (NIH), study staff, study monitors, and drug companies supporting this study. Also, 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.

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.]

What Are Some Reasons Why You May Be Withdrawn From This Activity Without Your Consent?
You may be withdrawn from the study without your consent for the following reasons:

- The research study, or this part of the study, is stopped or cancelled before you participate.

- The study staff feels that completing the study or this part of the study would be harmful to you or others.

Persons to Contact for Problems or Questions
For questions about this study or a research-related injury, 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 as a research participant, contact:

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

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.

Pre Exposure Prophylaxis (PrEP) Initiation and Adherence among Black Men who have Sex with Men (BMSM) in Three US Cities
(HPTN 073)

Final Version 1.0
21 February 2013
DAIDS Document ID: 11894

US National Institute of Allergy and Infectious Diseases (NIAID)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)
US National Institute for Drug Abuse (NIDA)

Sponsor: NIAID, NIH and NIDA

INFORMED CONSENT FORM
FOCUS GROUP INFORMED CONSENT FORM – STUDY PARTICIPANTS

INVESTIGATOR OF RECORD: [*insert name*]
PHONE: [*insert number*]

SIGNATURE PAGE

If you have either read or have heard the information in this consent form, if all of your questions have been answered and if you agree to take part in the focus group, please sign your name on the line below.

_____	_____
Participant's Name (print)	Participant's Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date

14.0 REFERENCES

1. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med.* Dec 30 2010;363(27):2587-2599.

2. Paltiel AD, Freedberg KA, Scott CA, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. *Clin Infect Dis.* Mar 15 2009;48(6):806-815.

3. Diagnoses of HIV infection and AIDS in the United States and Dependent Areas, 2008. *HIV Surveillance Report, Volume 20*
2008; http://www.cdc.gov/hiv/surveillance/resources/reports/2008report/index.htm.

4. Hall HI, Song R, Rhodes P, et al. Estimation of HIV incidence in the United States. *JAMA.* 2008 Aug 6 2008;300(5):520-529.

5. Millett GA, Flores SA, Peterson JL, Bakeman R. Explaining disparities in HIV infection among black and white men who have sex with men: a meta-analysis of HIV risk behaviors. *AIDS.* 2007 Oct 1 2007;21(15):2083-2091.

6. Marek KD, Adams SJ, Stetzer F, Popejoy L, Rantz M. The relationship of community-based nurse care coordination to costs in the Medicare and Medicaid programs. *Res Nurs Health.* Jun 2010;33(3):235-242.

7. Katz MH, Cunningham WE, Fleishman JA, et al. Effect of case management on unmet needs and utilization of medical care and medications among HIV-infected persons. *Ann Intern Med.* Oct 16 2001;135(8 Pt 1):557-565.

8. Feigenbaum A, Pasternak S, Zusk E, Sarid M, Vinker S. Influence of intense multidisciplinary follow-up and orlistat on weight reduction in a primary care setting. *BMC Fam Pract.* Jan 29 2005;6(1):5.

9. Gilbody S, Bower P, Fletcher J, Richards D, Sutton AJ. Collaborative care for depression: a cumulative meta-analysis and review of longer-term outcomes. *Arch Intern Med.* Nov 27 2006;166(21):2314-2321.

10. Sommers LS, Marton KI, Barbaccia JC, Randolph J. Physician, nurse, and social worker collaboration in primary care for chronically ill seniors. *Arch Intern Med.* Jun 26 2000;160(12):1825-1833.

11. Noel PE. The impact of therapeutic case management on participation in adolescent substance abuse treatment. *The American Journal of Drug and Alcohol Abuse.* 2006;32:311-327.

12. Myers J, Zack, B., Kramer, K., Gardner, M., Rucobo, G., & Costa-Taylor, S. Get connected: An HIV prevention case management program for men and women leaving California prisons. *American Journal of Public Health.* 2005;95:1682-1684.

13. Rhodes W, & Gross, M. Case management reduces drug use and criminality among drug-involved arrestees: An experimental study of an HIV prevention intervention. 1997.

14. Adair CE, McDougall GM, Beckie A, et al. History and measurement of continuity of care in mental health services and evidence of its role in outcomes. *Psychiatr Serv.* Oct 2003;54(10):1351-1356.

15. Haggerty JL, Reid RJ, Freeman GK, Starfield BH, Adair CE, McKendry R. Continuity of care: a multidisciplinary review. *BMJ.* Nov 22 2003;327(7425):1219-1221.

16. CDC. HIV prevention case management: literature review and current practice. http://www.cdc.lgov/hiv/pubs/pcml/pcml-toc.htm, 1997.

17. CDC. HIV prevention case management: guidance. 1997.
18. Stille CJ, Jerant A, Bell D, Meltzer D, Elmore JG. Coordinating care across diseases, settings, and clinicians: a key role for the generalist in practice. *Ann Intern Med.* Apr 2005;142(8):700-708.
19. C. C. Care coordination model: Better care at lower cost for people with multiple health and social needs. In: Eby D, Whittington, J., ed. Cambridge, MA: Institute for Health Improvement: IHI Innovation Series white paper; 2011.
20. Noel PE. The impact of therapeutic case management on participation in adolescent substance abuse treatment. *Am J Drug Alcohol Abuse.* 2006;32(3):311-327.
21. Myers J, Zack B, Kramer K, Gardner M, Rucobo G, Costa-Taylor S. Get Connected: an HIV prevention case management program for men and women leaving California prisons. *Am J Public Health.* Oct 2005;95(10):1682-1684.
22. Rhodes W, Gross M, National Institute of Justice (U.S.), National Institute on Drug Abuse. *Case management reduces drug use and criminality among drug-involved arrestees : an experimental study of an HIV prevention intervention.* Washington, D.C.: U.S. Dept. of Justice, Office of Justice Programs, National Institute of Justice; 1997.
23. Ickovics JR. "Bundling" HIV prevention: integrating services to promote synergistic gain. *Prev Med.* Mar 2008;46(3):222-225.
24. Rotheram-Borus MJ, Swendeman D, Flannery D. Family wellness, not HIV prevention. *AIDS Behav.* Jun 2009;13(3):409-413.
25. Rotheram-Borus MJ, Swendeman D, Chovnick G. The past, present, and future of HIV prevention: integrating behavioral, biomedical, and structural intervention strategies for the next generation of HIV prevention. *Annu Rev Clin Psychol.* 2009;5:143-167.
26. Antonelli RC, Antonelli DM. Providing a medical home: the cost of care coordination services in a community-based, general pediatric practice. *Pediatrics.* May 2004;113(5 Suppl):1522-1528.
27. Bull SS, Vallejos D, Levine D, Ortiz C. Improving recruitment and retention for an online randomized controlled trial: experience from the Youthnet study. *AIDS Care.* Sep 2008;20(8):887-893.
28. Hightow L, MacDonald P, Pilcher C, et al. The unexpected movement of the HIV epidemic in the Southeastern United States: transmission among college students. *J Acquir Immune Defic Syndr.* 2005;38(5):531.
29. Williams GC, Rodin GC, Ryan RM, Grolnick WS, Deci EL. Autonomous regulation and long-term medication adherence in adult outpatients. *Health Psychol.* May 1998;17(3):269-276.
30. Kennedy A, Rogers A, Sanders C, Gately C, Lee V. Creating 'good' self-managers?: facilitating and governing an online self care skills training course. *BMC Health Serv Res.* 2009;9:93.
31. Levesque CS, Williams GC, Elliot D, Pickering MA, Bodenhamer B, Finley PJ. Validating the theoretical structure of the Treatment Self-Regulation Questionnaire (TSRQ) across three different health behaviors. *Health Educ Res.* Oct 2007;22(5):691-702.
32. Williams GC, Saizow RB, Ryan RM. The importance of self-determination theory for medical education. *Acad Med.* Sep 1999;74(9):992-995.
33. Hill C. Consensual qualitative research: A practical resource for investigating social science phenomena2011, Washington, DC.

34. Williams GC, McGregor HA, Zeldman A, Freedman ZR, Deci EL. Testing a self-determination theory process model for promoting glycemic control through diabetes self-management. *Health Psychol.* Jan 2004;23(1):58-66.
35. Kennedy S. Adherence to HIV Medications: Utility of the theory of self-determination. *Cognitive Therapy and Research.* 2004(28):611-628.
36. Williams GC, Minicucci DS, Kouides RW, et al. Self-determination, smoking, diet and health. *Health Educ Res.* Oct 2002;17(5):512-521.
37. McGuiness C, Sibthorpe B. Development and initial validation of a measure of coordination of health care. *Int J Qual Health Care.* Aug 2003;15(4):309-318.
38. Antonelli RC, Stille CJ, Antonelli DM. Care coordination for children and youth with special health care needs: a descriptive, multisite study of activities, personnel costs, and outcomes. *Pediatrics.* Jul 2008;122(1):e209-216.
39. Coleman EA, Smith JD, Frank JC, Eilertsen TB, Thiare JN, Kramer AM. Development and testing of a measure designed to assess the quality of care transitions. *Int J Integr Care.* 2002;2:e02.
40. Hendriks AA, Vrielink MR, Smets EM, van Es SQ, De Haes JC. Improving the assessment of (in)patients' satisfaction with hospital care. *Med Care.* Mar 2001;39(3):270-283.
41. Solomon LS, Hays RD, Zaslavsky AM, Ding L, Cleary PD. Psychometric properties of a group-level Consumer Assessment of Health Plans Study (CAHPS) instrument. *Med Care.* Jan 2005;43(1):53-60.