

**ATN 113 Version 2.0
February 3, 2014**

**PROJECT PrEPare – AN OPEN LABEL DEMONSTRATION PROJECT AND PHASE
II SAFETY STUDY OF PRE-EXPOSURE PROPHYLAXIS USE AMONG 15 TO 17
YEAR OLD YOUNG MEN WHO HAVE SEX WITH MEN (YMSM) IN THE UNITED
STATES**

A Multi-Center Study of the Adolescent Medicine Trials Network for HIV/AIDS Interventions
(ATN)

Sponsored by:

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(NICHD)
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ATN 113 PROTOCOL TEAM ROSTER

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SIGNATURE PAGE

Project PrEPare – An Open Label Demonstration Project and Phase II Safety Study of Pre-exposure Prophylaxis Use among 15 to 17 Year Old Young Men Who Have Sex with Men (YMSM) in the United States

Sponsored by:

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)

I, the Principal Investigator, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed. I also agree to maintain all study documentation for at least two years following the marketing approval for the study agent, FTC/TDF (Truvada®), for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the Food and Drug Administration (FDA) is notified that the Investigational New Drug application (IND) is discontinued.

I have read and understand the information in the FTC/TDF (Truvada®) Package Insert, including the potential risks and side effects of the product under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contributions to the study.

AMTU Site #

AMTU Name

Name of Investigator of Record

Signature of Investigator of Record

Date

REQUIREMENTS FOR SITE PARTICIPATION IN PROTOCOL

This study is open to a subset of Adolescent Medicine Trial Units (AMTUs) of the Adolescent Trials Network (ATN) (see Appendix III).

Each participating AMTU should have the following capabilities:

- Collaborative relationships with community-based organizations serving young men who have sex with men (YMSM) that have experience providing outreach services to this population;
- Ability to recruit YMSM between the ages of 15-17 years, inclusive;
- Ability to designate study staff time for subject study visits;
- Private space for conducting the behavioral interventions;
- An investigational pharmacy for storage, labeling, and dispensing of the study agent;
- Ability to perform dual-energy X-ray absorptiometry (DXA) scanning using a GE Lunar or Hologic DXA scanner that is accessible and operational for the duration of the study implementation period;
- Access to a processing laboratory with Laboratory Data Management System (LDMS) capability. (All biological specimens will be tracked using the LDMS); and
- At least one staff member or laboratory personnel who is certified with the International Air Transportation Association (IATA) to package dangerous goods, of which blood and blood products are included, for air shipment (see Chapter 5 of the ATN Manual of General Operations (MOGO)).

STUDY MANAGEMENT

Before the recruitment and enrollment of subjects, the participating AMTU must have the protocol and consent form approved by their local Institutional Review Boards (IRB). In addition, ATN study sites must receive protocol registration approval from the ATN Data and Operations Center (DOC). All original approved documents must be maintained at the clinical site. A detailed description of site and protocol registration procedures is included in Chapter 6 of the ATN MOGO.

All queries for this protocol should be sent to the ATN 113 Protocol Team using the ATN Protocol Query and Notification System (QNS) accessible via the ATN website (www.atnonline.org). The appropriate team member will respond to queries generally within 48 business hours via the ATN QNS and copy the other team members. The Protocol Specialist, with the help of other Westat personnel and/or NICHD, if necessary, will answer general protocol implementation, case report form (CRF) completion, and specimen shipping queries. The Protocol Co-Chairs or their designee will respond to eligibility, study and subject management, exemptions and/or adverse event queries. This study follows the Manual of Expedited Reporting of Adverse Events to the ATN/NICHD (EAE Manual) and ATN Policy for Guidance for Safety and Impact Reporting located in Appendix 1B.9 of the ATN MOGO. Queries and replies will automatically be archived at the ATN DOC. The Protocol Specialist will post those queries deemed relevant to all sites on the ATN website, where they will be available for future reference.

This study will use the Audio Computer-Assisted Self-Interview (ACASI) to collect study data. All questions related to the ACASI should be directed to the ACASI Help Desk at the ATN DOC. The ACASI Help Desk can be contacted either by calling the toll-free ACASI helpline at 1-888-222-6358 or by e-mailing ATNHELP@westat.com. The ACASI Help Desk at the ATN DOC will be available to provide technical assistance to sites.

LIST OF ABBREVIATIONS

| | |
|-----------------|---|
| 3MV | Many Men, Many Voices |
| ACASI | Audio Computer-Assisted Self-Interview |
| ACTG | AIDS Clinical Trials Group |
| AE | Adverse Event |
| AEE | Adverse Event Evaluation Form |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALT | Alanine aminotransferase |
| AMTU | Adolescent Medicine Trial Unit |
| ANC | Absolute neutrophil count |
| ART | Antiretroviral therapy |
| ARV | Antiretroviral |
| AST | Aspartate aminotransferase |
| ATN | Adolescent Medicine Trials Network for HIV/AIDS Interventions |
| BCAC | Body Composition Analysis Center at Tufts University |
| BMC | Bone mineral content |
| BMD | Bone mineral density |
| BUN | Blood urea nitrogen |
| Ca | Calcium |
| CBC | Complete blood count |
| CDC | Centers for Disease Control & Prevention |
| CFM | Confirmatory Testing |
| CFR | Code of Federal Regulations |
| CI | Confidence interval |
| Cl | Chloride |
| CO ₂ | Carbon dioxide |
| CrCl | Creatinine clearance |
| CRF | Case report form |
| DBS | Dried blood spots |
| DHHS | U.S. Department of Health and Human Services |
| DOC | Data and Operations Center |
| DSMB | Data and Safety Monitoring Board |
| DXA | Dual-energy X-ray Absorptiometry |
| EAE | Expedited Adverse Event |
| EAP | Ethics Advisory Panel |
| EPH | Extension Phase |
| FDA | Food and Drug Administration |
| FTC | Emtricitabine |
| FTC-TP | Emtricitabine-triphosphate |
| FTP | File Transfer Protocol |
| GCP | Good Clinical Practice |
| HAART | Highly active antiretroviral therapy |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| HTRM | HIV Treatment Readiness Measure |
| IATA | International Air Transportation Association |
| ICH | International Conference on Harmonization |
| IDU | Injection drug user |
| IMB | Information, Motivation, Behavioral Skills model |

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| IND | Investigational New Drug Application |
| iNSC | Integrated Next Step Counseling |
| iPrEx | The Study of Pre-Exposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men |
| IRB | Institutional Review Board |
| ITT | Intent to treat |
| K | Potassium |
| LDMS | Laboratory Data Management System (at FSTRF) |
| LFT | Liver function test |
| LGBT | Lesbian, Gay, Bisexual, Transgender |
| LLD | Lower limit of detection |
| MAR | Missing at random |
| MCAR | Missing completely at random |
| MEMS | Medication Event Monitoring System |
| MOGO | Manual of General Operations |
| Na | Sodium |
| NAAT | Nucleic acid amplification test |
| NICHHD | National Institute of Child Health and Human Development |
| NIDA | National Institute on Drug Abuse |
| NIH | National Institutes of Health |
| NIMH | National Institute of Mental Health |
| NMAR | Not missing at random |
| OC-RDC | Oracle Clinical-Remote Data Capture |
| OHRP | Office of Human Research Protection |
| OLE | Open Label Extension |
| OSHA | Office of Occupational Safety and Health Administration |
| Partners PrEP | Parallel Comparison of Tenofovir and Emtricitabine/Tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples |
| PCC | Personalized Cognitive Counseling |
| PEP | Post-exposure prophylaxis |
| PFLAG | Parents, Families and Friends of Lesbians and Gays |
| PI | Principal Investigator |
| PID | Patient Identification number |
| PO ₄ | Phosphorous, Phosphate |
| PoR | Pharmacist of Record |
| PPI | Proton pump inhibitor |
| PrEP | Pre-exposure prophylaxis |
| QA | Quality assurance |
| QNS | Query and Notification System |
| RNA | Ribonucleic acid |
| RPR | Rapid plasma reagin (test for syphilis) |
| sAb | Surface antibody |
| SAE | Serious adverse event |
| sAg | Surface antigen |
| sCr | Serum creatinine |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SHIV | Simian/Human Immunodeficiency Virus |
| SID | Study Identification number |
| SLE | Systemic lupus erythematosus |
| SNRI | Serotonin and norepinephrine reuptake inhibitor |

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|--------|---|
| SP | Seropositive |
| SSRI | Selective serotonin reuptake inhibitor |
| STI | Sexually transmitted infection |
| SUSAR | Suspected, Unexpected Serious Adverse Reactions |
| TDF | Tenofovir disoproxil fumarate (the orally bioavailable form of tenofovir) |
| TDF2 | Study of the Safety and Efficacy of Daily Oral Antiretroviral Use for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana |
| TFV | Tenofovir |
| TFV-DP | Tenofovir-diphosphate |
| TLFB | Time-line follow-back |
| ULN | Upper limit of normal |
| UP/C | Urine protein to creatinine ratio |
| WBC | White blood count |
| WHO | World Health Organization |
| YMSM | Young men who have sex with men |

STUDY ABSTRACT

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| DESIGN: | This pre-exposure prophylaxis (PrEP) demonstration project and phase II safety study aims to obtain additional data on the safety of emtricitabine/tenofovir (FTC/TDF (Truvada®)) and to evaluate patterns of use, rates of adherence, and patterns of sexual risk behavior among YMSM (inclusive of transgender women) who are provided with open label FTC/TDF (Truvada®) and information on the safety and efficacy of PrEP from prior studies. Furthermore, this project will explore the feasibility and acceptability of implementing two different types of efficacious risk reduction interventions prior to the provision of PrEP – Many Men, Many Voices (3MV) and Personalized Cognitive Counseling (PCC). |
| SAMPLE SIZE : | Approximately 100 YMSM will be recruited for participation in this study. |
| DURATION: | The usual duration of study participation is 48 weeks. However, subjects could be on study for as long as 120 weeks. Subjects who become Human Immunodeficiency Virus (HIV) infected during the course of the study will be followed for 24 weeks after HIV infection is confirmed. Those subjects who meet specific bone or renal criteria at the Week 48 visit or the 24-Week HIV Seropositive visit (SP3) will be followed for an additional 48 weeks in the Extension Phase to more closely monitor longer-term outcome of potential concerns. (See Schematic of Study Followup). |
| POPULATION: | HIV-1 uninfected YMSM ages 15 years and 0 days through 17 years and 364 days, inclusive, at the time of signed informed consent. Subject must be at high risk of acquiring HIV infection, tests HIV negative at time of screening, and be willing to provide contact information, take FTC/TDF (Truvada®) as PrEP, and participate in a behavioral intervention. |
| TREATMENT/ INTERVENTION: | Subjects will complete the behavioral intervention (3MV or PCC) available at their site. All subjects will be provided with daily FTC/TDF (Truvada®) as PrEP for 48 weeks. Follow-up visits will include evaluations for safety monitoring, collection of specimens for measuring study drug levels, and audio computer-assisted self-interview (ACASI) to assess acceptability, patterns of use, rates of adherence, and patterns of risk behaviors. |
| STRATIFICATION: | <ul style="list-style-type: none"> • AMTUs will be assigned to one of two behavioral interventions: 3MV and PCC. All subjects enrolled at a given AMTU will receive the same behavioral intervention. • Subjects at selected AMTUs will use the Wisepill device for assessing patterns of study agent, FTC/TDF (Truvada®), use. |
| OBJECTIVES: | <p>Primary Objectives:</p> <ul style="list-style-type: none"> • To provide additional safety data regarding FTC/TDF (Truvada®) use among HIV-uninfected YMSM. • To examine acceptability, patterns of use, rates of adherence and measured levels of drug exposure when YMSM are provided open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from |

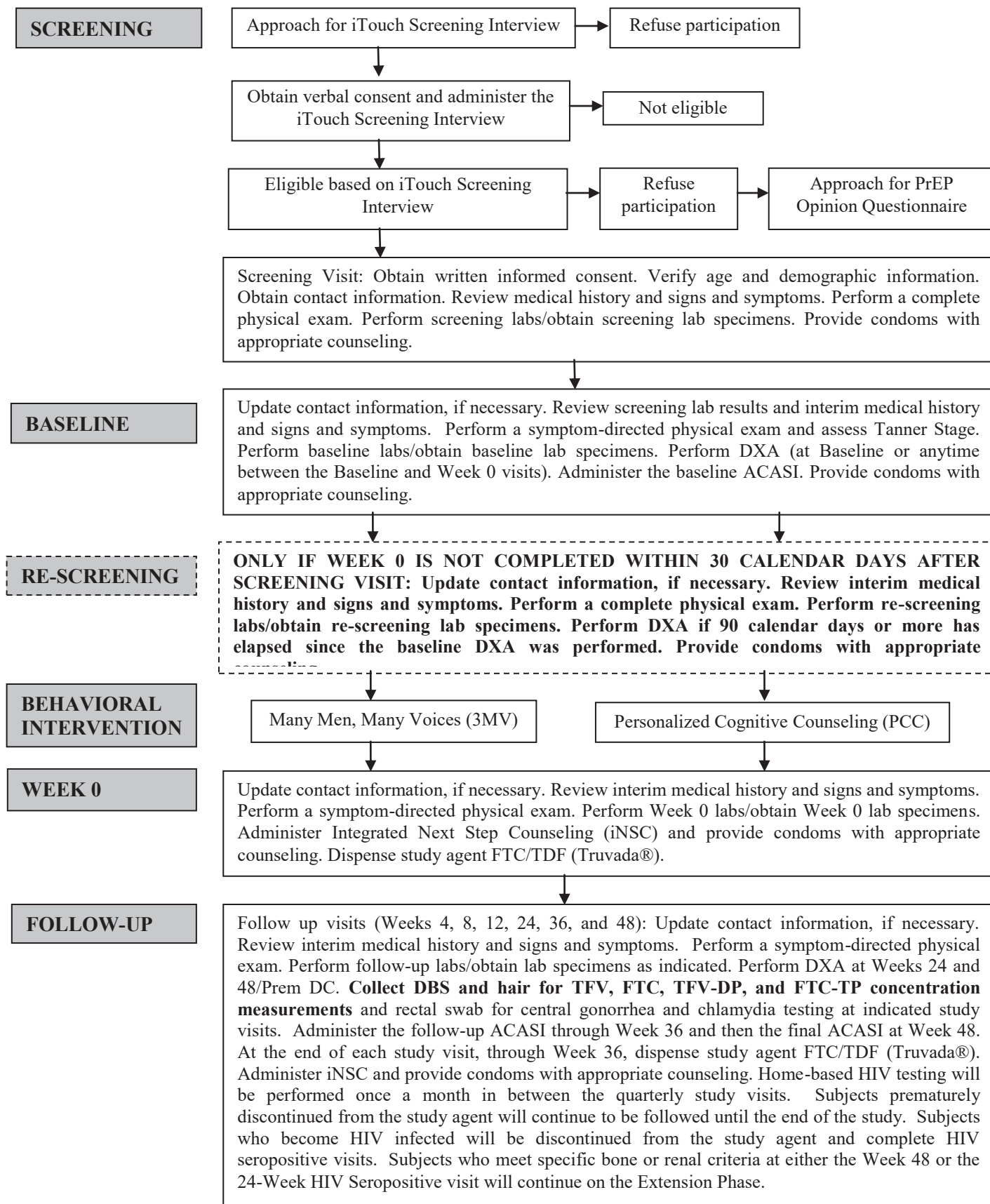
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| | <p>prior studies.</p> <ul style="list-style-type: none"> To examine patterns of risk behavior when YMSM are provided a behavioral intervention as well as open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies. <p>Secondary Objectives:</p> <ul style="list-style-type: none"> To evaluate the process of protocol implementation to better understand how to best implement PrEP research and program practice at adolescent medicine sites, including an evaluation of consent procedures and the acceptability/feasibility of allowing youth minors to consent for their own participation in this HIV prevention intervention, to the extent allowable by local laws and regulations, and to allow youth minor participation in a clinical trials without requiring disclosure of their sexual orientation and risk behaviors to their parents or guardians. To explore the acceptability and feasibility of implementing two types of efficacious sexual risk reduction interventions (intensive group-level or brief individual-level) prior to the provision of PrEP. To explore the acceptability and feasibility of implementing a text messaging adherence reminder intervention for youth who self-report less than 80% adherence to the study regimen. To explore potential demographic and/or behavioral differences between youth who stay on PrEP compared to those who discontinue use. To explore potential demographic and/or behavioral differences between youth who are interested in participating in a PrEP study versus those who are not. To explore the discussions and recommendations of local IRBs on this approach to minor YMSM inclusion in PrEP studies. |
| <p>SUBJECT MANAGEMENT:</p> | <p>After enrolling and completing the Baseline visit, subjects will complete either the 3MV or PCC behavioral intervention according to the behavioral intervention to which the respective AMTU was assigned. After completion of the behavioral intervention, subjects will receive the study agent FTC/TDF (Truvada®) as PrEP at the Week 0 visit. Follow-up visits will occur at Weeks 4, 8, 12, 24, 36, and 48. Assessment for toxicities and review of interval symptoms will be done at all time points. Subjects who become HIV infected during the course of the study will be discontinued from the study agent. These subjects will no longer follow the original study visit schedule, but will complete three HIV Seropositive visits (SP1, SP2, and SP3) at 4, 12, and 24 weeks after HIV infection is confirmed. Subjects who meet specific bone or renal criteria at the Week 48 visit or the SP3 visit will complete two Extension Phase visits (EPH1 and EPH2) at 24 and 48 weeks after the Week 48 visit or the SP3 visit (see Schematic of Study Followup).</p> |
| <p>DATA COLLECTION:</p> | <ul style="list-style-type: none"> Contact information at every visit Demographics at Screening Medical history: lifetime history of bone disease, bone fractures, renal |

| | |
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| | <p>disease, hospitalizations (not including emergency room visits), and any other clinically significant systemic diagnosis as determined by the site investigator at Screening and then interim medical history at follow-up visits</p> <ul style="list-style-type: none"> • Medication history: prior 12 month history use of steroids, glucocorticoids, hormones, anticonvulsants, selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), proton pump inhibitors (PPI) and prior 30 day history of all other medications (including herbal therapies, vitamins and other supplements at Screening and then interim medications at follow-up visits • Review of signs and symptoms in the past 30 days at Screening and then interim signs and symptoms at follow-up visits • A complete physical exam at Screening and then symptom-directed physical exam at follow-up visits • HIV diagnostic testing, serum creatinine (sCr), and urine gonorrhea and chlamydia testing at every study visit • Serum chemistries and complete blood count (CBC) with differential and platelets at indicated study visits • Spot urine for protein to creatinine ratio (UP/C) and urine dipstick for protein and glucose at indicated study visits • Syphilis testing, hepatitis B surface antigen (HBsAg) and surface antibody (HBsAb) testing, and HIV-1 RNA PCR (viral load) at indicated study visits • Dried blood spots (DBS) and hair samples for tenofovir (TFV), emtricitabine (FTC), tenofovir-diphosphate (TFV-DP), as well as emtricitabine-triphosphate (FTC-TP) concentration measurements at indicated study visits • Rectal swab for central gonorrhea and chlamydia testing at indicated study visits • DXA scans at indicated study visits • Data on demographics, HIV prevention readiness, risk behavior and disinhibition, substance use and abuse, sexual partner, and support from others will be collected at every visit via the ACASI. HIV prevention readiness, beliefs about condom use, beliefs related to HIV risk, STIs, study-related reduced HIV risk, study pill adherence and acceptability of the study agent, FTC/TDF (Truvada®), and PrEP in general and beliefs about PrEP at indicated study visit via the ACASI • Session evaluation forms will be completed by subjects at the end of the behavioral intervention session to elicit information about the subject's experience with the session |
| <p>VARIABLES TO MEASURE:</p> | <p>Implementation Process Evaluation:</p> <ul style="list-style-type: none"> • IRB-related written/e-mailed correspondence • IRB-related verbal communication log • IRB-related discourse captured by the ATN Query and Notification System |

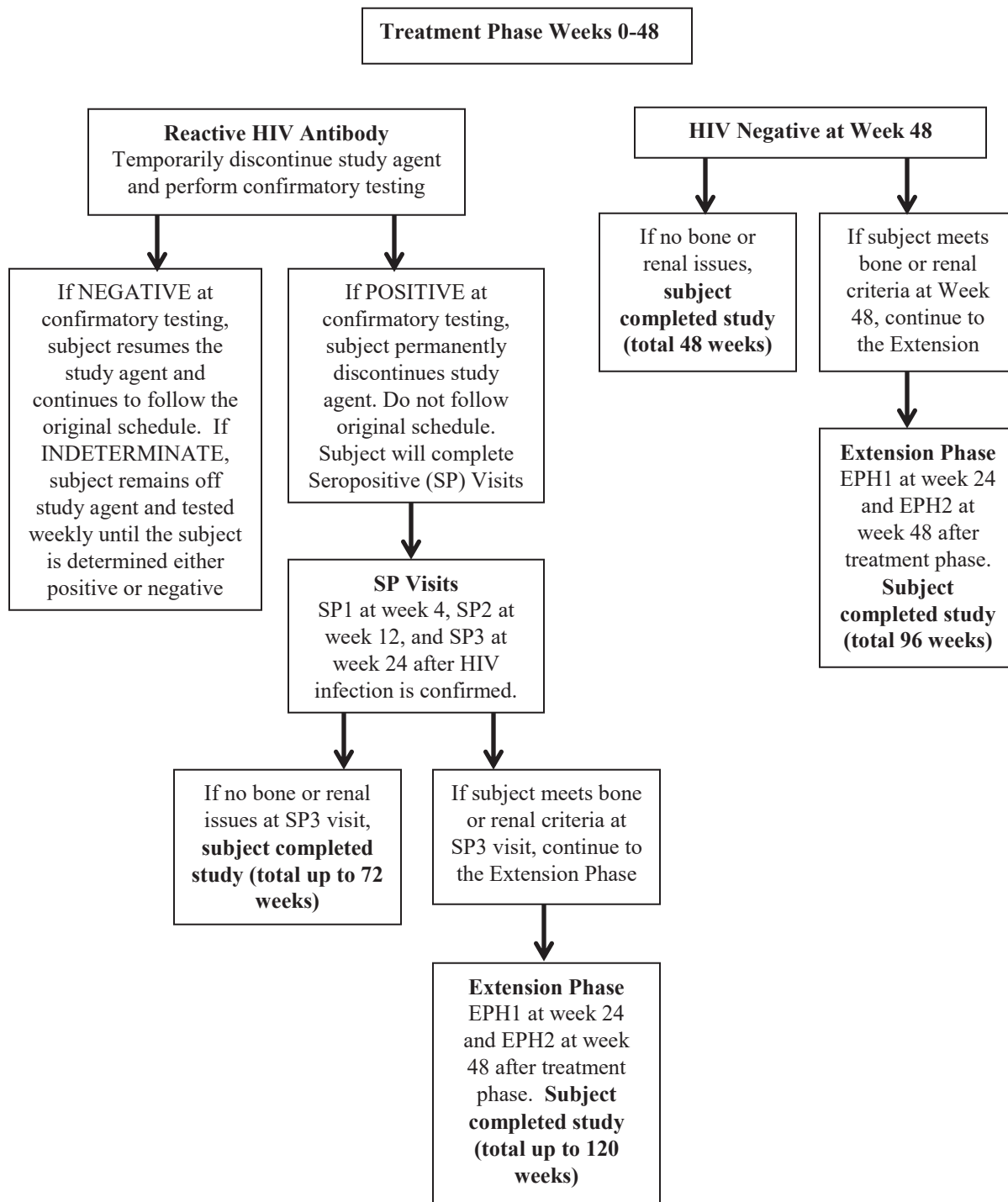
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| | <p>(QNS)</p> <ul style="list-style-type: none"> • IRB-related documents • Key informant interview data <p>Safety:</p> <ul style="list-style-type: none"> • Serum creatinine (sCr) • Bone mineral density (BMD) and bone mineral content (BMC) • Safe sex practices <p>Acceptability/Feasibility:</p> <ul style="list-style-type: none"> • Acceptability Assessment Tool • PrEP Questions • Beliefs About PrEP • Support from Others • Session Evaluation Form • Feasibility Assessment <p>Medication Adherence:</p> <ul style="list-style-type: none"> • Prevention Medication Readiness • Time-Line Follow-Back • Sex Life and Pills • Medication Gaps • AIDS Clinical Trial Group Adherence Follow-up Questionnaire • Medication Levels • Wisepill <p>Behavioral Disinhibition/Risk Compensation:</p> <ul style="list-style-type: none"> • Sexual Activity and Sexual Risk Assessment • Beliefs Related to highly active antiretroviral therapy (HAART) • Treatment-Related Reduced HIV Risk • Beliefs About Condom Use • Substance Use and Abuse |
| <p>MONITORING:</p> | <p>Routine team monitoring of adverse events (AE) and untoward events of the study will rely on the ATN QNS, a real-time, web-based interactive reporting system. Email notifications generated by the QNS are continuously reviewed by all team members including the NICHD Medical Monitor, and answered within two business days by the Protocol Co-Chairs or their designee. This assures continuous, prompt oversight of all potentially serious adverse clinical or laboratory events. Furthermore, sites will record and enter in the study database all AEs and untoward events associated with study participation. All reported events will be reviewed on the monthly monitoring calls attended by the ATN 113 Protocol Team, including the NICHD Medical Monitor and the ATN DOC Statistician. This allows periodic group review of all AEs and untoward events, ensuring identification of patterns or recurring problems that might be otherwise missed. All Serious Adverse Events (SAE) will be reported on the <i>ATN Expedited Adverse Event (EAE) Form</i> and submitted expeditiously to the Sponsor through the Regulatory Affairs Office at the ATN DOC and the FDA.</p> |

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| REGULATORY OVERSIGHT: | This trial will be conducted in compliance with the protocol, the applicable FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312), the OHRP regulations (45 CFR Part 46), and the ICH Good Clinical Practice (GCP) guidelines. |
|--------------------------|--|

STUDY SCHEMA



SCHEMATIC OF STUDY FOLLOWUP



1.0 INTRODUCTION

Among all men who have sex with men (MSM), adolescents and young adults aged 13 - 24 had the greatest percentage increase (44%) in diagnoses of HIV infection from 2007 through 2010 (Centers for Disease Control and Prevention (CDC), 2012). Among young MSM (YMSM) in the United States, youth of color are disproportionately impacted by HIV. For example, young black/African American MSM experienced the largest increase in numbers of diagnoses of HIV infection of all racial/ethnic groups - from 2,925 diagnoses in 2007 to 4,358 diagnoses in 2010 (CDC, 2012). Of all MSM aged 13 - 24 years diagnosed with HIV infection in 2009, an estimated 58% were black/African American, followed by Hispanics/Latinos (20%) and white (19%) (CDC, 2012). These epidemiological data clearly show that HIV/AIDS is a public health crisis among YMSM and YMSM of color in particular in the U.S. Effective interventions are urgently needed. Please note, in this protocol, the term “MSM” is used rather than gay, bisexual, or other terms in order to be consistent with terminology used in the CDC Surveillance Reports. The term MSM should also be considered inclusive of male-to-female transgender youth (i.e., transwomen) for this protocol.

One promising biomedical intervention recently approved by the U.S. Food and Drug Administration (FDA) for primary HIV prevention in adults is FTC/TDF (Truvada®) as oral antiretroviral pre-exposure prophylaxis (PrEP) (FDA, 2012). Following encouraging safety data from smaller PrEP trials (CDC, 2011b), the Study of Pre-Exposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men (iPrEx), a randomized, placebo-controlled trial of 2499 MSM showed that MSM at high risk for HIV infection who were randomized to take a single daily tablet containing emtricitabine and tenofovir (FTC/TDF (Truvada®)) experienced an average of 43.8% fewer HIV infections than those who received a placebo pill (95% CI 15.4 to 62.6%; P=0.005) (Grant, et al., 2010). The results also suggest that PrEP was more protective among those who reported strong adherence. Among subjects who were 50% adherent, as measured by pill counts, bottle counts and self-reports, risk of HIV infection fell by 50.2% (95% CI 17.9-69.7%; P=0.006); among those who were 90% adherent, PrEP reduced infection risk by 72.8% (95% CI 40.7-87.5%; P=0.001). These results, as well as results from the CAPRISA 004 trial (Abdool Karim, et al., 2010), highlight the need for behavioral strategies targeting adherence as well as ongoing risk behavior. Furthermore, while no evidence of behavioral disinhibition has been seen in PrEP clinical trials to date, concerns persist for younger populations in particular. Thus, combined behavioral and biomedical approaches for PrEP implementation are crucial to assist youth through a vulnerable developmental period by providing a biomedical prevention strategy along with behavioral skills to reduce risk. Additionally, since young MSM were not adequately represented in the US iPrEx sample and no minor YMSM were enrolled, targeted strategies for PrEP use must be explored further.

This study of the Adolescent Trials Network for HIV/AIDS Interventions (ATN) aims to launch a PrEP demonstration project and phase II safety study. The aims are to obtain additional data on the safety of FTC/TDF (Truvada®) and to evaluate patterns of use, rates of adherence, and patterns of sexual risk behavior among YMSM who are provided with open label FTC/TDF (Truvada®), as well as, information on the safety and efficacy of PrEP from prior studies. This project will incorporate multiple methods of adherence assessment and monitoring. Furthermore, this project will explore the acceptability and feasibility of implementing two types of efficacious risk reduction interventions prior to the provision of PrEP. Finally, this project will evaluate the process of implementing a biomedical research protocol for adolescents, including the IRB approval process and issues around consent. Approximately 100 YMSM, ages 15 to 17 years, inclusive, will be recruited across all participating Adolescent Medicine Trial Units (AMTUs) and their collaborating community partners. The type of behavioral intervention will be assigned at the level of the site. Subjects will first complete the behavioral intervention offered at their respective site and then be provided FTC/TDF (Truvada®). Behavioral and biomedical data will be collected at baseline and 0, 4, 8, 12, 24, 36 and 48 weeks.

1.1 Background and Significance

1.1.1 Epidemiology of HIV among YMSM

From 2007 through 2010, male-to-male sex was the largest HIV transmission category in the US and the only one associated with an increasing number of HIV/AIDS diagnoses (CDC, 2012). Of all age groups of MSM, HIV/AIDS cases increased most among YMSM ages 13-24 years. Of all YMSM, black YMSM bear the greatest burden. Close to three times as many black YMSM were diagnosed with HIV/AIDS in 2010 as their white or Hispanic counterparts (CDC, 2012). Black and Hispanic MSM are more likely to become infected at a younger age (13 - 29 years), whereas white MSM are more likely to become infected when they are older (Mackellar, et al., 2005).

Recent CDC data demonstrate that 75% of all adolescents between the ages of 13-19 diagnosed with HIV were black, and 89% of those HIV diagnoses among 13-19 year olds were attributed to male-to-male sexual contact (CDC, 2010b). Studies have reported high rates of unprotected sexual activity, multiple partners, and unrecognized HIV infection among black YMSM (Wolitski, Jones, Wasserman, & Smith, 2006; CDC, 2002; Martinez & Hosek, 2005; Miller, Serner, & Wagner, 2005; Valleroy, MacKellar, Behel, Secura, & The Young Men's Survey Study Group, 2004; CDC, 2001). Although risk behaviors lead to infection in this population, data demonstrate that these risks are not higher in young black MSM compared to other groups. In the Young Men's Study, black YMSM subjects reported a median of two male sex partners in the past 6 months, 77% reported anal sex with another man, and 37% reported unprotected anal sex (CDC, 2001). Additionally, 16% of black YMSM in the study tested positive for HIV and 93% of those were unaware of their status (Wheeler, 2006).

Young Latino/Hispanic MSM have also been disproportionately impacted by HIV and AIDS (CDC, 2010). In 2009, the rate of new infections among Latino men was two and a half times as high as that of white men (39.9/100,000 vs. 15.9/100,000) (CDC, 2011c). In this same year, Latino MSM accounted for 81% (6,000) of new HIV infections among all Latino men and 20% among all MSM. Among Latino MSM, 45% of new HIV infections occurred in those under age 30.

1.1.2 The State of PrEP Science

The scientific basis for testing PrEP in iPrEx and other trials came from animal studies in which PrEP strategies have shown that dosing with antiretrovirals (ARV) prior to exposure reduces risk of infection among animals challenged with strains of SHIV (Simian/Human Immunodeficiency Virus - an HIV-like virus that can cause disease in monkeys). (Subbarao, et al., 2006; Garcia-Lerma, et al., 2008; Tsai, et al., 1995). Other relevant data come from humans. ARVs are given to HIV-negative infants born to HIV-positive pregnant women as part of effective strategies to reduce the risk of vertical transmission (Dao, et al., 2007). The ARVs taken by the HIV-negative infants may contribute to their reduced risk of HIV infection. ARVs are also used for *post*-exposure prophylaxis (PEP) to decrease the risk of infection following occupational exposure or high-risk sexual contact.

To date, there are no existing PrEP trials among adolescent minors. There are, however, a number of ongoing and completed PrEP trials that have enrolled over 20,000 subjects, worldwide (see Table 1 below). Oral PrEP trials are testing, or have tested, either TDF, or a combination of TDF plus FTC. The majority of current studies have focused on TDF and FTC/TDF because these drugs require only a single daily dose for treatment, have relatively low rates of side effects, and there are significant data on their long-term safety and resistance profiles in HIV-infected individuals. In fact, FTC/TDF (Truvada®) was approved by the FDA for use to reduce the risk of HIV infection in HIV-1 uninfected adults who are at high risk of HIV infection in July 2012.

Table 1. Funded Studies of Oral PrEP

| Funder | Population | Location | N | Regimen/Expected Completion |
|--------------------------------|---|---|----------|---|
| Completed Studies | | | | |
| FHI Safety Study - USAID/Gates | High Risk Females - ages 18 to 35 | Cameroon, Ghana, Nigeria | 936 | Phase II - TDF daily <i>Completed 2006</i> |
| CDC 4323 | MSM - ages 18 to 60 | United States | 400 | Phase II - TDF daily <i>Completed 2009</i> |
| CDC 4940 (TDF2) | Young males and females – ages 18 to 29 | Botswana | 1219 | Phase III - Truvada® daily <i>Completed 2011</i> <i>FTC/TDF conferred 63% additional protection (P=0.03; Thigpen, NEJM 2012)</i> |
| iPrEx study - NIH/Gates | MSM – ages 18 and up | Brazil, Ecuador, Peru, South Africa, Thailand, US | 2499 | Phase III - Truvada® daily <i>Completed 2010</i> <i>Randomization to FTC/TDF associated with 44% decrease in incidence of HIV (P=0.005; Grant, NEJM 2010)</i> |
| Ongoing Studies | | | | |
| Partners PrEP - Gates | Discordant couples – ages 18 to 60 | Uganda, Kenya | 4747 | Phase III - Truvada® vs. TDF daily <i>Placebo arm discontinued early after DSMB review in July 2011. Relative reductions of 67 and 75% in HIV incidence in TDF and FTC/TDF groups, respectively (both P<0.001; Baeten, NEJM 2012)</i> |
| CDC 4370 | Injection drug user (IDU) – ages 20 to 60 | Thailand | 2413 | Phase II/III - TDF daily Participants taking TDF had a 49% reduction in risk of HIV acquisition overall (Choopanya, Lancet 2013) |
| FemPrEP - USAID/Gates | High Risk Females – ages 18 to 35 | Kenya, Malawi, South Africa, Tanzania | 2120 | Phase III - Truvada® daily <i>Study closed early due to lack of efficacy. Authors attributed lack of efficacy to low adherence of less than 25% (Van Damme, NEJM 2012)</i> |
| VOICE study - NIH | Females – ages 18 to 35 | South Africa, Uganda, Zimbabwe | 5029 | Phase IIb - Truvada® or TDF daily Lack of efficacy attributed to low adherence of less than 30% (Marrazzo, CROI 2013) |
| Open Label | | | | |
| iPrEx OLE - NIH/Gates | MSM | South America, South Africa, US, Thailand | 1770 | Open label extension <i>Completion early 2014</i> |

iPrEx (The Study of Pre-Exposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men). iPrEx was a randomized, double-blind, placebo-controlled event-driven study to evaluate the safety and efficacy of once daily oral co-formulated FTC 200 mg/ TDF 300 mg (Truvada®) for prevention of HIV acquisition among men who are highly exposed to HIV (Grant, et al., 2010). A total of 2,499 individuals at high risk of HIV infection participated in the trial implemented at 11 sites in Peru, Ecuador, Brazil, the United States, South Africa, and Thailand. All study subjects received a comprehensive package of prevention services designed to reduce their risk of HIV infection throughout the trial, including HIV testing, intensive safer sex counseling, condoms and treatment and care for sexually transmitted infections (STI). Subjects randomized to Truvada® experienced an average of 43.8% fewer HIV infections than those who received a placebo pill. The iPrEx study also found that Truvada® was more protective among those who reported taking the medication more regularly. Among subjects who used PrEP on 50% or more of days, as measured by pill counts, bottle counts and self-reports, risk of HIV infection fell by 50.2%; among those who used PrEP on 90% or more of days, as determined by the same measures, Truvada® reduced infection risk by 72.8%. Even more striking was the finding that subjects who had detectable levels of FTC and/or TDF in their blood reduced their risk for HIV infection by 92%. More recent data on intracellular tenofovir-DP concentrations associated with PrEP efficacy has been published by Anderson and colleagues (2012). Their analysis estimated HIV risk reduction associated with dosing as follows: 2 doses/week providing 76% reduction, 4 doses/week providing 97% reduction, and 7 doses/week providing 99% reduction (Anderson, et al., 2012). Finally, the concern that the use of the PrEP pill could cause study subjects to relax their use of safer sex practices was not demonstrated in the iPrEx study. In fact, self-reported HIV risk behavior decreased among subjects in both arms of the study and condom use increased.

More research is needed to see how risk behavior may change now that information is available about PrEP safety and efficacy. The iPrEx OLE (Open Label Extension) is a continuation of the iPrEx study designed to provide additional information about long-term efficacy; long-term safety; pill taking and adherence; changes in subjects' sexual behavior; drug resistance among those who become HIV-infected; effects on bone mineral density (BMD) and fat distribution; and impact on hepatitis infection.

Despite the strong results from the iPrEx study and the high percentage of youth enrolled internationally (~50%), the youth served by the ATN sites were not well represented in the iPrEx cohort. Only two of the 11 study sites in iPrEx were located in the United States. The iPrEx cohort as a whole was 9% black, including African Americans, Afro-Peruvians, Afro-Brazilians, and black South Africans. Although the median age of the iPrEx cohort worldwide is 25 years, the median age at sites in the United States was greater than 30 years. Table 2 below is the racial breakdown of subjects (n=28) below the age of 25 that were enrolled at US iPrEx sites. These data are similar to other PrEP trials for MSM. The CDC's domestic PrEP safety trial among MSM was predominantly white (73%) with a very small number of young MSM enrolled (n=19). Again, no data exists on 15 to 17 year olds from any of the aforementioned PrEP trials.

Table 2. iPrEx Subjects Less Than 25 Years of Age Enrolled in the U.S.

| Race | Frequency | Percent |
|------------------------|-----------|---------|
| Black/African-American | 5 | 17.86 |
| White | 13 | 46.43 |
| Mixed/Other | 5 | 17.86 |
| Asian | 5 | 17.86 |
| Total | 28 | 100.0 |

Partners PrEP (Parallel Comparison of Tenofovir and Emtricitabine/Tenofovir Pre-Exposure Prophylaxis to Prevent HIV-1 Acquisition within HIV-1 Discordant Couples). This study is led by the University of Washington's International Clinical Research Center and involves a randomized, double-blind, placebo-controlled trial including 4,758 HIV sero-discordant couples, from nine research sites in Kenya and Uganda (Baeten, et al., 2012). Study results through May 31, 2011 have demonstrated that individuals at high risk for HIV infection who took a daily tablet containing an HIV medication – either the antiretroviral medication tenofovir or tenofovir in combination with emtricitabine (Truvada®) – experienced significantly fewer HIV infections (67% and 75%, respectively) than those who received a placebo pill. These findings present clear evidence that PrEP substantially reduces HIV infection risk among heterosexual discordant couples. All study subjects received a comprehensive package of HIV prevention services, which included intensive safer sex counseling (both individually and as a couple), HIV testing, free condoms, testing and treatment for STIs, and monitoring and care for HIV infection. In the study, adherence to the daily PrEP medication was very high – more than 97% of dispensed doses of the study medications were taken based on pill counts and more than 96% of subjects were retained in study follow-up. There was no evidence of behavioral disinhibition (Baeten, et al., 2012).

CDC TDF2 (Study of the Safety and Efficacy of Daily Oral Antiretroviral Use for the Prevention of HIV Infection in Heterosexually Active Young Adults in Botswana). This study was a randomized, double-blind, placebo-controlled trial examining the safety and efficacy of a once-daily tablet containing FTC/TDF (Truvada®) for reducing the risk of HIV acquisition among heterosexual men and women at two sites in Botswana (Thigpen, et al., 2012). In addition to study medication, all subjects received a comprehensive package of HIV prevention services. The study provides further evidence that a daily oral dose of antiretroviral drugs used to treat HIV infection can reduce HIV acquisition among uninfected individuals exposed to the virus through heterosexual sex. The study found that Truvada® reduced the risk of acquiring HIV infection by roughly 62% overall in the study population and by 78% in the as-treated analysis. Adherence (as measured by pill count) was high, both among those receiving Truvada® and among those receiving placebo (84.1% and 83.7%, respectively). Reported sexual risk behavior was similar between the two study arms. Consistent with other PrEP studies, preliminary analyses did not identify any significant safety concerns associated with daily use of Truvada®.

1.1.3 Why It Is Time to Enroll 15- to 17-Year Olds in a PrEP Trial

YMSM, particularly ethnic minority MSM, is one of the largest groups of people living with HIV/AIDS and one of the primary populations that stand to benefit from efficacious HIV prevention products. The determination to include youth in HIV prevention efficacy trials is very complex and varies by product (i.e., vaccines vs. microbicides vs. PrEP). For PrEP, the state of the science is moving quickly and adolescent-specific data are needed in order to inform implementation. Regulators and ethicists have recently suggested a timeline for enrolling adolescents in PrEP trials (Nelson, Lewis, Struble, & Wood, 2010). Such a timeline would include proof-of-concept from adult efficacy trials, sufficient adult safety data from prevention trials and/or pediatric safety data from treatment trials, and the enrollment of adolescents ages 15-17 in initial trials followed by lower age groups. For PrEP, there are extensive HIV treatment safety data along with newer adult prevention safety data that warrant earlier consideration of youth participation (Kapogiannis, et al., 2010).

Given the progress in the PrEP science arena, the considerations outlined above, and the expertise of the ATN in conducting adolescent trials, the ATN is poised to add a unique contribution to the growing PrEP scientific field by launching a demonstration project and safety study for YMSM ages 15-17. This study, which will launch in parallel to ATN 110, a study with same design but in an older age group, will strive to obtain the maximum amount of information necessary to inform the implementation of PrEP for youth in clinical settings, by examining a combined behavioral-biomedical approach, exploring patterns of use

and rates of adherence, examining patterns of sexual risk behavior, and exploring the uptake of a text-message reminder system for those struggling with pill adherence. Additionally, this protocol will evaluate the process of protocol implementation, by evaluating consent procedures and the acceptability/feasibility of allowing youth minors to consent for their own participation in this HIV prevention intervention, to the extent allowable by local laws and regulations, to protect them from potential harms of disclosure of their sexual orientation and risk behaviors to their parents or guardians.

1.1.4 Concerns Regarding PrEP Implementation and Use

Adverse Events and Drug Resistance

The risk of adverse drug events resulting from chronic antiretroviral therapy (ART) use in HIV-uninfected individuals requires further evaluation. Most current PrEP trials use TDF with or without FTC. These agents were chosen because of promising data from animal studies, as well as, the overall low rate of toxicity associated with these agents. TDF is associated with low-level side effects including nausea, vomiting, and loss of appetite. Side effects associated with FTC/TDF (Truvada®) include diarrhea, nausea, fatigue, headache and rash (CDC, 2011a). There have also been reports of impaired kidney function and reduced bone density among HIV-positive individuals on these medications, which were mostly reversed when the person stopped taking the drug (CDC, 2011a). In a CDC study in 200 HIV-negative MSM, those randomized to TDF had a net BMD loss of 1.1% (95% CI 0.4 to 1.9%, $p = 0.004$) femoral neck and 0.8% (95% CI 0.3 to 1.3%, $p = 0.003$) in the total hip, relative to placebo (Liu, et al. 2011). In a larger international trial of TDF-FTC versus placebo in 2499 HIV-negative MSM or transgender women (Grant, et al. 2010), preliminary data from a sub-study in 503 subjects measured change in BMD at weeks 24, 48, and 72 (Mulligan, et al., 2011). At week 24, BMD decreased in those randomized to TDF-FTC ($N = 247$) but increased in those randomized to placebo ($N = 256$), both at the hip (difference - 0.65; 95% CI -1.03 to -0.28; $p = 0.001$) and at the spine (difference -0.95; 95% CI -1.51 to -0.39; $p = 0.001$). The increase in BMD in the placebo group is likely due to the inclusion of adolescent and young adults in this study, in which 48% of subjects were 18 to 24 years of age (Mulligan, et al., 2011), a time when bone mass is still increasing (Heaney, et al., 2000).

The iPrEx trial found that daily use of PrEP with FTC/TDF (Truvada®) was safe and generally well-tolerated, with no difference in adverse events between study drug and placebo arms (Grant, et al., 2010). There were no differences between groups in laboratory abnormalities related to liver function, pancreatitis, electrolytes, glucose, phosphate, and complete blood count (CBC). Nausea was the most common side effect. Data on markers of bone turnover, renal tubular toxicity, and parathyroid hormone concentrations have not yet been reported on iPrEx subjects.

Because PrEP is not triple combination therapy, the concern about PrEP subjects who may sero-convert developing drug resistance, has been raised. Results from the iPrEx trial demonstrate very little drug resistance, with no one developing resistance to TDF. Three cases of FTC-resistant infections occurred in iPrEx subjects who were already newly HIV-infected at enrollment thus reflecting transmitted resistance virus. No drug resistance was observed among those who became infected during the study (Grant, et al., 2010). In the TDF2 trial, two cases of drug resistance emerged. One subject in the active drug arm with unrecognized acute wild-type HIV infection at enrollment demonstrated high levels of K65R, M184V and A62V. One subject in the placebo group showed K65R only in very low levels (<1%) (Thigpen, et al., 2012).

Adherence

Measuring adherence in clinical trials is vitally important because inadequate adherence can affect clinical response (Miller & Hays, 2000). Rates of adherence among adolescents and young adults with

chronic illnesses, such as HIV, diabetes, and cancer are concerning and are often estimated to be about 50% overall (LaGreca & Schuman, 1995; Murphy, Wilson, Durako, Muenz, & Belzer, 2001). It is important to assess closely whether individuals at risk for HIV infection will be willing and able to maintain consistent use of a daily medication regimen that is used for prevention and thus, not treating an illness they have.

Results of medication adherence from the Peterson and colleagues PrEP study demonstrated adherence rates of approximately 74% across sites (Peterson, et al., 2007). Preliminary results from the Bangkok PrEP study show subject adherence rates of 92% in the week prior to study visit (Choopanya, et al., 2008). According to investigators in the ongoing Partners PrEP study, adherence levels of 99% were achieved by subjects during an average four-month period during the two-year study (Haberer, et al., 2011). However, both iPrEx and CAPRISA 004 data demonstrate the bias of self-report in over-reporting adherence. In the iPrEx trial, non-adherence to study medication was strongly associated with infection risk with only 9% of those newly infected having detectable drug in their blood despite high levels of self-reported adherence (Grant, et al., 2010). Thus, optimizing adherence and its measurement are critical for interpretation of efficacy data and implementation planning (Buchbinder & Liu, 2011).

Behavioral Disinhibition/Risk Compensation

Risk compensation or risk homeostasis theory is based on the presumption that persons have an inherent set-point that determines their willingness to take risk (Wilde, 1982; Wilde, 1998). According to this theory, any modification in the environment that reduces the external probability of risk will lead an individual to increase their risk-related behaviors (i.e., behavioral disinhibition) in order to maintain the homeostatic set point, thereby neutralizing the benefits of risk-reduction strategies. In this manner, risk compensation has the potential to threaten the benefits of emerging HIV prevention technologies. For example, because typical condom use offers at least 90% protection against HIV, any significant reductions in condom use can offset the protective value of the new prevention technology (Wasserheit, 1992; Fleming & Wasserheit, 1999).

Concerns regarding behavioral disinhibition and risk compensation have been addressed to some degree by completed PrEP trials. In the West Africa PrEP trial (Peterson, et al., 2007), the mean number of sexual partners during the previous month dropped from 21 partners at screening to 14 partners at follow-up. Condom use increased from 52% at screening to 92% at 3, 6, & 9-month visits and 95% at the 12-month visit (Guest, et al., 2008; Peterson, et al., 2007). In the Bangkok study of IDUs, injection risk behavior also decreased, with 14% of subjects reporting needle sharing before enrollment and 4% of subjects reporting needle sharing at 12-month follow-up (Choopanya, et al., 2008). A similar pattern of declines in risk behavior were also seen in CAPRISA 004 and iPrEx (Abdool Karim, et al., 2010; Grant, et al., 2010). Despite these encouraging results, levels of risk compensation may be higher outside of clinical trials, particularly after efficacy has been demonstrated (Padian, Buve, Balkus, Serwadda, & Cates, 2008).

Given the concentration of the HIV epidemic among YMSM, the lack of youth-specific data from iPrEx and other PrEP studies, and the need for targeted data in the aforementioned areas to inform PrEP implementation strategies for youth, we are proposing a second phase of Project PrEPare (ATN 082) to evaluate the safety profile of PrEP and how open label access to PrEP and information about PrEP efficacy and safety affects behavior related to pill taking and sexual risk among YMSM in the United States.

1.2 Rationale

PrEP and information about PrEP may have different effects in different populations, depending on age, level of education, social and sexual networks, and other factors. The ATN is the only network in the United States poised to contribute to the growing evidence of PrEP by implementing a demonstration project and phase II safety study of PrEP among YMSM in the United States, who are most representative of people at risk for HIV infection domestically.

As the focus on PrEP implementation grows, the CDC has issued interim guidelines for PrEP implementation (CDC, 2011b). These guidelines along with a surge in recent literature on PrEP implementation (Buchbinder & Liu, 2011; Myers & Mayer, 2011; Underhill, Operario, Mimiaga, Skeer, & Mayer, 2010) strongly support a combined behavioral/biomedical approach. CDC (CDC, 2011b) guidance states *“PrEP has the potential to contribute to effective and safe HIV prevention for MSM if 1) it is targeted to MSM at high risk for HIV acquisition; 2) it is delivered as part of a comprehensive set of prevention services, including risk-reduction and PrEP medication adherence counseling, ready access to condoms, and diagnosis and treatment of sexually transmitted infections; and 3) it is accompanied by monitoring of HIV status, side effects, adherence, and risk behaviors at regular intervals.”*

The use of combined behavioral/biomedical strategies to prevent HIV might be the most developmentally-appropriate and cost-effective way to implement PrEP among youth. For adolescent and young adult MSM, the use of PrEP may be most useful in preventing HIV infection during the high-risk years of youth. A growing body of neurobiological research and imaging studies suggests that adolescents may be especially prone to engage in risky behaviors, including sexual risk and substance abuse, due to developmental changes in the brain that begin during the adolescent years and continue through the mid-20s (Galvan, et al., 2006; Galvan, Hare, Voss, Glover, & Casey, 2007). Thus, PrEP in youth may be best viewed as a time-limited strategy that can bridge the developmental period between sexual debut and adulthood. If so, the inclusion of a behavioral intervention in this project not only addresses our ethical responsibility of providing at least the minimum risk reduction education to all subjects given the high HIV risk of our study population, but also builds behavioral skills to assist subjects in reducing their risk when not taking PrEP.

Thus, the study is significant in its focus on YMSM domestically, is innovative in its combined behavioral/biomedical design, and is consistent with the ATN’s mission and scientific agenda.

1.3 Research Design Considerations

1.3.1 Decision to Allow Youth to Consent for Themselves

A significant challenge in conducting this research will be to ensure the appropriate inclusion of the specific populations of youth minors (<18 years) who are at risk for acquiring HIV infection and thus to ensure that much needed data on the safety and effectiveness of PrEP are obtained from these youth. There are many factors driving the domestic HIV epidemic among such youth, including social stigma, homophobia, social/cultural sexual networks and mixing patterns, age-discordant relationships, co-morbid undiagnosed STIs and likely high grade viremia among many sexual network members who are unaware of their own HIV infection (likely to be recent based on sexual debut in youth); these factors work synergistically to fuel incident HIV infection among the most vulnerable of youth. In this context, the issue of parental consent is particularly a problem; the youth most representative of the domestic epidemic would be excluded from these studies if parental permission were to be a requirement for their participation, given that they typically have not disclosed their sexual orientation or their risk behaviors to their parents or guardians. In addition, Food and Drug Administration (FDA) regulations do not allow waiver of parental permission in IND studies (21 CFR 50.55). For MSM populations, the FDA’s approved indication for Truvada as PrEP supports the evidence for efficacy, safety, and the prospect of

direct benefit to the participants. Where local regulations include a provision for mature minors (usually defined by state law as a minor that is near the age of maturity, displays sufficient understanding of medical procedures, and can be medically emancipated in the treatment of certain conditions, including venereal disease, pregnancy, and drug abuse) to seek medical care without parental permission for HIV and other STIs, these mature minors may be entitled to consent for their own participation in research specifically related to HIV and other STIs.

To explore this approach to enrolling minors without parental consent further, external consultation was obtained by the ATN from their Ethics Advisory Panel (EAP) who recommended unanimously that youth ages 15 to 17 have the capacity to consent for medical care for STIs and pregnancy prevention and therefore also have the capacity to consent for HIV prevention methods using efficacious interventions such as PrEP, allowing each local IRB to determine if this is consistent with their public health regulations. The recommendations from the EAP were then taken to the Office for Human Research Protections (OHRP) with a request for consultation on the consent approach for this protocol. The response from OHRP was that the advisory panel's assessment, with which FDA concurred, is both reasonable and consistent with 45 CFR Part 46, assuming that subjects are able to consent to such procedures under local law.

1.3.2 Decision to Conduct a Process Evaluation of Protocol Implementation

As the state of PrEP science continues to advance, it becomes critical to gather information on those that might be a likely target of PrEP interventions. To date there are no adolescent-specific PrEP protocols that would provide such information. Without this data, implementation procedures for future PrEP studies and programming will be developed blindly. Unfortunately, HIV research with Lesbian, Gay, Bisexual, Transgender (LGBT) youth under the age of 18 is often avoided because of concerns around the ability to obtain IRB approval (Mustanski, 2011; Miller, Forte, Wilson & Greene, 2006). Thus, understanding the review process by IRBs at adolescent medicine sites will further understanding of how to best implement PrEP research and program practice. Part of that IRB review process will be evaluating consent procedures and the acceptability/feasibility of allowing youth minors to consent for their own participation in this HIV prevention intervention, to the extent allowable by local laws and regulations, to protect them from potential harms of disclosure of their sexual orientation and risk behaviors to their parents or guardians. By evaluating the implementation of this protocol at multiple points, the team can develop approaches to avoid future roadblocks for adolescent PrEP implementation and ultimately decrease health disparities and increase the health and well-being of the YMSM community (Mustanski, 2011).

1.3.3 Decision to Measure Adherence Using Multiple Methods

Many previous studies on the measurement of adherence have demonstrated that self-reports of adherence correlate with objective measures (Fairley, Permana, & Read, 2005; Naar-King et al., 2006), yet this has not been the case with PrEP studies to date. To that end, it is our decision to incorporate both traditional self-report measures of adherence in conjunction with more objective measures.

First, subjects will rate their adherence over the past month on a scale of 0% to 100%. Second, a calendar method time-line follow-back (TLFB) will be used to cross-validate the subject's self-report of adherence. The calendar will serve as a temporal ordering cue to help subjects piece together their adherence rates over the past month. Third, subjects will report the reasons for missing doses using the AIDS Clinical Trials Group (ACTG) follow-up questionnaire.

In addition to the aforementioned self-report measures, we will collect dried blood spots (DBS) as an easy-to-collect biological measure of PrEP drug exposure in subjects. Based on data on a small number of subjects (Anderson, et al., 2012), one DBS provides TFV and FTC concentrations that

mirror plasma concentrations, as well as TFV-DP and FTC-TP, which are long half-life markers of cumulative drug exposure.

We will also monitor medication gaps, the period of time that a subject's supply of study agent is assumed to be exhausted, by comparing the actual refill dates for the study agent with the expected refill dates. In a multivariate model, Amico and colleagues (Amico, 2010) found that refill assessment was the only significant independent predictor of drug detection (OR 5.2, $p = 0.01$) among iPrEx trial subjects.

Finally, in order to directly monitor patterns of pill taking, a subsample of subjects ($n = 40$) will use a real-time data adherence technology that has recently been utilized with ART adherence monitoring (Haberer, et al., 2010). The Wisepill adherence monitor communicates real-time medication utilization through transmission of a patient identifier and date-time stamp over cellular phone networks. In a previous study, median adherence levels were 93% (87-97%) for Wisepill, 100% (99-100%) by unannounced pill count, 100% by self-report, and 92% (79-98% by Medication Event Monitoring System (MEMS) caps. Thus, adherence rates were similar between Wisepill and MEMS caps, although a significant added benefit of Wisepill was gathering real-time data (Haberer, et al., 2010). By incorporating this multi-method approach to medication adherence, we will be able to adequately report on adherence to PrEP among youth as well as the acceptability of a variety of adherence measures.

In order to support the importance of adherence in PrEP implementation, we will incorporate adherence counseling into each study visit. We will use an interactive, client-centered, motivational approach for PrEP pill taking called Integrated Next Step Counseling (iNSC) (See Appendix XVIII). iNSC (Amico, 2010) was designed during the original iPrEx trial and was found to be highly acceptable by both subjects and staff. This enhanced counseling method focuses on barriers and facilitators of pill use regardless of reported level of use. iNSC fosters interaction, neutral assessment and pill use promotion through customized goals and a supportive atmosphere.

For youth who self-report barriers to adherence during iNSC and who subsequently report less than 80% adherence to the prescribed PrEP regimen, a more intensive adherence intervention will be offered, which consists of daily text message reminders. We will examine uptake of this intervention along with acceptability, feasibility, and trends toward improving adherence.

1.3.4 Decision to Evaluate Efficacious Behavioral Interventions as an Integrated Component to PrEP Implementation

The large literature on HIV prevention interventions across diverse populations (e.g., MSM, adolescents, heterosexual women) has yielded a core set of factors that predict successful risk reduction and are the critical elements of successful behavior change interventions (Kelly, et al., 1990; Kelly, 1995; Sacco, Levine, Reed, & Thompson, 1991; Sikkema, et al., 1995). As summarized by Kelly (Kelly, 1995), behavioral interventions should include “activities that strengthen self efficacy to enact change, help individuals accurately appraise their risk, provide normative support for avoiding high risk behaviors or making behavior change, teach skills needed to communicate effectively with partners to decline sexual pressure or negotiate safer sex, and reinforce and support behavior change efforts.” A more recent meta-analysis on interventions to reduce sexual risk among adolescents found that behavioral interventions were successful at reducing incident infections, increasing condom use, reducing or delaying penetrative sex, and increasing skills to negotiate safer sex (Johnson, Scott-Sheldon, Huedo-Medina, & Carey, 2011). Johnson and colleagues (Johnson, et al., 2011) report that the most successful interventions had 1) a greater number of intervention sessions; 2) no focus on abstinence as a goal; 3) provided a greater amount of condom skills training; and 4) a greater amount of motivational training in each session. We propose to implement two efficacious behavioral interventions that incorporate many of these core factors – Many Men, Many Voices (3MV) and Personalized Cognitive Counseling (PCC).

Many Men, Many Voices (3MV)

3MV, based on Social Cognitive Theory and the Transtheoretical Model of Behavior Change, is recognized as a best-evidence intervention in the CDC's (2009) Compendium of Evidence-Based HIV Prevention Interventions. Many Men, Many Voices (3MV) is a group-level intervention that addresses behavioral and social determinants and other factors influencing the HIV/STI risk and protective behaviors of MSM of color. The other factors include cultural, social and religious norms, racial identity and degree of connectedness to communities, HIV/STI interactions, sexual relationship dynamics, and the social influences of racism and homophobia. Due to the disproportionate impact of HIV among racial and ethnic minority youth, culturally-appropriate approaches to PrEP need to be explored (Myers & Mayer, 2011).

In the original randomized controlled trial of 3MV (Kelly, St Lawrence, Hood, & Brasfield, 1989), subjects reduced their frequency of unprotected anal intercourse and increased their use of condoms significantly more than subjects in the wait-list control condition at the 8-month follow-up point. More recently, Wilton and colleagues (Wilton, et al., 2009) evaluated the intervention in a weekend retreat format as compared to a wait-list control condition. At the 6-month follow-up, the 3MV intervention subjects reported significantly fewer episodes of any unprotected anal intercourse with casual partners ($p = .012$) and unprotected insertive anal intercourse with casual partners ($p = .005$) compared to the wait-list control subjects. At the 6-month follow-up, the 3MV intervention subjects were also significantly more likely to report HIV testing behavior compared to the wait-list control subjects ($p = .023$).

Personalized Cognitive Counseling (PCC)

PCC, based on the Model of Relapse Prevention and Gold's Self-Appraisal of Risk Behavior, is also recognized as a best-evidence intervention in the CDC's compendium of evidence-based HIV prevention interventions (CDC, 2009). The PCC intervention is a one-hour, single-session, individual level intervention administered by a trained counselor in a clinic setting. During the session, counselors ask the client to recall a recent encounter of unprotected anal sex with another man of unknown or sero-discordant HIV status. The client describes the encounter with as much detail as possible. The client is then encouraged to identify and express the thoughts, feelings, or attitudes that might have led to the high-risk behavior. Together, the client and the counselor examine the encounter to identify any thoughts that may have led the client to make a decision to engage in high transmission risk sex. Finally, the client and the counselor agree on strategies that can be used to deal with similar situations in the future.

In a randomized controlled trial of PCC, Dilley and colleagues found that men receiving the PCC intervention had a significant decrease in percent ($p < 0.002$ and $p = 0.001$, respectively) and in mean number of episodes ($p < 0.008$ and $p < 0.001$, respectively) of unprotected anal sex, compared to those receiving standard HIV counseling, at both the 6 and 12-month follow-up points (Dilley, et al., 2002).

By implementing two different types of readily available behavioral interventions, one intensive, group-based and one less intensive individual-based, we can explore the feasibility and acceptability of both formats for youth in order to inform future implementation strategies.

1.3.5 Decision to Evaluate Bone Mineral Density/Content by Whole-Body and Regional Hip and Spine Dual-Energy X-Ray Absorptiometry

We will use dual-energy X-ray absorptiometry (DXA) scans to evaluate BMD and bone mineral content (BMC). DXA scanners are widely available, and scans can be acquired quickly with minimal radiation exposure. Site-specific DXA scanning is regarded as the criterion technique for measuring BMD in regions most susceptible to fracture, including the lumbar spine and the proximal hip. Measurements of

BMC can also be made of the whole body. BMC is typically used in studies of children during periods of growth (Heaney, 2003). DXA studies are useful to define fracture risk. Whole-body and regional (hip and spine) DXA scans will be performed, using standard operating procedures defined by the manufacturer and the ATN (see **ATN 110/113 DXA Manual of Operations on the ATN website (www.atnonline.org)**) in order to allow comparability between study sites as well as generalizability to subjects outside of the study protocol. All raw unanalyzed scan data will be sent for central reading at the Body Composition Analysis Center (BCAC) at the Tufts University Friedman School of Nutrition Science and Policy. This centralized system of analyzing the DXA scans will further ensure the comparability between study sites and generalizability to subjects outside of the study protocol.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

- To provide additional safety data regarding FTC/TDF (Truvada®) use among HIV-uninfected YMSM.
- To examine acceptability, patterns of use, rates of adherence and measured levels of drug exposure when YMSM are provided open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies.
- To examine patterns of risk behavior when YMSM are provided a behavioral intervention as well as open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies.

2.2 Secondary Objectives

- To evaluate the process of protocol implementation to better understand how to best implement PrEP research and program practice at adolescent medicine sites, including an evaluation of consent procedures and the acceptability/feasibility of allowing youth minors to consent for their own participation in this HIV prevention intervention, to the extent allowable by local laws and regulations, and to allow youth minor participation in a clinical trial without requiring disclosure of their sexual orientation and risk behaviors to their parents or guardians.
- To explore the acceptability and feasibility of implementing two types of efficacious sexual risk reduction interventions (intensive group-level or brief individual-level) prior to the provision of PrEP.
- To explore the acceptability and feasibility of implementing a text messaging adherence reminder intervention for youth who self-report less than 80% adherence to the study regimen.
- To explore potential demographic and/or behavioral differences between youth who stay on PrEP compared to those who discontinue use.
- To explore potential demographic and/or behavioral differences between youth who are interested in participating in a PrEP study versus those who are not.
- To explore the discussions and recommendations of local IRBs on this approach to minor YMSM inclusion in PrEP studies.

3.0 STUDY DESIGN

This demonstration project and phase II safety study aims to obtain additional data on the safety of FTC/TDF (Truvada®) and to evaluate patterns of use, rates of adherence, and patterns of sexual risk behavior among YMSM who are provided with open label FTC/TDF (Truvada®) and information on the safety and efficacy of PrEP from prior studies. Furthermore, this project will explore the feasibility and acceptability of implementing two different types of efficacious risk reduction interventions prior to the provision of PrEP – 3MV and PCC. Approximately 100 YMSM, between the ages of 15 and 17 inclusive will be enrolled across all participating AMTUs. Assignment to behavioral intervention will occur at the site level. Subjects will first complete the behavioral intervention offered at their respective site and will then be provided PrEP. Behavioral and biomedical data will be collected at baseline and at 4, 8, 12, 24, 36 and 48 weeks. Subjects who become HIV infected during the course of the study will be discontinued from the study agent, FTC/TDF (Truvada®), and complete three HIV Seropositive visits at 4, 12, and 24 weeks (SP1, SP2, and SP3 visits, respectively) after the study visit at which HIV infection is confirmed. Subjects who meet specific bone or renal criteria at the Week 48 visit or the SP3 visit will be followed for two additional visits (EPH1 and EPH2) over 48 weeks in the Extension Phase to more closely monitor longer-term outcome of potential concerns. The usual duration of study participation is 48 weeks. However, subjects could be on study for as long as 120 weeks.

3.1 Study Population

Subjects in this study will be HIV-1 uninfected YMSM ages 15 through 17 years, inclusive, at high risk of acquiring HIV infection, tests HIV negative at time of screening, and willing to provide locator information, take FTC/TDF (Truvada®) as PrEP and participate in either of the two behavioral interventions. Subjects will be recruited through all participating AMTUs and their community venues.

3.2 Sample Size

Approximately 100 YMSM (approximately 50 at 3MV sites and 50 at PCC sites) will be recruited for participation in this study.

3.3 Behavioral Intervention and Wisepill Device Assignments

Assignment to the behavioral intervention (3MV or PCC) will occur at the site level in a non-random fashion. The ATN 113 Protocol Co-Chairs, taking into consideration each AMTU's geographic location and availability of facilitators trained to administer the interventions in its vicinity, will assign each site to the 3MV or the PCC behavioral intervention. Attempts will be made to equally distribute the two interventions across sites in order to maximize the geographic diversity of each group. All subjects enrolled at a particular AMTU will receive the same intervention to which the site is assigned. In addition, a subset of subjects enrolled in the study will be assigned to use the Wisepill device for their study agent. The ATN 113 Protocol Co-Chairs will make the Wisepill device assignment at the site level in a non-random fashion.

4.0 SITE AND PROTOCOL REGISTRATION

Before the enrollment of subjects, the participating site must have the protocol approved by its local IRB. The site must then register the protocol with the Regulatory Office at the ATN **Data and Operations Center** (DOC) by completing the protocol registration checklist and submitting all required regulatory documents. See Chapters 5 and 6 of the ATN MOGO. The ATN DOC will review the materials to ensure that the site has the necessary resources to fulfill study requirements and to follow federal and

local IRB regulations. Sites may not begin enrollment prior to receiving registration approval from the DOC. All original approved documents must be maintained at the clinical site.

5.0 SELECTION AND ENROLLMENT OF STUDY SUBJECTS

5.1 Inclusion Criteria

To be considered eligible for enrollment, an individual must meet all the criteria listed below.

- 5.1.1** Willing and able to provide written informed consent;
- 5.1.2** Male gender at birth;
- 5.1.3** Age 15 years and 0 days through 17 years and 364 days, inclusive, at the time of signed informed consent;
- 5.1.4** Self reports evidence of high risk for acquiring HIV infection including at least one of the following:
 - At least one episode of unprotected anal intercourse with an HIV-infected male partner or a male partner of unknown HIV status during the last 6 months;
 - Anal intercourse with 3 or more male sex partners during the last 6 months;
 - Exchange of money, gifts, shelter, or drugs for anal sex with a male partner during the last 6 months;
 - Sex with a male partner and has had a STI during the last 6 months or at screening;
 - Sexual partner of an HIV-infected man with whom condoms were not consistently used in the last 6 months; or
 - At least one episode of anal intercourse where the condom broke or slipped off during the last 6 months;
- 5.1.5** Tests HIV antibody negative at time of screening;
- 5.1.6** Willing to provide locator information to study staff;
- 5.1.7** Willing to take PrEP;
- 5.1.8** Willing to participate in behavioral intervention;
- 5.1.9** Reports intention not to relocate out of AMTU study area during the course of the study; and
- 5.1.10** Does not have a job or other obligations that would require long absences from AMTU study area (greater than 4 weeks at a time).

5.2 Exclusion Criteria

To be considered eligible for enrollment, an individual must not meet any of the criteria listed below.

- 5.2.1** Appears visibly distraught or presence of active serious psychiatric symptoms (e.g., active hallucinations, suicidal, homicidal, or exhibiting violent behavior) at the time of consent;
- 5.2.2** Intoxicated or under the influence of alcohol or other drugs at the time of consent;

- 5.2.3 Any significant uncontrolled, active or chronic disease process that, in the judgment of the site investigator, would make participation in the study inappropriate. (Appropriately managed conditions, like well-controlled diabetes, would not preclude enrollment; the site is encouraged to contact the ATN 113 Protocol Team if they are having difficulty making the judgment.);
- 5.2.4 History of bone fractures not explained by trauma;
- 5.2.5 Acute or chronic hepatitis B infection as indicated by positive hepatitis B sAg test at time of screening;
- 5.2.6 Confirmed renal dysfunction (Creatinine Clearance (CrCl) < 75 ml/min calculated based on bedside Schwartz formula: $GFR = (0.413 \times (\text{height in centimeters})) / (\text{serum creatinine in mg/dl})$), or serum creatinine \geq upper limit of normal (ULN), or history of renal parenchymal disease or presence of only one kidney at time of screening;
- 5.2.7 Confirmed \geq Grade 2 hypophosphatemia at time of screening;
- 5.2.8 Confirmed \geq Grade 2 hematologic system abnormality (White Blood Count (WBC), Absolute Neutrophil Count (ANC), hemoglobin, or platelets) at time of screening;
- 5.2.9 Confirmed \geq Grade 2 hepatobiliary system abnormality (Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), or bilirubin) at time of screening;
- 5.2.10 Confirmed proteinuria as indicated by urine dipstick result \geq 1+ at time of screening, regardless of urine protein to creatinine ratio (UP/C);
- 5.2.11 UP/C > 0.37 g/g at time of screening, regardless of urine dipstick protein result;
- 5.2.12 Confirmed normoglycemic glucosuria as indicated by urine dipstick result \geq 1+ in the presence of normal serum glucose (<120 mg/dL) at time of screening;
- 5.2.13 A confirmed Grade \geq 3 toxicity on any screening evaluations;
- 5.2.14 Known allergy/sensitivity to the study agent or its components;
- 5.2.15 Concurrent participation in an HIV vaccine study or other investigational drug study, including oral or topical PrEP (microbicide) studies;
- 5.2.16 Use of disallowed medications (see Section 5.3); or
- 5.2.17 Inability to understand spoken English.

5.3 Disallowed Medications

Subjects who are receiving any of the following medications are not eligible for this study. Those who receive any of the following medications between the Week 0 and Week 48 study visits will be discontinued from the study agent, FTC/TDF (Truvada®), but continue to be followed on study. (The site is encouraged to contact the ATN 113 Protocol Team if they are having difficulty making a judgment about whether other medications fall into one of the disallowed categories.)

- Nephrotoxic drugs (e.g., cidofovir, amphotericin, aminoglycosides, dapsone, tacrolimus, foscarnet, ACE inhibitors)
- All diuretics
- Drugs that may interfere with TFV excretion:
 - (Val)ganciclovir

- Cyclosporin A
- Sirolimus
- Antineoplastics
- Drugs (not including mineral and vitamin supplements) used for treatment of osteoporosis (e.g., alendronate and other bisphosphonates, teriparatide, denosumab, and calcitonin)
- Chronic use of oral or systemic steroids (i.e., daily use for two weeks or more is not allowed)
- Experimental medications that are not Food and Drug Administration (FDA)-approved
- FTC/TDF (Truvada®) received outside of the study

There are no restrictions on medications before or during study participation other than those listed above. Subjects in this study are healthy volunteers; in case medical treatment is needed, subjects will receive medications according to standard of care.

5.4 Recruitment and Screening

Potential subjects will be recruited from coffee houses, gay youth centers, book clubs, school clubs, House Ball community gatherings, etc. We will also engage parent groups, such as Parents, Families and Friends of Lesbians and Gays (PFLAG). At these venues, as well as clinic venues caring for this population, potential subjects will be approached by project staff for their interest in the study. Screening will be done via a handheld device (iTouch). Use of the iTouch allows potential subjects to have more privacy answering the questions than having the recruiter perform a face-to-face interview. The iTouch Screening Interview (see Appendix XII) will be programmed using software for conducting computerized personal interviews using handheld devices (iForms). The screener consists of a number of items that are used to determine eligibility, as well as a few “red herring” unrelated items. Potential subjects will be given the iTouch Screening Interview after providing verbal consent to be screened. The iTouch Screening Interview uses a self-administered interview format that parallels the format used for computer-assisted self-interviews.

AMTUs will also have the option to use geosocial networking applications (i.e., Grindr, etc.) to approach potential subjects. These applications utilize geo-locating features of cell phones to sort users by geographic proximity, as well as other demographic values such as age, to offer staff at the AMTUs a targeted recruitment tool. With this tool, staff may create profiles, identifying themselves as recruiters. Once they identify and locate potential subjects, the recruitment process will become the in-person process.

Once the potential subject has completed the screening interview, the iTouch will bring up a screen saying “*Thank you for answering the questions. Please give the device back to the recruiter.*” The software will automatically determine whether the individual meets the eligibility requirements without staff input or assistance. When the individual gives the iTouch to the recruiter, the recruiter will enter a special password to learn whether to invite the individual to enroll in the study; the recruiter will not know the reason for ineligibility if the individual is ineligible. If the individual is not eligible for the study, the recruiter will thank the individual and give the individual a bag with condoms. If the individual is eligible, the individual will be informed of the nature of the study and the additional laboratory tests and clinical assessments required before entry into the study. If still interested, the individual will be scheduled for a screening visit at the participating AMTU.

If an individual who is eligible for the study declines to participate, the individual will be asked about willingness to complete a brief survey regarding the individual’s opinions about PrEP. If interested, the

individual will be given an iTouch that is programmed with the PrEP Opinion Questionnaire after verbal consent is obtained. When the potential subject has completed the questions, the iTouch will bring up a screen saying “*Thank you for answering the questions. Please give the device back to the recruiter.*” Individuals who complete the PrEP Opinion Questionnaire will be given a gift card for their participation along with condoms.

Each individual who is approached, verbally consented and/or screened with the iTouch Screening Interview for recruitment in the study will have the following information recorded on the *ATN 113 Recruitment Log* that will be maintained at a secure area at the AMTU site: initials of the individual, age, race, ethnicity, and recruitment status, along with the reason(s) for refusing the iTouch Screening Interview and whether agreed to taken the iTouch PrEP Opinion Interview, if applicable.

Each individual who is eligible based on the iTouch Screening Interview and/or provides written consent for recruitment for study participation in ATN 113 will have the following information entered on the *ATN 113 Screening Log* that will be maintained in a secure area at the AMTU site: name, age, race, ethnicity, and the reason(s) for not enrolling in the study, if applicable. Only those individuals that provided written informed consent to participate, but were not enrolled, will have their screening log information, excluding their names, entered in the ATN 113 study database. Individual names will remain on the screening log only.

AMTU staff will also have the option to provide potential subjects a link to a web-based version of the iTouch Screening Interview. An online form builder service (i.e., Wufoo, etc.) will be used to build the web-based version of the screening interview. Once the individual has completed the screening interview, the web form will bring up a screen with either an eligibility or ineligibility notice. The software will automatically determine whether the individual meets the eligibility requirements without staff input or assistance. If not eligible for the study, the recruiter will thank the individual. If eligible, the individual will be informed of the nature of the study and the additional laboratory tests and clinical assessments required before entry into the study. If still interested, the individual will be scheduled for a screening visit at the participating AMTU.

At the end of the study, the Protocol Team may make a request for tabulated information on individuals who participated in the recruitment process but did not provide informed consent and the reasons these individuals refused to participate. These data collected will provide general information of the population that is recruited at the ATN sites into this study.

5.5 Informed Consent

Verbal consent will be obtained from individuals for completion of the iTouch Screening Interview. Consent to complete the interview will be documented on the iTouch programmed with the screening interview.

Verbal consent will also be obtained from individuals who decline to participate in the study but are willing to complete the brief PrEP Opinion Questionnaire. Consent to complete the survey will be documented on the iTouch programmed with the PrEP Opinion Questionnaire in which the subject’s responses will be entered.

Individuals who are eligible based on the iTouch Screening Interview will be scheduled for the Screening visit at the participating AMTU. Prior to any screening assessments, the purpose, procedures, requirements, risks and benefits of the study will be thoroughly discussed with the individual. An “assessment of understanding” questionnaire (see Appendix IX) will also be administered to ensure that the study is fully understood by the individual. No study-specific assessments will be conducted until

after signed informed consent is obtained. **The informed consent process may be performed on a different day than, but prior to, the day of the Screening visit.**

5.6 Contact Information

Once signed informed consent is obtained, site study staff will complete a Contact Form with the subject. Subjects will be asked to provide a working phone number, a valid email address, and Facebook (or other social media) handle through which they can be reached. Subjects will also be asked to provide valid contact information for a family member and/or friend who can be called in the event the subject cannot be reached by phone or email. Subjects will be asked if messages can be left at the numbers provided. Study staff will not leave messages unless expressly permitted to do so by the subject, which also will be documented on the form. If permission is given to leave messages, site staff will ensure that messages left with a family member or friend only ask that the subject contact study staff and will not include any protected health information or information related to study participation. Locator information will be reviewed with the subject at each study visit and updated as needed.

The *ATN 113 Contact Form* will not contain any study data. The form will be maintained under double locks at the study site, separately from all other study records, with access limited to designated site staff.

5.7 Subject Registration and Enrollment

If this is the first time an individual is participating in an ATN-sponsored study and the subject does not already have an ATN Patient Identification number (PID), site staff will assign the subject a PID in consecutive order from the PID list provided by the ATN DOC and record the assignment in the PID Assignment Log. Subjects with an existing PID number will continue to use the same number. Upon receiving protocol registration approval, the ATN DOC will provide a list of Study Identification (SID) numbers to each of the participating sites. If a subject is determined to be eligible for the study, the site staff will assign the subject a unique SID number specific to this protocol.

Subjects will be enrolled in the study at the Baseline visit after all inclusion/exclusion criteria are confirmed, including the results of the screening lab tests, and the Eligibility and Enrollment Form is completed.

If a subject fails to complete the Week 0 visit within 30 **calendar** days after the Screening visit, **the subject must complete a Re-screening visit in order to remain in the study and continue with the Week 0 visit. If this does not occur, the subject will be discontinued from the study and no further evaluations will be required.**

5.8 Co-enrollment Guidelines

Co-enrollment in other studies may be considered at the discretion of the ATN 113 Protocol Team. Requests for “blanket” co-enrollment approvals into other relevant open protocols during the implementation of this protocol will be considered by the ATN 113 Protocol Team and, if meritorious, will be granted prior to implementation of this protocol.

Studies that open after this protocol is implemented can be considered for co-enrollment either by requesting a blanket, one-time approval from the ATN 113 Protocol Team or by requesting case-by-case permission for co-enrollment in writing from the ATN 113 Protocol Team via the ATN QNS.

6.0 STUDY AGENT MANAGEMENT

6.1 Study Agent Administration

All subjects will be provided daily FTC (200 mg)/TDF (300 mg) (Truvada®) as PrEP. Subjects will be instructed to take one tablet once per day, whether or not they anticipate engaging in sex. Subjects will be counseled not to share their medication with anyone else.

Subjects will be prescribed the established standard dosing of FTC/TDF (Truvada®) for adolescents and adults and the dose that has been used in all prophylaxis trials to date. This is a prophylaxis trial, and therefore, there is no “treatment period”.

6.2 Study Agent Supply and Distribution

FTC/TDF (Truvada®) tablets will be supplied by Gilead Sciences, Inc. in Foster City, CA, USA. Manufacturing, bottling, and labeling will be performed according to Gilead SOPs that are in compliance with FDA and International Conference on Harmonization (ICH) Good Manufacturing Practices. FTC/TDF (Truvada®) tablets will be packaged in bottles of 30 tablets each. Each bottle will be labeled with Gilead’s English commercial label that includes the medication name, formulation and strength, NDC number, storage instructions, lot number, expiration date, and manufacturer information. The study agent will be made available through the ATN Central Pharmacy at Catalent Pharma Solutions. Each AMTU’s pharmacist of record (PoR) or designee will obtain the study agent by following the instructions in the ATN MOGO.

6.3 Study Agent Formulation and Storage

FTC/TDF (Truvada®) is a fixed-dose combination tablet containing FTC and TDF. FTC is a synthetic nucleoside analogue of cytidine. TDF is the difumarate prodrug of TFV. In vivo, TDF is converted to TFV which is an acyclic nucleoside phosphonate (nucleotide) analog of adenosine 5’-monophosphate. TFV and FTC are phosphorylated intracellularly into forms that exhibit activity against HIV-1 reverse transcriptase. Each FTC/TDF (Truvada®) tablet contains 200 mg FTC plus 300 mg of TDF. FTC/TDF tablets should be stored at 25°C. Excursions are permitted between 15°C and 30°C.

6.4 Study Agent Labeling

All dispensed study agent must be labeled properly to ensure safe administration and use by subjects. The PoR at each AMTU must ensure that local and Federal labeling requirements are met for all filled prescriptions. Along with the manufacturer’s label for Truvada®, an additional label that includes any institutional requirements and the information from the list below that is not present on the manufacturer’s label must be affixed.

- The statement “Caution: New Drug – Limited by Federal (or United States) law to investigational use”
- Name, address, and phone number of dispensing pharmacy
- Subject name
- Dispensing date
- Medication name, formulation and strength
- Daily dosage
- Directions for use

- Amount dispensed
- Prescriber's name

6.5 Study Agent Dispensing

The PoR at the AMTU will ensure that each prescription is complete and is signed by the PI or a sub-investigator whose name is listed on the form FDA 1572, and whose signature is present on the Authorized Prescribers Signature Log. All original signed prescriptions must be kept in the pharmacy study files. The PoR or designee at each AMTU will be responsible for dispensing the study agent, FTC/TDF (Truvada®), as prescribed by the study investigator. At the end of each visit beginning at Week 0, after all study visit evaluations are completed, subjects will receive a supply of the study agent, FTC/TDF (Truvada®). At the Weeks 0, 4, and 8 study visits, subjects will receive a one-month supply of the study agent, FTC/TDF (Truvada®). At Weeks 12, 24, and 36 study visits, subjects will receive a 3-month supply.

For subject safety considerations, at the Weeks 12, 24 and/or 36 visits, if it is known that a subject has any of the following laboratory test results, the study agent will be held or only a limited supply (7-10 day supply) will be dispensed, per the discretion of the site clinician, until the abnormal test(s) is/are repeated:

- Serum creatinine result \geq Grade 2 or has an increase from baseline by \geq 50%;
- New or increased proteinuria, indicated by positive [\geq 1+] urine dipstick result; and/or
- Normoglycemic glucosuria defined as \geq 1+ by urine dipstick in the presence of normal serum glucose ($<$ 120 mg/dL).

This measure will ensure that the safety of these subjects is not compromised by continued use of the study agent before the abnormal laboratory test result(s) is/are repeated.

6.6 Study Agent Accountability

The PoR at each AMTU is responsible for developing internal policies and procedures for the safe and proper use of study products and for establishing a control system for effective tracking and inventory of study products from their ordering through their receipt, dispensation, and disposition on site (see Chapter 5 of the ATN MOGO). All unused study agent should be destroyed on-site per federal, local, and institutional regulations after the study is completed or terminated.

7.0 BEHAVIORAL EVALUATIONS

7.1 Many Men, Many Voices Intervention

The 3MV behavioral intervention will be conducted at the AMTU or centrally located community sites as a two-day seminar with approximately 10-20 subjects per session. After approximately 10-20 subjects are enrolled, a seminar will be conducted in order to minimize the waiting time for subjects. Data from the ATN 082 study suggest that it will take about two weeks to enroll 10 subjects. The seminar may be conducted with as few as five subjects.

7.2 Personalized Cognitive Counseling

The PCC behavioral intervention is a one-hour, single-session individual level intervention and will be administered by a trained counselor in the clinic setting.

7.3 Audio Computer-Assisted Self-Interview (ACASI)

An ACASI will be administered at each study visit (see Appendices XVI and XVII). The baseline ACASI will include questions on demographics, study pill adherence intentions, risk behavior and disinhibition, beliefs related to HIV risk and substance use and abuse. The follow-up ACASI at the Weeks 4 through 36 visits will include questions on study-related reduced HIV risk and support from others, in addition to the baseline ACASI assessments. Subjects will also be asked about study pill adherence in relation to sex life, and reasons for missed medication. In the final follow-up ACASI at the Week 48 visit (or SP1 visit), acceptability of the study agent, FTC/TDF (Truvada®), the study itself, and PrEP in general will also be assessed. Descriptions of the measures that will be included in the ACASI can be found in Section 7.6 below.

7.4 Youth Who Decline Participation

Youth who decline participation in the study, but are willing to complete a brief survey will be administered the PrEP Opinion Questionnaire (see Appendix XIII). This questionnaire was developed for use in ATN 082 based on the Vaccine Opinion Questionnaire (Meyers et al., 1994), which explores the issues that affect participation in HIV vaccine trials. This is a brief questionnaire to be completed on the same iTouch used for initial screening. The questionnaire asks about reasons for declining to participate in the study, if the individual had heard about/tried or knew anyone who has used PrEP previously, and the individual's interest in taking PrEP.

7.5 Implementation Process Evaluation

In order to better understand the institutional acceptability and feasibility of allowing minor youth to consent for their own participation, so as to inform the future enrollment of minor youth in subsequent PrEP and other biomedical prevention trials, a case study analysis of IRB review will be conducted across the network. This case study analysis will examine the process by which study investigators, in collaboration with local IRBs and other key study personnel, reach decisions regarding the inclusion of minor youth in this study; and chronicle the critical legal, ethical and practical issues that emerge during this process. Data will be collected using the methodologies addressed below, organized using a qualitative software package, and then analyzed to: (1) document the chronology of the decision-making process within each site, and identify the primary legal, ethical and practical themes that emerge; and then (2) compare the chronology of decision-making processes between sites, and identify common themes that emerge across the network. Data collection methodologies will include the qualitative review of IRB-related correspondence and documents generated during the IRB-review process, as well as key informant interviews. Correspondence data of interest include information captured in written and/or e-mailed communications between study investigators and IRB representatives, verbal communication logs documenting conversations between the same, and relevant discourse captured by the ATN QNS. Documents of interest include IRB-approved consent forms and related materials. The semi-structured key informant phone interviews will occur as soon as possible after a definitive decision has been made by the site PI regarding whether or not to proceed with implementation. These interviews will be digitally recorded and comprised primarily of open-ended questions, with prompts designed to elicit additional information, regarding personal prior experience with research requiring minor consent, report of perceived IRB experience with research requiring minor consent, issues that personally gave the informant pause, report of issues that gave the IRB pause, the process by which identified issues were

addressed, confidence that the best possible conclusion was reached, and practical lessons learned during the IRB approval process. Key informants to be interviewed include site primary investigators. The NICHD program officer and/or members of the ATN EAP may also be asked to participate.

7.6 Description of Measures

7.6.1 Acceptability/Feasibility

- Acceptability Assessment. Assessment of acceptability will be conducted at the Weeks 12 and 48 study visits. This instrument, used in ATN 082, assesses: 1) the usability of PrEP; 2) the user-friendliness of the medication regimen (including an assessment of side effects) and the delivery format; and 3) the acceptability of behavioral intervention sessions.
- PrEP Questions. These eight questions adapted from the iPrEx Open Label Extension (OLE) study explore the overall acceptability of PrEP and perceived efficacy of PrEP based on subjects' experiences in this trial.
- Beliefs about PrEP. These nine questions adapted from the iPrEx OLE study explore potential ways that PrEP may influence subjects' health, condom use, sexual behavior as well as reasons that subjects would chose not to take PrEP.
- Support from Others. This question, adapted from the VOICE trial, asks subjects who they have had discussion with about their PrEP trial participation.
- Session Evaluation Form (SEF; Harper, Contreras, Bangi, & Pedraza, 2003). The SEF is a brief 13-item questionnaire that will be given to study subjects at the end of the behavioral intervention session. This questionnaire consists of 10 items on a 4-point response scale aimed at eliciting information about the subject's experience with the session (i.e., was the session interesting, was it relevant to their life, did they learn from the session). Three open-ended items query subjects about what was most and least useful about the session.
- Feasibility Assessment. We will collect process indicators throughout the study period including: number screened, number eligible, number enrolled, number staying on PrEP, attendance at study visits, and retention rates.

7.6.2 Medication Adherence

- Prevention Medication Readiness. We will adapt the HIV Treatment Readiness Measure (HTRM; Fernandez, Hosek, Warren, & Martinez, 2011) for PrEP by utilizing extant literature from other diseases as well as behavioral theory to assess subjects' readiness to begin taking HIV prevention medication.
- Time-Line Follow-Back (TLFB; Sobell, et al., 1980). This calendar method, which was originally developed to gather information on daily alcohol consumption, will be adapted to explore the subject's self-report of adherence difficulties with PrEP. The TLFB will also serve as a temporal ordering cue to help subjects piece together their adherence rates over the past month. First, subjects will be shown a calendar of the last 30 days. They will then be asked to remember any significant events (i.e., holidays, birthdays, deaths) or daily occurrences (i.e., work/school schedule) that happened during that period. Finally, they will be asked about the number of missed doses of medication for each day. A proportion of medication adherence (number of days of missed medication/total number of days) will be calculated.
- Sex Life and Pill. These questions, adapted from the CDC's TDF2 study, explore whether a subject's study pill adherence changed based on current sexual behavior.

- Medication Gaps (Berg & Arnsten, 2006). Medication gaps, or the period of time that a subject's supply of study medication is assumed exhausted, will be documented by comparing the actual refill dates with the expected refill dates.
- AIDS Clinical Trial Group Adherence Follow-up Questionnaire (ACTG; Chesney, Morin, & Sherr, 2000). This scale will be adapted to examine the possible reasons for missing medication. The questionnaire presents a number of possible reasons for missing medication and asks subjects to rate how often they have missed taking their medications over the past month due to these reasons. Subjects rate the reasons for missing medications on a 4-point Likert scale ranging from Never to Often.
- **Medication Levels. DBS and hair samples** will be collected to assess plasma TFV and FTC concentrations, as well as intracellular TFV-DP and FTC-TP concentrations.
- Wisepill. The Wisepill device has a global system for mobile (GSM) communication chip and a wireless signal is sent to a central management system (Wisepill Web Server) whenever the device container is opened. Wisepill data (unique identifier and time/date stamp) will be received on a continual basis and stored on the secured Wisepill Web Server.

7.6.3 Behavioral Disinhibition/Risk Compensation

- Sexual Activity and Sexual Risk Assessment. This measure assesses subject's overall sexual history as well as in-depth analysis of the sexual behavior that occurred with the last sexual partner.
- Beliefs Related to HAART (Stolte, Dukers, Geskus, Coutinho, & de Wit, 2004). This 10-item scale measures perceptions of HIV-related threat and the need for continued safer sex in the age of HAART. The original scale demonstrates good internal reliability (0.75). This scale has been adapted to examine beliefs related to PrEP.
- Treatment-Related Reduced HIV Risk (Vanable, Ostrow, & McKirnan, 2003). This 6-item scale assesses decreased personal worry about engaging in unsafe sex and the potential for infecting others because of the availability of combination therapies. The scale utilizes a 5-point Likert scale and demonstrates internal reliability of 0.72. This scale was adapted for ATN 082 to examine beliefs related to PrEP.
- Post-exposure Prophylaxis-Related Beliefs (van der Snoek, de Wit, Mulder, & van der Meijden, 2005). This 6-item scale was developed to examine the association between knowledge of PEP and perceptions about HIV and safer sex. High internal reliability of 0.89 is reported. This scale was adapted for ATN 082 to examine beliefs related to PrEP.
- Beliefs about Condom Use. This 12-item questionnaire developed by Golub and colleagues for iPrEx and adapted for iPrEx OLE explores factors that may impact decisions to have sex with or without condoms.
- The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST; World Health Organization, 2002) This measure was developed for the World Health Organization (WHO) to detect psychoactive substance use and related problems in primary care patients across multiple cultures. Individuals respond to items assessing the frequency of drug and alcohol use over the past 30 days.

7.7 Training and Supervision of Behavioral Intervention

Protocol **Chair** (Hosek) and the **Counseling Coordinator (Balthazar)** will assume primary responsibility for training the intervention facilitators and the sites regarding the behavioral interventions.

The intervention facilitators will have previous experience facilitating HIV prevention sessions with youth. It is also preferable that they be trained in either 3MV or PCC. At least one facilitator at each site for the 3MV will identify as an MSM of color. Previous experience in conducting research studies is also desired, but not required.

7.8 Intervention Monitoring/Quality Control

The intervention facilitators will be trained centrally to carry out the intervention protocol, thus providing consistency in training experience. All intervention sessions during this study will be recorded using digital voice recorders. Digital recordings will be reviewed by the Protocol **Chair** (Hosek) and the Project Director (Brothers) to assess for competence and adherence to the protocol. A standardized measure of protocol adherence will be developed based on key elements for each session to be delivered. Whenever less than 90% of elements are addressed in a given session (drift), the Team will meet with facilitators via phone conference to address the difficulty they are having in adhering to the intervention protocol. If drift continues, facilitators will be re-trained. Intervention facilitators will also engage in group supervision via conference calls. In addition, intervention facilitators will complete session checklists at the end of each session to document which elements of the intervention were delivered and to record unique issues that arise. This method has proven successful in assisting interventionists in monitoring their adherence to the protocol and preventing the use of proscribed interventions in prior studies. By providing multiple layers of clinical oversight and ongoing feedback from several sources, deviations from fidelity will be easily detected and addressed.

8.0 STUDY EVALUATIONS

See Appendices I and II for a summary of the evaluations described below and their schedule of completion. The guidelines for specimen collection, processing, storage and shipping can be found in Appendices IV through VIII.

Medical and medication history will be collected via subject self-report, since it is not expected that the subjects are patients at the AMTU and therefore, medical records are unlikely to be available.

For every visit, subjects will be asked to bring all medications including over-the-counter medications, vitamins and herbal remedies they are currently taking with them to the visit to ensure that an accurate record of concomitant medications is obtained.

8.1 Screening Visit

Subjects identified eligible based on the iTouch Screening Interview will be scheduled for the Screening visit at the AMTUs within the next two weeks. At the Screening visit, after signed informed consent is obtained, the following will be completed.

8.1.1 Demographics and Medical History

- Contact information
- Demographics (i.e., date of birth, gender at birth, and race/ethnicity)
- Lifetime history of bone disease, bone fractures, renal disease, hospitalizations (not including emergency room visits), and any other clinically significant **systemic** diagnosis as determined by the site investigator **including, but not limited to:**

- **Type 1 diabetes**
- **Asthma for which the subject is on daily medications**
- **Systemic disease such as rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma**
- **History of cancer/malignancy**
- **Inflammatory bowel disease**
- **Mental illness requiring daily medications**
- **Seizure disorder requiring daily medications**
- Prior 12 month history of medications in the following categories: steroids, glucocorticoids, hormones, anticonvulsants, selective serotonin reuptake inhibitors (SSRI), serotonin and norepinephrine reuptake inhibitors (SNRI), proton pump inhibitors (PPI) (See Appendix XI for list of ATN 113 targeted medications)
- Prior 30 day history of all other medications (including herbal therapies, vitamins and other supplements)
- Review of signs and symptoms in the past 30 days, including signs and symptoms consistent with acute HIV-1 infection

8.1.2 Clinical Evaluations

- Complete physical exam to include vital signs (temperature, heart and respiratory rate, and blood pressure), **height and weight**, and a review of all body systems, including a symptom-directed evaluation to rule out STIs (inclusive of urethral, rectal and pharyngeal anatomical sites)

8.1.3 Laboratory Evaluations

- HIV testing using an FDA-approved rapid assay
- Serum chemistries: calcium (Ca), phosphate (PO₄), blood urea nitrogen (BUN), creatinine (sCr), glucose, electrolytes (sodium (Na), potassium (K), chloride (Cl), & carbon dioxide (CO₂)), amylase and liver function tests (LFTs) (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin)
- CBC with differential and platelets
- Spot urine protein to creatinine **ratio** (UP/C)
- Urine dipstick for protein and glucose
- Hepatitis B surface Antigen (HBsAg)

NOTE: Subjects that test HBsAg positive are not eligible for the study and will be referred for appropriate evaluation and care

At the end of the visit, subjects will receive condoms with appropriate counseling.

8.2 Baseline Visit

Results of the screening laboratory tests will be reviewed to confirm that the subject meets all eligibility requirements. The *ATN 113 Eligibility and Enrollment Form* will be completed and

entered in the Oracle Clinical-Remote Data Capture (OC-RDC) database for all eligible subjects. The subject is considered enrolled upon completion of entry of this form in the OC-RDC database. Ineligible individuals will be given an incentive to thank them for their time.

NOTE: If any screening laboratory test(s) exclude a subject from the study, the test(s) may be repeated. If the repeat laboratory test(s) result(s) meet inclusion criteria, the subject may be eligible for enrollment. These evaluations must be completed and reviewed prior to the Baseline visit.

8.2.1 Medical History

- Review information on *ATN 113 Contact Form* with the subject and update as needed
- Interim history of bone disease, bone fractures, renal disease, hospitalizations (including emergency room visits), and any other clinically significant **systemic** diagnosis as determined by the site investigator (**see Section 8.1.1**)
- Interim medication history - all prescription and non-prescription medications
- Interim signs and symptoms, including signs and symptoms consistent with acute HIV-1 infection

8.2.2 Clinical Evaluations

- Symptom-directed physical exam to include vital signs (temperature, heart and respiratory rate, and blood pressure), height and weight, Tanner stage assessment by genital exam or administration of the Self-Assessment of Tanner Stage Tool (see Appendix X), and review of body systems as clinically indicated, including a symptom-directed evaluation to rule out STIs (inclusive of urethral, rectal and pharyngeal anatomical sites)

8.2.3 Laboratory Evaluations

- HIV testing using an FDA-approved rapid assay
- Serum chemistries: Ca, PO₄, BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin)
- CBC with differential and platelets
- Hepatitis B surface antibody (HBsAb)
NOTE: Subjects that test HBsAb negative will be referred for hepatitis B vaccination.
- Syphilis testing using the rapid plasma reagin (RPR) test or another FDA-approved diagnostic test
- Urine gonorrhea and chlamydia testing using nucleic acid amplification test (NAAT) or another FDA-approved diagnostic test
NOTE: Subjects that screen positive for an STI will be referred for treatment.
- Rectal swab for central gonorrhea and chlamydia testing (see Appendix VIII)
- HIV-1 RNA PCR (viral load)

8.2.4 Other Diagnostic Procedure

- DXA to measure BMD in the hip and spine, and whole-body BMC. Three separate scans will be performed. The baseline DXA can be performed at the Baseline visit or anytime between the Baseline and the Week 0 visits. On rare occasions, a baseline DXA will have to be repeated if

image quality is not adequate for analysis. If this occurs, the repeat scan should be done as soon as possible, but no more than 14 calendar days after the first dose of study agent. Subjects whose weight exceeds the weight limit of the local DXA scan machine are exempt from DXA scanning. For additional details on DXA procedures, see **ATN 110/113 DXA Manual of Operations on the ATN website (www.atnonline.org)**.

8.2.5 Behavioral Assessments

- Baseline ACASI
- Evaluation for PEP

At the end of the visit, subjects will be provided with condoms and appropriate counseling.

8.3 3MV/PCC Behavioral Intervention

Once the Baseline visit is completed, the subject will be scheduled to attend the next available 3MV behavioral intervention (Appendix XIV) or the PCC session, depending on which intervention the AMTU was assigned. The *Session Evaluation Form* (Appendix XV) will be completed after completion of the behavioral intervention.

8.4 Re-Screening Visit

If the Week 0 visit is not completed within 30 calendar days after the Screening visit, subjects must complete a Re-screening visit in order to remain in the study.

8.4.1 Medical History

- Review information on *ATN 113 Contact Form* with the subject and update as needed
- Interim history of bone disease, bone fractures, renal disease, hospitalizations (including emergency room visits), and any other clinically significant systemic diagnosis as determined by the site investigator (see Section 8.1.1)
- Interim medication history - all prescription and non-prescription medications
- Interim signs and symptoms, including signs and symptoms consistent with acute HIV-1 infection

8.4.2 Clinical Evaluations

- A complete physical examination identical to the one required at the Screening visit

8.4.3 Laboratory Evaluations

- HIV testing using an FDA-approved rapid assay
- Serum chemistries: Ca, PO₄, BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin)
- CBC with differential and platelets
- Spot UP/C
- Urine dipstick for protein and glucose

- **Hepatitis B surface antigen, if HBsAb at Baseline visit was non-reactive**
- **Syphilis testing using the RPR test or another FDA-approved diagnostic test, if another FDA-approved test is clinically indicated**
- **Urine gonorrhea and chlamydia testing using NAAT or another FDA-approved diagnostic test, if clinically indicated**
- **Rectal swab for central gonorrhea and chlamydia testing if clinically indicated**
- **HIV-1 RNA PCR (viral load)**

8.4.4 Other Diagnostic Procedure

- **DXA to measure BMD in the hip and spine, and whole-body BMC, only if 90 calendar days or more has elapsed since the baseline DXA was performed. DXA scans must be obtained within seven calendar days before or after the Re-screening visit. On rare occasions, it may be necessary to repeat a DXA scan. If this occurs, the repeat scan should be done within 14 calendar days of the previous scan. Subjects whose weight exceeds the weight limit of the local DXA scan machine are exempt from DXA scanning.**

At the end of the visit, subjects will receive condoms with appropriate counseling.

8.5 Week 0 Visit

The Week 0 visit must occur within 30 calendar days after the Screening visit (i.e., Screening, Baseline, 3MV/PCC, and Week 0 visits all must occur within 30 calendar days) **or within 30 calendar days after the Re-screening visit, if applicable, as described above in Section 8.4. If this does not occur, the subject will be discontinued from the study and no further evaluations will be required.**

8.5.1 Medical History

- Review information on *ATN 113 Contact Form* with the subject and update as needed
- Interim history of bone disease, bone fractures, renal disease, hospitalizations (including emergency room visits), and any other clinically significant **systemic** diagnosis as determined by the site investigator (**see Section 8.1.1**)
- Interim medication history - all prescription and non-prescription medications
- Interim signs and symptoms, including signs and symptoms consistent with acute HIV-1 infection

8.5.2 Clinical Evaluations

- Symptom-directed physical exam to include vital signs (temperature, heart and respiratory rate, and blood pressure), **height and weight**, and review of body systems as clinically indicated, including a symptom-directed evaluation to rule out STIs (inclusive of urethral, rectal and pharyngeal anatomical sites)

8.5.3 Laboratory Evaluations

- HIV testing using an FDA-approved rapid assay
- Urine dipstick for protein and glucose

NOTE: Urine dipstick for protein and glucose must be negative or trace before a subject begins the study agent. A result of 1+ or greater for urine dipstick protein or 1+ or greater for urine dipstick glucose in the presence of normal serum glucose (< 120 ml/dL) must be repeated. If the repeat result is 1+ or greater, the subject will be prematurely discontinued from study (see Section 8.7.2). If the repeat test is not 1+ or greater, the subject may proceed with the study.

- HBsAg (for subjects with no documented positive HBsAb result only)

NOTE: Subjects that test HBsAg positive will be referred for appropriate evaluation and care.

- Urine gonorrhea and chlamydia testing using NAAT or another FDA-approved diagnostic test

NOTE: Subjects that screen positive for an STI will be referred for treatment.

- Rectal swab for central gonorrhea and chlamydia testing as clinically indicated (see Appendix VIII)

8.5.4 Behavioral Assessments

- iNSC
- Evaluation for PEP

At the end of the visit, subjects will receive condoms with appropriate counseling. The study agent, FTC/TDF (Truvada®), will be dispensed after site staff has reviewed the Baseline visit HIV-1 viral load result to make certain that subject is not HIV infected or seroconverting. Subjects will receive a 30-day supply of FTC/TDF (Truvada®). Select subjects at pre-selected AMTUs will be given the Wisepill container for use with their study agent. The study pills will be placed into the Wisepill container. Each time the container is opened, a signal with a unique identifier and time/date stamp will be sent to a secure server at the company, Wisepill Technologies.

8.6 Follow-up Study Visits

Follow-up study visits will begin four weeks from the date of the Week 0 visit. Visits will occur at Weeks 4, 8, 12, 24, 36, and 48. If a follow-up study visit cannot be conducted on its target visit date, the preferred timeframe for completion of that visit is within seven calendar days prior to or after the target visit date.

8.6.1 Medical History

- Review information on *ATN 113 Contact Form* with the subject and update as needed
- Interim history of bone disease, bone fractures, renal disease, hospitalizations (including emergency room visits), and any other clinically significant **systemic** diagnosis as determined by the site investigator (see **Section 8.1.1**)
- Interim medication(s) history - all prescription and non-prescription medications
- Interim signs and symptoms, including signs and symptoms consistent with acute HIV-1 infection

8.6.2 Clinical Evaluations

- **Height and weight**

- Symptom-directed physical exam to include vital signs (temperature, heart and respiratory rate, and blood pressure) and review of body systems as clinically indicated, including a symptom-directed evaluation to rule out STIs (inclusive of urethral, rectal and pharyngeal anatomical sites)

8.6.3 Laboratory Evaluations

- HIV testing using an FDA-approved rapid assay
- Serum chemistries (Weeks 12, 24, 36 and 48 only): Ca, PO₄, BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin)

NOTE: Subjects with known Grade 2 or higher sCr or an increase in sCr from baseline by $\geq 50\%$ at Week 12, 24 and/or 36 will have the study agent held or will receive only a limited supply (7-10 day supply) until the test is repeated. If the Grade 2 or higher sCr or increase in sCr from baseline by 50% or more is confirmed, the subject must be followed per Section 10.7.2.

- Serum creatinine (sCr) only (Weeks 4 and 8 only)
- CBC with differential and platelets (Weeks 12, 24, 36 and 48 only)
- Urine dipstick for protein and glucose

NOTE: Subjects with known new or increased proteinuria, indicated by positive [$\geq 1+$] urine dipstick result, and/or normoglycemic glucosuria defined as $\geq 1+$ by urine dipstick in the presence of normal serum glucose (< 120 mg/dL) at Week 12, 24 and/or 36 will have the study agent held or will receive only a limited supply (7-10 day supply) until the test(s) is/are repeated. If the test(s) is/are confirmed to be 1+ or greater, the subject must be followed per Section 10.7.2.

- HBsAg (Weeks 24 and 48 only for subjects with no documented positive HBsAb result)

NOTE: Subjects that test HBsAg positive will be referred for appropriate evaluation and care.

- Syphilis testing (Week 48 only) using the RPR test or another FDA-approved diagnostic test
- Urine gonorrhea and chlamydia testing using NAAT or another FDA-approved diagnostic test

NOTE: Subjects that screen positive for an STI will be referred for treatment.

- Rectal swab for central gonorrhea and chlamydia testing (Weeks 24 and 48 and as clinically indicated) (see Appendix VIII)
- HIV-1 viral load (Week 48 only)
- DBS for TFV, FTC, TFV-DP and FTC-TP concentration measurements (Weeks 4, 8, 12, 24, 36, and 48)
- Hair sample for TFV and FTC concentration (Weeks 4, 8, 12, 24, 36, and 48)
- HIV home testing kits will be provided to subjects at Weeks 12, 24, and 36 for home testing at Weeks 16, 20, 28, 32, 40 and 44

NOTE: At Weeks 12, 24, and 36, subjects will be provided with and instructed on the proper administration of the HIV home testing kits (see Section 10.2.3).

8.6.4 Other Diagnostic Procedure

- DXA (Weeks 24 and 48 only) to measure BMD in the hip and spine, and whole-body BMC. DXA scans must be obtained within seven calendar days before or after the corresponding study visit. On rare occasions, it may be necessary to repeat a DXA scan. If this occurs, the repeat scan should be done within 14 calendar days after the previous scan. Subjects whose weight exceeds the weight limit of the local DXA scan machine are exempt from DXA scanning.

8.6.5 Behavioral Assessments

- Follow-up ACASI (Weeks 4, 8, 12, 24, and 36); final ACASI (Week 48)
- iNSC
- Evaluation for PEP

At the end of each follow-up study visit, subjects will receive condoms with appropriate counseling. At the end of each follow-up study visit through Week 36, subjects will receive a supply of the study agent, FTC/TDF (Truvada®). The study agent will not be dispensed until all required visit evaluations are completed. **If it is known that a subject has any of the abnormal laboratory test results noted above, the study agent will be held or only a limited supply (7-10 day supply) will be dispensed, per the discretion of the site clinician, until the abnormal test(s) is/are repeated. If test remains abnormal, follow procedures in Section 10.7.2.** If a study visit is delayed or missed and the subject's study agent supply runs out, the number of days without study agent will be documented in the subject's research record. If at any time during the study, a subject self reports barriers to adherence and subsequently reports less than 80% adherence to the study agent, daily text message reminders will be offered. Subjects at selected AMTUs will receive the Wisepill device container for their study agent. Each time the container is opened, a signal with unique identifier and time/date stamp will be sent to a secure server at Wisepill Technologies.

8.7 Premature Discontinuation Evaluations

8.7.1 Subjects Who Prematurely Discontinue from Study Agent

Subjects who discontinue from the study agent, FTC/TDF (Truvada®), prior to the Week 48 visit will continue to complete all study visits as scheduled and complete all evaluations per the Follow-up study visits schedule (see Section 8.6). The exceptions are: 1) no specimens will be collected for TFV, FTC, TFV-DP, and FTC-TP concentration measurements; 2) the ACASI will not include questions related to study pill adherence; and 3) no study agent will be dispensed at the end of the visits.

If a subject has taken the study agent for any length of time since the previous study visit, all the evaluations for the standard study follow-up visit will be done at the first visit after discontinuing the study agent. At the completion of that study visit, the subject will be considered off study agent. Starting at the next follow-up visit, the evaluations for subjects who prematurely discontinued from study agent will be followed.

8.7.2 Subjects Who Prematurely Discontinue from Study

Subjects who discontinue from the study before completing Week 0 (before starting the study agent) will have no further study evaluations performed. Subjects who discontinue from the study after Week 0 (after starting the study agent), but prior to the Week 48 visit, will have all evaluations scheduled for the Week 48 visit completed at the time of study discontinuation.

8.8 HIV Seroconversion Visits

Subjects found to have a reactive HIV antibody test will be instructed to temporarily stop taking the study agent. Subjects will be counseled that additional HIV testing is required and will have blood drawn for confirmatory HIV serology and viral load, as well as additional evaluations as described in Section 8.8.1 below for the HIV Confirmatory Testing (CFM) Visit. Subjects with indeterminate result will be instructed to temporarily stop taking the study agent and return weekly for HIV testing only until the subject is confirmed either HIV infected or not HIV infected. If it is confirmed that a subject is HIV infected, the study staff will provide counseling and referral for primary HIV care. The subject will be permanently discontinued from the study agent, but will continue to participate in the study following the evaluations outlined in Section 8.8.2 below for the HIV Seropositive visits. If it is determined that the subject is not HIV infected, the subject will resume taking the study agent and return to the original Follow-up Study Visits schedule. **The ATN 113 Protocol Team must be notified of all confirmed HIV infections via the ATN QNS.**

8.8.1 HIV Confirmatory Testing Visit

8.8.1.1 Medical History

- Review information on *ATN 113 Contact Form* with the subject and update as needed
- Interim history of bone disease, bone fractures, renal disease, hospitalizations (including emergency room visits), and any other clinically significant **systemic** diagnosis as determined by the site investigator (**see Section 8.1.1**)
- Interim medication(s) history - all prescription and non-prescription medications
- Interim signs and symptoms, including signs and symptoms consistent with acute HIV-1 infection

8.8.1.2 Clinical Evaluations

- Symptom-directed physical exam to include vital signs (temperature, heart and respiratory rate, and blood pressure), **height and weight**, and review of body systems as clinically indicated, including a symptom-directed evaluation to rule out STIs (inclusive of urethral, rectal and pharyngeal anatomical sites)

8.8.1.3 Laboratory Evaluations

- Confirmatory HIV-1 serology test
- HIV-1 viral load
- Plasma for HIV drug resistance testing. Two aliquots will be processed, one for genotype testing at the local laboratory and another to be stored for central genotype and phenotype testing. Request the local laboratory to process and store the samples until the HIV-1 confirmatory test result is received. If confirmatory test result is negative, the samples may be discarded

The following will be done only if not done at the visit with the first reactive HIV antibody test:

- Serum chemistries: Ca, PO₄, BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin)
- CBC with differential and platelets
- Urine dipstick for protein and glucose
- Urine gonorrhea and chlamydia testing using NAAT or another FDA-approved diagnostic test

- HBsAg (if required to verify active hepatitis B infection status)
- Syphilis testing using the RPR test or another FDA-approved diagnostic test (if required to verify syphilis status)
- DBS for TFV, FTC, TFV-DP, **and FTC-TP concentration measurements**
- Hair sample for TFV and FTC concentration

At the end of the visit, subjects will receive condoms with appropriate counseling.

8.8.2 HIV Seropositive Visits

There are three HIV Seropositive visits, SP1, SP2, and SP3, at 4, 12, and 24 weeks, respectively, after HIV infection is confirmed. If at the SP3 visit, the subject meets specific bone or renal criteria, the subject will continue to be followed on the Extension Phase schedule (see Section 8.9).

8.8.2.1 Medical History

- Review information on *ATN 113 Contact Form* with the subject and update as needed
- Interim history of bone disease, bone fractures, renal disease, hospitalizations (including emergency room visits), and any other clinically significant **systemic** diagnosis as determined by the site investigator (see Section 8.1.1)
- Interim medication(s) history - all prescription and non-prescription medications
- Interim signs and symptoms

8.8.2.2 Clinical Evaluations

- **Height and weight**
- Symptom-directed physical exam to include vital signs (temperature, heart and respiratory rate, and blood pressure), and review of body systems as clinically indicated, including a symptom-directed evaluation to rule out STIs (inclusive of urethral, rectal and pharyngeal anatomical sites)

8.8.2.3 Laboratory Evaluations

- HIV-1 viral load (may be recorded from clinical care visit)
- CBC with differential and platelets (may be recorded from clinical care visit)
- CD4+ T cell count (may be recorded from clinical care visit)
- Serum chemistries: Ca, PO₄, BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin)
- Urine dipstick for protein and glucose (SP3 visit only)

8.8.2.4 Other Diagnostic Procedure

- DXA (SP3 visit only) to measure BMD in the hip and spine, and whole-body BMC. DXA scans must be obtained within seven calendar days before or after the corresponding study visit. On rare occasions, it may be necessary to repeat a DXA scan. If this occurs, the repeat scan should be done within 14 calendar days after the previous scan. Subjects whose weight exceeds the weight limit of the local DXA scan machine are exempt from DXA scanning.

8.8.2.5 Behavioral Assessments

- Final ACASI (SP1 visit only)
- iNSC

At the end of the visit, subjects will receive condoms with appropriate counseling.

8.9 Extension Phase Visits

Subjects who meet any of the bone or renal criteria below at the Week 48 or the SP3 visit will continue to be followed in the Extension Phase (**EPH**) and complete two additional visits, EPH1 and EPH2, at 24 and 48 weeks, respectively, after the Week 48 or the SP3 visit.

- Confirmed \geq Grade 1 sCr
- An increase in sCr of 50% or more from baseline (i.e., value at Screening visit)
- Confirmed CrCl $<$ 60 ml/min (**For subjects $<$ 18 years of age**, use the bedside Schwartz formula: $GFR = (0.413 \times \text{height in cm}) / (\text{serum creatinine in mg/dl})$. **For subjects \geq 18 years of age**, use the Cockcroft-Gault formula: $GFR = ((140 - \text{age in years}) \times (\text{weight in kg})) / (72 \times \text{serum creatinine in mg/dl})$)
- No increase from Baseline to Week 48 (or SP3 visit) in whole-body BMC or in BMD in lumbar spine
- Decrease from Baseline to Week 48 (or SP3 visit) in BMD z-score \geq 0.5 in
 - Total hip,
 - Femoral neck, or
 - Lumbar spine
- Confirmed \geq Grade 2 hypophosphatemia
- Confirmed proteinuria as indicated by urine dipstick result \geq 1+
- Confirmed normoglycemic glucosuria as indicated by urine dipstick result \geq 1+ in the presence of normal serum glucose ($<$ 120 mg/dL)

Confirmed means that the abnormality was detected at the Week 48 visit (or SP3 visit) and then confirmed on repeat measurement done within one week. At the end of the Week 48 visit or SP3 visit, the subject will be reminded that two additional visits may be required in approximately another 6 and 12 months based on the results of the evaluations done at the current study visit. The subject will be informed that the study staff will contact the subject about the need to return for the two additional visits and provide an approximate timeframe for that contact.

The following evaluations will be completed for all subjects at the EPH1 and EPH2 visits. See Appendix II for a summary of the evaluations described below.

8.9.1 Medical History

- Review information on *ATN 113 Contact Form* with the subject and update as needed

- Interim history of bone disease, bone fractures, renal disease, hospitalizations (including emergency room visits), and any other clinically significant **systemic** diagnosis as determined by the site investigator (see **Section 8.1.1**)
- Interim medication(s) history – all prescription and non-prescription medications
- Interim signs and symptoms, including signs and symptoms consistent with acute HIV-1 infection for HIV uninfected subjects

8.9.2 Clinical Evaluations

- Symptom-directed physical exam to include vital signs (temperature, heart and respiratory rate, and blood pressure), height and weight, and review of body systems as clinically indicated, including a symptom-directed evaluation to rule out STIs (inclusive of urethral, rectal and pharyngeal anatomical sites)

8.9.3 Laboratory Evaluations

- HIV testing using an FDA-approved rapid assay (HIV-uninfected subjects only)
- Serum chemistries: Ca, PO₄, BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin)
- CBC with differential and platelets
- Urine dipstick for protein and glucose

8.9.4 Other Diagnostic Procedure

- DXA to measure BMD in the hip and spine, and whole-body BMC. DXA scans must be obtained within seven calendar days before or after the corresponding study visit. On rare occasions, it may be necessary to repeat a DXA scan. If this occurs, the repeat scan should be done within 14 calendar days of the previous scan. Subjects whose weight exceeds the weight limit of the local DXA scan machine are exempt from DXA scanning.

8.9.5 Behavioral Assessments

- iNSC

At the end of the visit, subjects will receive condoms with appropriate counseling.

9.0 DATA COLLECTION AND SITE MONITORING

This study follows ATN standards and recommended guidelines for data management specified in Chapter 8 of the ATN MOGO.

9.1 Development of Protocol and Case Report Forms

The ATN DOC, in collaboration with the ATN 113 Protocol Team, is responsible for the development of this protocol as well as the case report forms (CRFs) needed to collect the information required to implement this protocol.

9.2 Data Records

Subject-related study information will be identified through the PID and SID on all subject CRFs, digital recordings and ACASI files. Subject names or other personally identifying information will not be used on any study documents. All study-related information will be kept in double-locked, limited access areas at each study site. A log that links the names of subjects to their PID and SID will also be kept under double locks separate from all other research records, accessible only to the study staff, ATN site monitors, and representatives from the NICHD. Original source documents for individual subjects will be maintained at the respective AMTU and will be accessible only to the study staff. Data from original source documents will be transcribed onto CRFs as applicable.

9.3 Data Collection

9.3.1 Case Report Forms

Study monitoring data, including information about eligibility, demographic data and monitoring of adverse events and untoward events, will be collected on CRFs. All CRFs for this study will be available for download from the ATN website (www.atnonline.org). Hard copies of CRFs may be ordered from the ATN DOC via an order form on the ATN website.

All CRFs must have corresponding source documentation on file at the clinical site to substantiate all submitted data (DAIDS Source Documentation Guidelines, see Appendix 4 of the ATN MOGO). Data edits through range checks and field inconsistencies will be built into the OC-RDC database to enable real time correction of key entries and CRF completion errors.

9.3.2 Digital Recordings

The 3MV intervention and PCC sessions will be recorded using digital voice recorders. All session digital recordings will be labeled with the site number, session date and time, and SID number (for individual sessions), and will be logged on the Digital Voice Recording Tracking and Destruction Log. No identifying information will appear on the label of the digital recordings. When not in use, all digital recordings will be securely maintained at the AMTU in a locked area with limited access.

AMTUs will upload digital recordings to a temporary secure server at the ATN DOC within one week after the 3MV intervention/PCC session and will notify the Protocol Chair and Project Director via email that the files can be securely downloaded. The Protocol Chair and Project Director will have one week to download the digital recording, before the digital recording is automatically deleted from the temporary secure server at the ATN DOC.

The digital recordings will be stored at the AMTU until the Protocol Chair and Project Director have completed fidelity review. Upon completion of fidelity review, the Study Coordinator (or designee) at the AMTU and the Protocol Chair and Project Director will ensure that all digital recordings are appropriately destroyed according to the ATN Guidelines for the Destruction of Sensitive Study-Related Records and Media (see Appendix 1A-9 of the ATN MOGO). Destruction will occur at each AMTU and with the Protocol Chair and Project Director. Destruction of digital recordings will be documented on the Digital Voice Recording Tracking and Destruction Log.

9.3.3 iForm/ACASI Data

All data collected using iForms will be installed on the iTouch device. All data collected using the ACASI will be installed on a portable laptop computer. The iForm (iTough Screening Interview and

iTouch PrEP Opinion Questionnaire) data will remain anonymous. The ACASI data will remain confidential. No protected health information will be collected during the computer sessions.

iForm Data Security

Only authorized users with a login name and password will be able to access and open the iTouch interviews. As each section of the interview is completed, the section will be saved and encrypted so that no one is able to look back at previous screens to view the data.

ACASI Data Security

After a subject completes the survey, the ACASI data will be saved in a password-protected compressed file using a FIPS 140-2 and NIST-certified encryption and decryption engine developed by PGP, a leader in the security marketplace.

As each section of the interview is completed, the section will be saved and encrypted so that no one is able to look at previous screens to view the data. If the subject completing the interview requires a short break, it is possible to stop the interview and return later to complete it. Only authorized users with a login name and password will be able to open the survey on the laptop.

9.4 Data Submission

9.4.1 Case Report Forms

AMTUs must follow ATN guidelines for CRF completion and entry that are specified in Chapter 8 of the ATN MOGO. Once the study database is developed, the OC-RDC screens are available for data entry and protocol training has been completed, research staff at the sites will be responsible for ensuring that CRF data are entered into OC-RDC within the timeframe specified below. The ATN DOC will provide instructions for recording study data on the CRFs as well as instructions for entry of study data into the OC-RDC database.

The *Eligibility and Enrollment Form* must be entered into OC-RDC within 24 hours after the Baseline visit. The *Adverse Event Evaluation Form*, *Monitoring Untoward Event Form*, *Death Report Form* must be entered in OC-RDC within 3 working days of site awareness. The *Specimen Tracking Form* must be entered within 21 days of the specimen collection date. All other CRFs must be completed and entered into the database within 14 calendar days from the date of the study visit.

9.4.2 iTouch Data Transmission

The iTouch data will be transferred to the ATN DOC via laptop modem within 7 calendar days after data collection. It is recommended that completed interviews be transmitted to the ATN DOC at the end of each day to avoid accidental loss or damage.

9.4.3 ACASI Data Transmission

The ACASI file will be transferred to the ATN DOC via laptop modem within 7 calendar days after data collection. It is recommended that completed interviews be transmitted to the ATN DOC at the end of each day to avoid accidental loss or damage. Detailed instructions are provided in the ATN 113 ACASI Operating Guide, which is available at each AMTU. Upon transfer of the encrypted data to the ATN DOC, the data will be stored on Westat's secured network (with firewall protection), which cannot be accessed by anyone outside of Westat.

9.4.4 Wisepill Data

Wisepill data will be received on a continual basis (the wireless signal with unique identifier and time/date stamp is activated when the container is opened) and stored on a secure server at Wisepill Technologies.

9.4.5 Dual-Energy X-Ray Absorptiometry Data

All DXA scan data will be sent to the BCAC at Tufts University and will be read centrally. DXA scan data will be labeled with the subject's SID and will not have any personally identifying information. No reading will be done at the site level. DXA readings will be sent to Westat for archiving.

9.5 Data Quality Assurance

Investigators receiving federal funding must adhere to the Code of Federal Regulations (CFR) and FDA regulations to protect research subjects and produce reliable study information. The Investigator at each AMTU is responsible for the overall conduct of research activities at the site. AMTUs participating in research sponsored by the NICHD need to have an internal quality assurance (QA) plan that will identify problems and correct errors in research study records. AMTUs are responsible for following ATN data QA procedures (see Chapter 9 of the ATN MOGO).

9.6 Role of Data Management

The ATN DOC will provide instructions concerning the recording of study data on the CRFs, entry of the data into OC-RDC database, and ACASI administration and transmission. It is the responsibility of the ATN DOC to assure the quality of computerized data for each ATN study. This role extends from protocol development to generation of the final study databases.

9.7 Clinical Site Monitoring and Record Availability

9.7.1 Site monitors from the ATN DOC will visit participating clinical research sites' investigational pharmacies to review the overall study agent management, including receipt, storage, disposition and accountability of study agent. Regulatory files kept within the pharmacy will also be inspected to ensure that regulatory requirements are being followed.

9.7.2 The site investigator will make study documents (e.g., consent forms, CRFs) and pertinent hospital and clinic records readily available for inspection by the local IRB, the site monitors, the NICHD, the Office of Human Research Protection (OHRP), the FDA, or the sponsor's designee for confirmation of the study data.

9.8 Retention of Clinical Research Records

All clinical research records, including essential and source documents and records, in any form, that describe or record the methods, conduct, and/or results of a trial, and the actions taken, must be retained for a minimum of two years after a marketing application is approved for the drug for the indication for which it was being investigated (21 CFR 312.57 and ICH E6 4.9 and 5.5.6 – 5.5.8). Alternatively, if no application will be filed or if the application is not approved for the requested indication, the records must be retained for a minimum of two years after the investigation is discontinued and the FDA has been so notified.

10.0 SUBJECT MANAGEMENT

10.1 Tracking Subjects / Follow up

All study subjects will be contacted before each study visit. Multiple contact methods will be used for youth who are difficult to reach (e.g., mail, alternate phone numbers, email, text message, Facebook) (see Section 5.6). Subjects will be asked whether messages can be left for each of the phone numbers that they provide. They will be informed that messages will not contain any information regarding the nature of the project.

10.2 Study Visit Management

10.2.1 Study Visit Windows

All study visits are to be conducted according to the Schedule of Evaluations in Appendices I and II. There should be no more than 30 **calendar** days between the Screening and Week 0 visits, i.e., Screening, Baseline, the 3MV/PCC, and Week 0 visits must all occur within 30 calendar days. **If a Re-screening visit is conducted, there should be no more than 30 calendar days between the Re-screening and Week 0 visits.** If any of the follow-up study visits (Weeks 4, 8, 12, 24, 36, and 48 visits), HIV Seroconversion visits, or Extension Phase visits cannot be conducted on the target visit date, the preferred timeframe for these visits is within seven calendar days prior to or after the target visit date. If the subject is unable to complete a visit within this timeframe, the site staff should work with the subject to identify a day closest to the scheduled visit to perform the visit. Extension of the visit window must first be communicated to and approved by the ATN 113 Protocol Team via the ATN QNS. If not approved, the visit will be considered a “missed visit.” Protocol Team approval does not change the out-of-window status of a late visit. Scheduling of study visits will not be recalibrated based on the actual date that a visit was made. All follow-up study visits must be made based on the elapsed time from the date of the Week 0 visit.

At the end of each study visit, from Weeks 0 through 36, after all study evaluations have been completed, the study agent, FTC/TDF (Truvada®), will be dispensed to subjects who continue to be on the study agent. See section 6.5 for details.

10.2.2 Evaluation for PEP

At the end of each study visit and after subjects complete the ACASI, a debriefing interview will be conducted with each subject to evaluate the need for prescribing PEP based on current CDC recommendations located at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.htm#fig1>.

This will be done by determining:

- Whether a high-risk exposure to HIV (unprotected sexual contact with a known or suspected HIV positive individual) has occurred in the past 72 hours;
- If in that timeframe any of the PrEP doses were missed and if so, how long before the exposure was the last dose taken; and
- If indicated and recommended, whether the subject would be willing to take PEP consisting of three antiretroviral medications from at least two different ARV classes for one month.

The site investigator, based on evaluation and discussion with the youth, will determine if PEP will be prescribed to a subject. If PEP is prescribed, the subject will be temporarily discontinued from taking the study agent, FTC/TDF (Truvada®), until at least 30 days after initiation of the PEP course. At that time,

acute HIV infection should be ruled out by an ultrasensitive quantitative HIV RNA assay before the subject is allowed to resume study agent according to the original schedule.

Subjects who contact the site outside of a study visit with concerns about high-risk HIV exposure to someone with known or suspected HIV infection should be evaluated and managed similarly.

10.2.3 HIV Home Testing

HIV home testing kits (Home Access® HIV-1 Test System with modified study-specific packaging and instructions, see ATN 110/113 Home Access® HIV-1 Test Kit Manual) will be provided to subjects at the end of study visits at Weeks 12, 24, and 36 for home testing at Weeks 16, 20, 28, 32, 40, and 44. Two HIV home testing kits will be provided at Week 12 (for home testing at Weeks 16 and 20), Week 24 (for home testing at Weeks 28 and 32) and Week 36 (for home testing at Weeks 40 and 44). Prior to providing the kits, the study staff will review with the subject the instructions to collect and ship the sample for testing. The study staff will also explain to the subject how the test results will be reported.

Subjects who choose not to perform home HIV testing at any of the required study weeks indicated above should not be provided with Home Access HIV-1 test kits to cover those study weeks. In these circumstances, HIV testing must be done at the clinic, and preferably by using the Home Access HIV-1 test kits. In addition, if the subject was provided with the home test kit but does not complete home testing, site staff should attempt to bring the subject into the clinic for testing, preferably using the Home Access HIV-1 test kit. Study staff will contact the subject within 3 days prior to when home testing is due to remind the subject about the test and follow up with the subject within 2 days after the date home testing is due to make sure that the test sample was collected and sent for testing. Study staff will report test results to the subject. The test results will be transmitted to the ATN DOC via secured File Transfer Protocol (FTP) and the results will be made available to study staff. Study staff may also obtain test results directly from the Home Access® testing lab. Non-reactive results may be reported over the telephone. For reactive or indeterminate test results, the subject must be contacted to return to the clinic as soon as possible. The subject will be informed of reactive test results by the study staff in person in the clinic.

10.3 Study Subject Management

Subjects Who Become HIV-Infected

Subjects who are found to have a reactive HIV diagnostic test during study participation will be instructed to temporarily stop the study agent, FTC/TDF (Truvada®). Subjects will be counseled that additional HIV testing is required, and will have blood drawn for confirmatory HIV serology and viral load, as well as additional tests including serum chemistries and CBC with differential and platelets. If it is determined that the subject has become HIV-infected, at the visit when the result is confirmed, the study staff will provide counseling, information, and referral for primary HIV care. The subject will be permanently discontinued from the study agent and be followed for the next 24 weeks, in order to understand whether PrEP use altered the natural history of HIV in subjects who become HIV-infected. Drug resistance testing (genotypic) will be performed for all newly diagnosed seroconverters at the site's local laboratory for subject management. A separate sample will be stored for central laboratory drug resistance testing (genotypic and phenotypic). See Section 8.8.2 for the study evaluations to be performed for subjects who become HIV-infected.

Subjects Who Become Hepatitis B Surface Antigen Positive

If at any time during study participation a subject tests HbsAg positive, the subject will be referred for appropriate evaluation and care of hepatitis B infection. The subject will be permanently discontinued from the study agent, FTC/TDF (Truvada®) following clinical evaluation for hepatitis B.

10.4 Compensation

Compensation will be provided for subjects at each study visit. The amount of such compensation will be determined by the local ATN staff and each site's IRB and will be included in the site-specific consent form.

10.5 Withdrawal/Premature Discontinuation

10.5.1 Premature Discontinuation of Subject from Study Agent

Administration of study agent, FTC/TDF (Truvada®), will stop permanently and the subject will remain on study and continue to follow their original study visit schedule until the end of the study if any of the following occurs:

- Subject has a confirmed \geq Grade 3 clinical or laboratory toxicity that is deemed **related** to study agent that persists at \geq Grade 3 for \geq 14 days or recurs after re-challenge with study agent (see Section 10.7);
- Subject has a confirmed Grade 4 clinical or laboratory toxicity that is deemed **related** to study agent (see Section 10.7);
- Subject has a confirmed \geq Grade 3 sCr;
- Subject has a confirmed recurrence of sCr \geq Grade 2, or confirmed elevation by \geq 50% from baseline, upon resumption of study agent temporarily discontinued due to this toxicity;
- Subject has a confirmed CrCl $<$ 60 ml/min (**For subjects $<$ 18 years of age, use the bedside Schwartz formula: $GFR = (0.413 \times \text{height in cm}) / (\text{serum creatinine in mg/dl})$. For subjects \geq 18 years of age, use the Cockcroft-Gault formula: $GFR = ((140 - \text{age in years}) \times (\text{weight in kg})) / (72 \times \text{serum creatinine in mg/dl})$);**
- Subject has confirmed proteinuria as indicated by urine dipstick result \geq 1+;
- Subject has confirmed normoglycemic glucosuria as indicated by urine dipstick result \geq 1+ in the presence of normal serum glucose ($<$ 120 mg/dL);
- Subject experiences persistent vomiting or diarrhea that precludes administration or absorption of study agent;
- Subject receives treatment with a disallowed medication;
- Subject becomes HIV infected;
- Subject develops acute hepatitis B infection; or
- Subject experiences new onset of illness that, in the opinion of the investigator, requires discontinuation of subject from the study agent.

Also see Sections 10.7.1 and 10.7.2 for criteria for temporary discontinuation of the study agent.

10.5.2 Premature Discontinuation of Subject from Study

Subjects may be discontinued prematurely from the study if any of the following occurs:

- Subject fails to complete the Week 0 visit within 30 **calendar** days after completing the Screening visit **and then does not complete a Re-screening visit**;
- **Subject is found ineligible based on the Re-screening visit evaluations or subject completes a Re-screening visit, but does not complete the Week 0 visit within the next 30 calendar days**;
- Subject has an HIV-1 viral load at the Baseline visit that is not below the lower limit of detection (LLD);
- Subject fails to comply with the study requirements so as to cause harm to self or seriously interfere with the validity of the study results;
- Investigator determines that further participation would be detrimental to the health or well-being of the subject;
- Subject develops a health problem and needs treatment that would affect the results of this study;
- Subject becomes incarcerated or detained for a time impeding the ability to adhere to the study intervention and causing more than one study visit to be missed;
- Subject withdraws consent;
- Subject moves out of the area or is lost to follow-up;
- Study is stopped by a government agency such as the National Institutes of Health (NIH) or the FDA; or
- Study has to stop for other administrative reasons.

10.6 Intervening on “Social Harms”

All AMTUs have specific policies governing the treatment of human subjects. These policies specify that medical and psychological assistance will be available in the immediate environment in the event a subject should experience any adverse reactions resulting from study procedures.

While subjects will be informed that they may refuse to answer any question at any time, responses or reactions to certain questions may indicate distress on the part of the subjects. If at any time during the study, a subject divulges being at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the subject reports suicidal/homicidal intentions, measures will be taken to ensure the subject’s safety per each site’s IRB requirements and safety protocol. Reporting will be done as appropriate to the specific situation and the local legal statutes, including reporting to child protection agencies or other appropriate agencies and referrals will be provided to appropriate support, counseling, or treatment resources. In addition, social harms will be reported to the ATN 113 Protocol Team as part of study conduct.

10.7 Toxicity Management

The ATN Table for Grading the Severity of Adverse Events (Version 1.0, October 2006; Clarification March 2011) will be used to grade the severity (intensity) of all clinical AEs and aberrant laboratory values. The ATN Toxicity Table is available in Chapter 11 of the ATN MOGO and on the ATN website (www.atnonline.org).

Acute management of AEs will be according to best clinical practices and the judgment of the site investigator. The relationship between the AE and the study intervention will be presumed unless a clearly recognized alternate etiology is identified. The management of toxicities deemed related to the medication provided through this study (FTC/TDF (Truvada®)) will be considered in the toxicity management Sections 10.7.1 and 10.7.2, but all Grade 3 or higher toxicities according to the criteria specified in the ATN Toxicity Table will be reported. Toxicities related to non-study agents should be handled according to the most recent package insert (**available on the ATN website (www.atnonline.org)**) and by best medical judgment. Alternative explanations for clinical or laboratory abnormalities must be sought prior to study agent discontinuation.

10.7.1 General Toxicity Management

All Grade 3 or higher clinical and laboratory toxicities, regardless of relatedness, must be reported to the ATN 113 Protocol Team via the ATN QNS within 48 hours of the site becoming aware of the toxicity and their proposed management that is consistent with protocol requirements must be specified.

Grade 1 or 2 Toxicities:

Subjects who develop a Grade 1 or 2 AE or toxicity may continue the study agent without alteration of the dosage, unless the site clinician deems that the pattern of toxicity warrants study agent discontinuation and with the exceptions noted in Section 10.7.2. If study agent discontinuation is deemed necessary, this decision should first be communicated to the ATN 113 Protocol Team via the ATN QNS.

Grade 3 and 4 Toxicities:

- All Grade 3 and 4 laboratory toxicities should be repeated for verification within 72 hours of the site becoming aware of the abnormality and the ATN 113 Protocol Team must be notified via the ATN QNS within 48 hours of site awareness with the exceptions noted in Section 10.7.2.
- Subjects may continue taking the study agent while waiting for repeat confirmatory laboratory testing, at the discretion of the site clinician; the site clinician must notify the ATN 113 Protocol Team if he or she plans to discontinue the subject from the study agent.
- If after the Baseline visit, a subject develops a persistent \geq Grade 3 clinical or laboratory toxicity, the subject will not be permitted to start the study agent until the toxicity has resolved to \leq Grade 2 with the exception noted in Section 10.7.2.
- **All confirmed Grade 3 clinical and laboratory toxicities occurring during the study** that are **related** (i.e., there is a reasonable possibility that the AE may be related to the study agent) to the study agent must be monitored at least weekly for resolution to \leq Grade 2. The study agent must be temporarily discontinued during this time, with the exceptions noted in Section 10.7.2. The study agent must be permanently discontinued if either of the following occurs:
 - If the toxicity does not resolve to \leq Grade 2 within 14 days; or
 - If after resolution to \leq Grade 2, the subject is re-challenged with the study agent and the toxicity returns to \geq Grade 3.
- **All confirmed Grade 4 clinical and laboratory toxicities occurring during the study** that are **related** to the study agent must be monitored at least weekly for resolution to \leq Grade 2 and the study agent must be permanently discontinued.

10.7.2 Protocol-Specific Toxicity Management

Serum Creatinine Elevations

If at any time sCr is \geq Grade 2 or has increased from baseline (i.e., value at Screening visit) by \geq 50%, the sCr must be repeated within seven days. Subjects with confirmed sCr \geq Grade 2, or with a confirmed increase from baseline by \geq 50%, will temporarily discontinue study agent and will have sCr monitored monthly or more frequently at the discretion of the site investigator until sCr is $<$ ULN, or has returned to no higher than 25% above the subject's baseline sCr, at which time study agent may be restarted. If after the study agent is resumed, there is a confirmed recurrence of sCr \geq Grade 2, or confirmed elevation by \geq 50% from baseline, the study agent will be permanently discontinued. For confirmed sCr \geq Grade 3, administration of study agent will be permanently discontinued (see Section 10.5.1). Subject will remain on study and complete all follow-up evaluations. Subject will be followed monthly or more frequently at the discretion of the site investigator until sCr is $<$ ULN, or has returned to no higher than 25% above the subject's baseline sCr. All sCr toxicities will be reported to the ATN 113 Protocol Team via the ATN QNS.

New or Increased Proteinuria

Subjects will have a urine dipstick performed at every follow-up study visit.

Proteinuria, indicated by positive [\geq 1+] urine dipstick result (\geq Grade 1 according to the ATN Toxicity Table) must be repeated for verification within 72 hours. If the repeat test confirms proteinuria \geq 1+, the subject will be permanently discontinued from the study agent (see Section 10.5.1), but remain on study and complete all follow-up evaluations. Subjects will be followed weekly until proteinuria has resolved to trace or negative. All proteinuria toxicities will be reported to the ATN 113 Protocol Team via the ATN QNS.

Normoglycemic Glucosuria

Normoglycemic glucosuria defined as \geq 1+ by urine dipstick in the presence of normal serum glucose ($<$ 120 mg/dL) must be repeated within 72 hours. If the repeat test confirms normoglycemic glucosuria, the subject will be permanently discontinued from the study agent but remain on study and complete all follow-up evaluations. Serum glucose levels will be obtained. Subjects will be followed weekly for serum and urine dipstick glucose until normoglycemic glucosuria has resolved to trace or negative. Subjects with persistent normoglycemic glucosuria will be referred to a primary care physician for evaluation. All normoglycemic glucosuria toxicities will be reported to the ATN 113 Protocol Team via the ATN QNS.

Bone Mineral Density Concerns

If on review of DXA scan data, a BMD Z-score of -2.0 or less in the spine, total hip, or femoral neck or a drop in absolute BMD of greater than 5% from baseline is noted, this result will be communicated to the site investigator who will use his or her clinical judgment regarding medical consultation, referral, and appropriateness for subject to continue receiving the study agent.

11.0 MONITORING UNTOWARD EVENTS ASSOCIATED WITH OR RESULTING FROM STUDY

The protocol-specified reporting period for untoward events continues from time of the Screening visit to the end of study follow-up for that subject.

Site staff must first follow their local IRB's procedure for reporting and managing untoward events. ATN Behavioral and Community Prevention protocols also follow the ATN's Guidance for Safety and Impact Reporting (See Appendix 1B.9 of the ATN MOGO). All untoward events must be reported to the ATN 113 Protocol Team via the ATN QNS and on the *ATN 113 Monitoring Untoward Event Form*.

There are three types of untoward events to be identified: 1) those related to the subject, 2) those related to the study staff, and (3) those related to the neighborhood/community, if applicable.

First, the study will catalogue any untoward event related to the subject. Reporting is required for occurrences including social harms, psychological distress, and serious life threatening events such as suicide attempts. These may be immediately apparent to the study staff, for example, after completing the ACASI the subject's emotional state may require referral for counseling; or they may be delayed and reported later to study staff, such as physical harm to an individual for having participated in the study. Study staff will notify the ATN 113 Protocol Team of these untoward events using the ATN QNS. Site staff must also follow their own IRB's procedure for reporting these untoward events. Study staff will be educated during the training on the scope of possible untoward events and instructed how to report these events.

Second, study staff may encounter untoward events during sessions that personally affect them. Training and guidance will seek to minimize this risk. Nonetheless, an assessment of the cost of conducting this study must include cataloguing these events as well. The ATN 113 Protocol Team should be notified of these events so that they may be immediately addressed, evaluated, and guidance modified or expanded to minimize similar risk to other staff.

Third, a critically important area any community-based study intends to evaluate is the impact, including untoward events, of the project on the community. The ATN QNS will be used to notify the ATN 113 Protocol Team of any unanticipated negative impact the project may be having on the community. In this way, the event may be immediately addressed, evaluated, and guidance provided to minimize similar events on other communities or to other staff.

12.0 EXPEDITED REPORTING AND MONITORING OF ADVERSE EVENTS

12.1 Safety Monitoring

This protocol follows the FDA regulations for safety monitoring and reporting. The Protocol Co-Chairs, Statistician, NICHD Scientific Director, Program Scientist, and Medical Monitor, site investigators, and other study team members will work closely to monitor subject safety and respond to occurrences of toxicity in a timely manner. The ATN DOC will produce monthly reports covering both AEs and trial conduct. These reports will include comparative clinical and laboratory toxicity rates, and measures of trial conduct including, but not limited to, accrual and retention.

The ATN 113 Protocol Team will have conference calls every month (or more frequently as considered necessary) to review all reported AEs. The NICHD Medical Monitor and the ATN 113 Protocol Team will monitor study conduct closely with a focus on issues relating to subject safety, quality of trial conduct, such as overall and site-specific rates of recruitment, adherence to study interventions and visit schedules, and retention.

The ATN Data and Safety Monitoring Board (DSMB) will also monitor this trial for safety. DSMB members are independent of the study investigators and are experts in the areas of infectious disease,

statistical analysis, clinical trial design, bioethics, and other expertise as required. The ATN DSMB's responsibilities are to review the protocol before it is implemented, review the implementation and progress of the study, and review the accumulating endpoint and safety data by study group to detect evidence of early significant benefit or harm for subjects while the trial is in progress.

The ATN DSMB has reviewed the ATN 113 protocol and has determined that scheduled meetings will be held at least once a year following study opening. The Chair of the DSMB, in consultation with the NICHD Medical Monitor and DSMB Executive Secretary, will determine if a conference call may be used in place of a face-to-face meeting. Interim comprehensive reporting to the ATN DSMB by the ATN DOC via conference call will be initiated at 6-month intervals following study opening. The Chair of the DSMB will determine the need for unscheduled ATN DSMB meetings, based on the results of the interim reporting. In addition, the ATN DSMB will be convened if the NICHD Medical Monitor, in consultation with the Protocol Co-Chairs, Protocol Team Members, and Protocol Statistician determine from the safety monitoring activities that a full ATN DSMB review is required.

A synopsis of the DSMB report indicating whether there are safety or ethical concerns with the trial and whether the DSMB has recommended the continuation of ATN 113, will be transmitted to the clinical sites for submission to their individual IRBs, approximately every 6 months.

12.2 Adverse Events and Reporting Requirements

The FDA regulations define an AE as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32).

The site investigator or designee will review the results of clinical and laboratory investigations and evaluate for presence of adverse events. In addition, research subjects will be routinely asked about any side effects they may have experienced at each study visit. All AEs occurring during study participation, including clinical adverse experiences and aberrant laboratory values, will be graded according to the ATN Toxicity Table for Grading Severity of Adolescent Adverse Experiences (Version 1.0, October, 2006; Clarification March 2011).

The site investigator must notify the ATN 113 Protocol Team using the ATN QNS within 48 hours, regardless of relatedness, of all \geq Grade 3 toxicities and their proposed management consistent with protocol requirements (see Section 10.7). Clinical and laboratory toxicities \geq Grade 3 must be assessed within 48 hours of awareness and documented on the *ATN 113 Adverse Event Evaluation (AEE) Form* and entered into the ATN 113 database within 3 working days of awareness. Each toxicity should be monitored at least weekly until the toxicity resolves to \leq Grade 2 or until it stabilizes to a state where no further resolution is expected. Each follow-up evaluation requires documentation on an *ATN 113 AEE Form*.

For protocol-specific AEs, see section 10.7.2 for management and reporting requirements.

12.3 Expedited Reporting of Adverse Events

To ensure compliance with FDA regulations (21 CR 312.64), site investigators must report immediately all AEs that meet the serious adverse event (SAE) criteria, regardless of presumed relationship to the investigational agent, to the Sponsor, NICHD, via the ATN DOC Regulatory Office. The Sponsor will carefully review the SAE information to monitor the investigational drug's toxicity profile and patient safety. If any event meets the FDA's reporting criteria, it will be submitted to the FDA as an IND Safety Report (21 CFR 312.32).

This protocol follows the **Serious Adverse Event (SAE)** reporting category that is defined in the Manual for Expedited Reporting of Adverse Events to ATN/NICHHD (EAE Manual) (Version 2.0, March 2011). The ATN EAE Manual and the ATN Table for Grading Severity of Adverse Events are available in the ATN MOGO and on the ATN website (www.atnonline.org). All SAEs must be recorded on the *ATN EAE Report Form* and submitted to the ATN DOC Regulatory Office as described in the ATN MOGO.

The ATN MOGO, Chapter 11, stipulates the characteristics of an SAE that would require it to be reported to the ATN Regulatory Office at the DOC. In general, seriousness, severity, and relationship to study agent are the main criteria used to determine the reportability of an SAE to the ATN DOC Regulatory Office.

Any AE following exposure to the study agent that results in the following conditions must always be reported on an expedited basis, regardless of relatedness or expectedness, by phone or fax to the ATN Regulatory Office as soon as possible after the research staff becomes aware of the event, followed by submission of the EAE form within 3 reporting days of the research staff becoming aware of the event:

1. Results in death;
2. Is life-threatening; (*The term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*)
3. Requires inpatient hospitalization or prolongation of existing hospitalization; (*Per ICH SAE definition, hospitalization itself is not an AE, but is an outcome of the event.*)
4. Results in persistent or significant disability/incapacity;
5. Is a congenital anomaly/birth defect; or
6. Is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples include the following: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; etc.

The investigator or designee will assess the relationship of all AEs to the study agent based on the guidelines outlined in this protocol, the ATN MOGO, the approved product label, and his or her clinical judgment.

12.4 Adverse Events Reporting Period

The protocol-specified reporting period **for adverse events starts after study drug exposure and continues** to the end of study follow-up for that subject. After the protocol-defined AE reporting period, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) will be reported to ATN/NICHHD if the study staff becomes aware of the events on a passive basis from publicly available information (see ATN/NICHHD EAE Manual).

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This demonstration project and phase II safety study aims to obtain additional data on the safety of FTC/TDF (Truvada®) and to evaluate patterns of use, rates of adherence, and patterns of sexual risk

behavior among YMSM who are provided with open label FTC/TDF (Truvada®) and information on the safety and efficacy of PrEP from prior studies. Furthermore, this project will explore the feasibility and acceptability of implementing two different types of efficacious risk reduction interventions prior to the provision of PrEP – 3MV and PCC. Behavioral intervention assignment will occur at the site level. Behavioral and biomedical data will be collected at baseline and at 4, 8, 12, 24, 36 and 48 weeks. Subjects who become HIV infected during the course of the study will be discontinued from the study agent and complete three HIV Seropositive visits at 4, 12, and 24 weeks (SP1, SP2, and SP3 visits, respectively) after the study visit at which HIV infection is confirmed. Subjects who meet specific bone or renal criteria at either the Week 48 visit or the SP3 visit will be followed for two additional visits (EPH1 and EPH2) over 48 weeks in the Extension Phase to more closely monitor longer-term outcome of potential concerns.

13.2 Subjects and Study Population

Approximately 100 YMSM (approximately 50 at 3MV sites and 50 at PCC sites), ages 15 through 17 years inclusive, will be recruited across participating AMTUs and their community venues. Subjects will receive one of two behavioral interventions, 3MV or PCC and will be provided FTC/TDF (Truvada®) as PrEP. Attrition is expected to be about 10%; subjects will not be replaced.

The analysis for this study will be done following the Intent to Treat (ITT) principle. All enrolled subjects will be included in the data analysis.

13.3 Study Objectives

Primary Objectives:

- To provide additional safety data regarding FTC/TDF (Truvada®) use among HIV-uninfected YMSM.
- To examine acceptability, patterns of use, rates of adherence and measured levels of drug exposure when YMSM are provided open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies.
- To examine patterns of risk behavior when YMSM are provided a behavioral intervention as well as open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies.

Secondary Objectives:

- To evaluate the process of protocol implementation to better understand how to best implement PrEP research and program practice at adolescent medicine sites, including an evaluation of consent procedures and the acceptability/feasibility of allowing youth minors to consent for their own participation in this HIV prevention intervention, to the extent allowable by local laws and regulations, and to allow youth minor participation in a clinical trial without requiring disclosure of their sexual orientation and risk behaviors to their parents or guardians.
- To explore the acceptability and feasibility of implementing two types of efficacious sexual risk reduction interventions (intensive group-level or brief individual-level) prior to the provision of PrEP.
- To explore the acceptability and feasibility of implementing a text messaging adherence reminder intervention for youth who self-report less than 80% adherence to the study regimen.

- To explore potential demographic and/or behavioral differences between youth who stay on PrEP compared to those who discontinue use.
- To explore potential demographic and/or behavioral differences between youth who are interested in participating in a PrEP study versus those who are not.
- To explore the discussions and recommendations of local IRBs on this approach to minor YMSM inclusion in PrEP studies.

13.4 Primary Study Endpoints

Primary Objective #1 – Safety

- Serum creatinine (sCr)
- BMD
- Safe sex practices (refer to Behavioral Disinhibition/Risk Compensation endpoint below)

Primary Objective #2 – Acceptability, Patterns of use, Rates of adherence, Measured levels of drug exposure and Risk behavior

- Acceptability
 - Usability of PrEP
 - User-friendliness of the medication regimen (including an assessment of side effects) and the delivery format
- Feasibility
 - Process indicators: number screened, number eligible, number enrolled, number choosing to take PrEP
 - Attendance for study visits
 - Retention rates
- Medication Adherence
 - Proportion of medication adherence (number of days of missed medication/total number of days) will be calculated
 - Period of time that a subject's supply of study medication is assumed to be exhausted (Actual refill dates minus expected refill dates)
 - **DBS samples** will be collected to assess TFV and FTC, as well as TFV-DP and FTC-TP concentrations

Primary Objective #3 – Behavioral Disinhibition/Risk Compensation

- Number of sexual partners, female and male
- Number of times engaged in each type of sex act (with and without a condom)
- Number of partners of each HIV serostatus
- Number of partners taking PrEP
- How many partners of each HIV serostatus they had unprotected insertive and receptive anal sex with

- How many times they engaged in each sex act, protected and unprotected, with each HIV serostatus partner
- How often partner's HIV serostatus was known prior to sexual encounter
- How often partner's HIV serostatus influenced sexual behavior
- Alcohol or recreational drug use before or during last sexual encounter
- Exchanged sex for money, drugs, food or a place to stay during last sexual encounter
- What HIV risk reduction measures were taken with last sexual partner
- 10-item scale measures perceptions of HIV-related threat and the need for continued safer sex in the age of PrEP
- 6-item scale assesses decreased personal worry about engaging in unsafe sex and the potential for infecting others because of the availability of combination therapies
- 9-item scale that assesses whether adherence to PrEP is ever based on sex life
- 10-item scale that examines what factors impact decisions to have sex with or without condoms

13.5 Secondary Study Endpoints

Secondary Objectives #1 and #6 – Evaluation of Process of Protocol Implementation

There are no endpoints associated with this objective. Brief phone interviews and review of written IRB correspondence will be conducted for all sites whether the study is approved at that site or not. If approved, the ATN 113 Protocol Team will examine what steps were needed for approval and how barriers were addressed. If the study was rejected, the Protocol Team will examine the reasons for disapproval, the IRB's interpretation of the risk of PrEP, and other barriers. Furthermore, each AMTU will complete a survey specific to their IRB's responses of minor YMSM inclusion in PrEP studies.

Secondary Objective #2 – Acceptability and Feasibility of Implementing Two types of Efficacious Sexual Risk Reduction Interventions

- Session Evaluation
 - Was the session interesting
 - Was it relevant to their life
 - Did they learn from the session

Secondary Objective #3 – Acceptability and Feasibility of Text Message Reminders – Same endpoints as Primary Objective #2

- Subjects rate the reasons for missing medications on a 4-point Likert scale ranging from Never to Often

Secondary Objectives #4 and #5 – Demographic and/or Behavioral Differences between Groups – Same endpoints as Primary Objective #3

13.6 Power Analysis, Sample Size and Precision

The sample size for this study is set to 100 with one treatment arm: open label FTC/TDF (Truvada®). The primary aims of the study are focused on safety, acceptability, patterns of use, rates of adherence and measured levels of drug exposure. A Pearson Chi-square test will be used to compare safety endpoints to adults in earlier studies and against rates seen in the companion ATN 110 study (same study design but in 18 to 22 year olds). Data analysis for other study endpoints will focus on frequencies, proportions, means, and other basic statistical measures. Table 3 shows precision for estimating proportions ranging from 0.10 to 0.50 based on the expected sample size of 90 subjects (100 enrolled with 10% attrition).

Table 3. Precision for estimating proportions *

| Sample Size | Observed Proportion | | |
|-------------|---------------------|------|------|
| | 0.10 | 0.25 | 0.50 |
| 90 | 0.06 | 0.09 | 0.10 |
| 100 | 0.06 | 0.08 | 0.10 |
| 110 | 0.06 | 0.08 | 0.09 |

*Values shown in Table 3 represent half-widths of 95% confidence intervals (CIs). Thus, with a sample size of 90 (10% lost to follow-up), an observed proportion of 25% would have a 95% CI width of ± 9 percentage points. Precision is based on standard normal approximation for CIs.

Table 4. 95% Confidence Intervals for estimating proportions *

| Sample Size | Observed Proportion | | |
|-------------|---------------------|-------------|-------------|
| | 0.10 | 0.25 | 0.50 |
| 90 | (4.7-18.1) | (16.9-35.8) | (39.3-60.7) |
| 100 | (4.9-17.6) | (16.9-34.7) | (39.8-60.2) |
| 110 | (5.1-17.2) | (16.8-33.7) | (40.3-59.7) |

*Values shown in Table 4 represent 95% CIs. Thus, with a sample size of 90 (100 enrolled with 10% lost to follow-up), an observed proportion of 25% would have a 95% CI width of ± 8 to 11 percentage points. CIs are based on Clopper-Pearson CIs. No entries correspond to interval widths narrower than 10%.

Since this study has only one arm, the safety endpoints will be monitored against rates seen in adults in earlier studies and against rates seen in the companion ATN 110 study. External estimates of toxicity rates will be derived from the iPrEx study (Grant, et al., 2010) and two recent PrEP studies (Grohskopf, et al., 2010; Liu, et al., 2011). However, it is recognized that results from external studies may differ from this study due to differences in study population, study procedures, or lack of synchronization. Thus, toxicity rates will also be compared between ATN 110 and 113.

Powers for comparisons with external data are shown in Tables 5, 6, and 7. Table 5 shows power for comparing rates with the iPrEx study, which had approximately 2500 subjects. Table 6 shows power for comparing rates with the Liu study, which had approximately 210 subjects. Finally, Table 7 shows power for making comparisons between ATN 110 and 113. Power will be relatively low for seeing differences in creatinine toxicity, which are expected to be low, but will be sufficient for detecting differences in BMD change.

Table 5. Power for comparing toxicity rates between adults and adolescents: ATN 113 vs. iPrEx*

| iPrEx Study N = 2500 | ATN 113 N = 90 | | | | | |
|-------------------------|-------------------|------|------|------|------|------|
| | 0.02 | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 |
| 0.02 | | 49 | 93 | 99 | 99 | 99 |
| 0.05 | 15 | | 54 | 91 | 99 | 99 |
| 0.10 | 86 | 29 | | 26 | 80 | 96 |
| 0.15 | 99 | 85 | 22 | | 27 | 69 |
| 0.20 | 99 | 99 | 69 | 18 | | 22 |
| 0.25 | 99 | 99 | 96 | 59 | 17 | |

*Values shown in the table represent power (in %) for testing for differences in toxicity rates between study subjects in the ATN 113 and iPrEx studies. The sample sizes are 90 adults (10% lost to follow-up in ATN 113) and approximately 2500 in iPrEx. For example, there would be 80% power to detect a difference between an observed toxicity rate of 0.10 in the iPrEx subjects and 0.20 in the ATN 113. Cells shaded in gray represent combinations that have at least 80% power. Power calculations were performed using a two-group Pearson Chi-square test with a two-sided significance level of 0.05, using nQuery 7.0 software.

Table 6. Power for comparing toxicity rates between adults and adolescents: ATN 113 vs. Liu*

| Liu Study N = 210 | ATN 113 N = 90 | | | | | |
|----------------------|-------------------|------|------|------|------|------|
| | 0.02 | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 |
| 0.02 | | 32 | 81 | 96 | 99 | 99 |
| 0.05 | 18 | | 37 | 79 | 95 | 99 |
| 0.10 | 71 | 27 | | 25 | 64 | 89 |
| 0.15 | 96 | 72 | 19 | | 19 | 54 |
| 0.20 | 99 | 95 | 56 | 16 | | 16 |
| 0.25 | 99 | 99 | 87 | 48 | 14 | |

*Values shown in the table represent power (in %) for testing for differences in toxicity rates between subjects in the Liu and ATN 113 study subjects. The sample sizes are 90 adults (10% lost to follow-up in ATN 113) and 210 in the Liu study. For example, there would be 81% power to detect a difference between an observed toxicity rate of 0.02 in the Liu group and 0.10 in the ATN 113 group. Cells shaded in gray represent combinations that have at least 80% power. Power calculations were performed using a two-group Pearson Chi-square test with a two-sided significance level of 0.05, using nQuery 7.0 software.

Table 7. Power for comparing toxicity rates between adults and adolescents: ATN 110 vs. 113*

| ATN 113 (Adolescent) N = 90 | ATN 110 (Adult) N = 180 | | | | | |
|-----------------------------------|----------------------------|------|------|------|------|------|
| | 0.02 | 0.05 | 0.10 | 0.15 | 0.20 | 0.25 |
| 0.02 | | 18 | 69 | 95 | 99 | 99 |
| 0.05 | 30 | | 26 | 70 | 94 | 99 |
| 0.10 | 78 | 35 | | 19 | 55 | 85 |
| 0.15 | 95 | 76 | 23 | | 15 | 46 |
| 0.20 | 99 | 94 | 61 | 18 | | 14 |
| 0.25 | 99 | 99 | 87 | 51 | 15 | |

*Values shown in the tables represent power (in %) for testing for differences in toxicity rates between the adolescent and adult study subjects in the ATN 113 and 110 studies, respectively. The sample sizes are 180 adults (10% lost to follow-up in ATN 110) and 90 adolescents (10% lost to follow-up in ATN 113). For example, there would be 94% power to detect a difference between an observed toxicity rate of 0.05 in the adult group and 0.20 in the adolescent group. Cells shaded in gray represent combinations that have at least 80% power. Power calculations were performed using a two-group Pearson Chi-square test with a two-sided significance level of 0.05, using nQuery 7.0 software.

13.7 Stratification Procedures

Assignment of AMTUs to one of two behavioral intervention conditions, 3MV or PCC, will be determined by the ATN 113 Protocol Co-chairs taking into consideration its geographic location and availability of facilitators trained to administer the interventions.

13.8 Interim Analysis

No interim analyses will be performed for this study.

13.9 Stopping Rules

Stopping Rule for Adverse Events: To ensure subject safety, an early stopping rule for monitoring serious adverse events among the first 50 subjects will be used. The stopping rule will be invoked should the proportion of study subjects experiencing at least one of the events below exceeds 30%:

- Confirmed \geq Grade 3 or higher events determined to be attributable to the study agent
- Confirmed \geq Grade 2 sCr
- Confirmed proteinuria \geq 1+
- Confirmed normoglycemic glucosuria \geq 1+ in the presence of normal serum glucose
- Decrease in absolute BMD $>$ 10% from baseline in at least one region (spine, hip, or whole body)

The stopping rule is as follows:

Stop accrual/suspend study if:

- 3 among the first 10 subjects experience one or more serious adverse events
- 4 among the first 13 subjects experience one or more serious adverse events

- 5 among the first 16 subjects experience one or more serious adverse events
- 6 among the first 20 subjects experience one or more serious adverse events
- 7 among the first 23 subjects experience one or more serious adverse events
- 8 among the first 26 subjects experience one or more serious adverse events
- 9 among the first 30 subjects experience one or more serious adverse events
- 10 among the first 33 subjects experience one or more serious adverse events
- 11 among the first 36 subjects experience one or more serious adverse events
- 12 among the first 40 subjects experience one or more serious adverse events
- 13 among the first 43 subjects experience one or more serious adverse events
- 14 among the first 46 subjects experience one or more serious adverse events
- 15 among the first 50 subjects experience one or more serious adverse events

The stopping probabilities (based on sequential Bernoulli outcomes) of this stopping rule are displayed in Table 8 below.

Table 8. Probability of stopping in terms of true adverse event rate and number of subjects already on study

| | 25% | 30% | 40% |
|-------------|-----|-----|-----|
| 10 subjects | .47 | .62 | .83 |
| 16 subjects | .55 | .70 | .90 |
| 20 subjects | .58 | .74 | .93 |
| 26 subjects | .60 | .77 | .95 |
| 30 subjects | .62 | .79 | .96 |
| 36 subjects | .63 | .81 | .97 |
| 40 subjects | .64 | .82 | .98 |
| 46 subjects | .65 | .83 | .98 |
| 50 subjects | .66 | .84 | .99 |

For example, if the true adverse event rate is 30%, then the probability of terminating accrual on this arm at the 16th subject is 70%. However, if true adverse event rate is 40%, the probability of stopping at the 10th subject is 83%.

Temporary Stopping Rule for HIV Seroconversion: In addition to the stopping rule for SAEs, ATN 113 will have a separate temporary stopping rule to consider a potential imbalance in the rate of seroconversion between the two behavioral intervention groups, 3MV and PCC. Rates of seroconversion will be evaluated as each group of 20 enrolled subjects completes 50% of study follow-up (Week 24 study visit). More specifically, rates of seroconversion will be compared when 10% of subjects have been enrolled and those remaining on study have completed the Week 24 visit; the analysis will test the hypothesis of equal rates in the two behavioral intervention groups. This comparison will be repeated when 20% have been enrolled and those on study have completed the Week 24 visit, when 30% have been enrolled and completed the Week 24 visit, and so forth, following the schedule shown in the table below:

| Evaluation | Subjects enrolled | Critical point | Nominal significance |
|------------|-------------------|----------------|----------------------|
| 1 | 20 | 2.27 | 0.0116 |
| 2 | 40 | 2.27 | 0.0116 |
| 3 | 60 | 2.27 | 0.0116 |
| 4 | 80 | 2.27 | 0.0116 |
| 5 | 100 | 2.27 | 0.0116 |
| 6 | 120 | 2.27 | 0.0116 |
| 7 | 140 | 2.27 | 0.0116 |
| 8 | 160 | 2.27 | 0.0116 |
| 9 | 180 | 2.27 | 0.0116 |
| 10 | 200 | 2.27 | 0.0117 |

If the critical value for the test exceeds the critical point shown in the table (2.27) in absolute value, the stopping rule will be invoked. Enrollment will be temporarily stopped while the team reviews the data on seroconversion and reports these results to the DSMB for consideration. The nominal significance level for each evaluation level is 0.0116 (as shown above). The overall significance level for the stopping rule is 0.05. (Note: Critical points were calculated using EaSt software, version 2.0.)

13.10 Statistical Analysis

Note: Any deviations from the analysis plans outlined above or in the sections that follow will be documented in the Statistical Analysis Plan developed for this protocol.

Due to constrained network resources, there will be a pause in enrollment after approximately 50 subjects have been enrolled, after which it will be decided whether the study will reopen to enrollment. An initial analysis will be done on the approximately 50 subjects initially enrolled. In the event that enrollment is not reopened, this analysis on the approximately 50 enrolled subjects will become the final definitive analysis for the study. However, if enrollment is reopened, the final definitive analysis will be done on all 100 subjects as stated in this section.

13.10.1 Primary Objectives Analysis

Objectives:

- To provide additional safety data regarding FTC/TDF (Truvada®) use among HIV-uninfected YMSM.
- To examine acceptability, patterns of use, rates of adherence and measured levels of drug exposure when YMSM are provided open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies.
- To examine patterns of risk behavior when YMSM are provided a behavioral intervention as well as open label FTC/TDF (Truvada®) and information regarding the safety and efficacy of PrEP from prior studies.

Analysis:

There are three safety endpoints that will be monitored at Baseline and Weeks 4, 8, 12, 24, 36 and 48: sCr, BMD, and safe sex practices.

- SCr levels will be graded using standard toxicity tables; severity grades of 1 and greater will be considered a toxicity endpoint. The iPrEx study reported this level of toxicity in about 2% of subjects (Grant, et al., 2010).
- BMD will be measured both as percent change from baseline and as change in Z-score from baseline. Either a percent decrease of 5% in BMD or BMC or a decrease in Z-score of 0.5 will indicate a toxicity endpoint. BMD will be available at baseline and weeks 24 and 48. Liu reported that about 13% of study subjects taking TDF had decreases of 5% or greater during 24 months of follow-up.
- Behavioral disinhibition will be measured as reports of unprotected intercourse in the prior 12 weeks. More specifically, the proportion of subjects reporting unprotected intercourse in the prior 12 weeks will be monitored during the study.

As discussed above, this study has only one arm, so safety endpoints will be monitored against rates seen in adults in earlier studies and against rates seen in the companion ATN 110 study.

13.10.2 Secondary Study Objectives Analysis

Objectives:

- To evaluate the process of protocol implementation to better understand how to best implement PrEP research and program practice at adolescent medicine sites, including an evaluation of consent procedures and the acceptability/feasibility of allowing youth minors to consent for their own participation in this HIV prevention intervention, to the extent allowable by local laws and regulations, and to allow youth minor participation in a clinical trial without requiring disclosure of their sexual orientation and risk behaviors to their parents or guardians.
- To explore the acceptability and feasibility of implementing two types of efficacious sexual risk reduction interventions (intensive group-level or brief individual-level) prior to the provision of PrEP.
- To explore the acceptability and feasibility of implementing a text messaging adherence reminder intervention for youth who self-report less than 80% adherence to the study regimen.
- To explore potential demographic and/or behavioral differences between youth who stay on PrEP compared to those who discontinue use.
- To explore potential demographic and/or behavioral differences between youth who are interested in participating in a PrEP study versus those who are not.
- To explore the discussions and recommendations of local IRBs on this approach to minor YMSM inclusion in PrEP studies.

Analysis:

Data analysis for the secondary objectives will focus on frequencies, proportions, means, and other basic statistical measures. For example, acceptance rates will be evaluated and estimated. Demographic and risk behaviors will be compared between youth who stay on PrEP and those who discontinue. Risk behaviors will also be compared between participants in the two behavioral intervention conditions, 3MV or PCC.

Rates of adherence will be compared between those who participated in text messaging to those who opted not to participate. Furthermore, each AMTU will complete a survey specific to their IRB's responses of minor YMSM inclusion in PrEP studies.

13.11 Missing, Unused and Spurious Data

Missing data often occur in longitudinal studies. As a result of missing data, the analyses can be seriously affected. Every effort should be made to ensure that the amount of missing data is kept at a minimum since their presence complicate the statistical analyses. The first step will be to assess the extent and pattern of missing data.

The types of analyses will be affected by the type and amount of missing data (Fairclough, 1998). In general, multivariate analyses (repeated measures) require complete data vectors or that the proportion of subjects with missing assessments should be small (<5%) and be missing completely at random (MCAR). That is, "missingness" is completely unrelated to the subject's outcome measurement and covariates. The MCAR assumption is strong and, if violated, the estimates of treatment effect could be biased. In the weaker assumption, missing at random (MAR), "missingness" depends on covariates and the non-missing outcomes (behaviors or sexually transmitted infection (STI) diagnosis) but is independent of the value of the missing outcomes. In both MAR and MCAR, the missing data are ignored and one can simply perform the standard analyses as outlined above. Fortunately, mixed effects models are sufficiently robust in the presence of up to 20% missing outcomes, even if the outcomes are MAR (Fairclough, 1998).

In the worst-case scenario, the missing outcomes are not missing at random (NMAR). In NMAR, "missingness" depends on the value of the missing observation. For example, the missing observations arise when subjects do not return for follow up for various reasons. The remaining subjects may appear healthier (also known as informative censoring) because the sample is shrinking down to an even smaller complement of healthier subjects. Imputation schemes should be used if missing data are NMAR.

Single imputation methods include 'mean imputation' and 'regression imputation'. In 'mean imputation', the average time-specific value of the outcome measure is substituted for the missing observations. In 'regression imputation', the predicted value of the outcome measure for a subject is estimated with a regression model based on factors considered predictive of outcome. The subject's individual values for the explanatory factors are used to estimate a predicted outcome value and then substituted for the missing assessment(s). The criticism of the single imputation methods is that most methods of analysis treat imputed values simply as observed values and underestimate the uncertainty by ignoring the measurement error, among-subject variability, and the incomplete knowledge of the reason for non-response.

Multiple imputation (Rubin, 1987; Rubin & Schenker, 1991; Rubin, 1996) overcomes the criticism against single imputation methods, moreover, it can deal with both NMAR and MAR by imputing non-randomly missing values using a statistical model for the outcome given the missing value indicator. The software package, SOLAS or SAS PROC MI, simplifies the implementation of multiple imputation schemes considerably.

Unused or spurious data will be documented and discussed when disseminating results of this study.

14.0 HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, the applicable FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312), the OHRP regulations (45 CFR Part 46) and the ICH Good Clinical Practice (GCP) guidelines. Approvals from all applicable regulatory authorities (IRBs, FDA, and the NIH) will be obtained prior to initiating any study procedures with human subjects.

14.1 Subject Confidentiality

All study-specific laboratory specimens, questionnaires, evaluation forms, reports, and other records will be identified by a coded number only, to maintain confidentiality. **All records must be stored in a secured location under double-lock when not in use, and with restricted access during work hours and/or when unattended.** All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject (or parent or legal guardian, when applicable), except as necessary for monitoring by the ATN DOC or the NICHD. Any blood, urine, or hair samples remaining at the end of the study after all study-specified analyses are done will be destroyed.

14.1.1 Certificate of Confidentiality

To further protect the privacy of the study subjects, the ATN has obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). With this Certificate in place, the ATN researchers cannot be forced to turn over identifying information about a study subject in any Federal, State, or local criminal, administrative, legislative, or other proceedings. This Certificate does not prevent a study subject from volunteering to turn over their research information nor does it prevent researchers from providing research-related information to others when requested by the study subject or when required by law such as in cases of suspected or actual harm to or by the study subject.

14.2 Risks and Benefits

14.2.1 Risks Associated with Participation in This Study

The ATN 113 Protocol Team has determined that participation in this study involves procedures or interventions that are greater than a minor increase over minimal risk, but present the prospect of direct benefit to the individual subjects.

The measurements that are involved in this study require venipuncture to collect blood samples. This procedure may cause local discomfort, bleeding, or bruising; rarely small clot or infection can occur at the blood draw site. This measurement should not be considered greater than minimal risk in and of itself given its routine use in general health care delivery.

During DXA scanning, subjects are exposed to a small dose of radiation. Such doses of radiation may be potentially harmful, but the risks are so small that they are difficult to measure.

Subjects on PrEP may experience side effects from taking the study agent FTC/TDF (Truvada®). The most common side effects from the study agent include dizziness, diarrhea, nausea, vomiting, headache, fatigue, depression, insomnia, abnormal dreams, rash, and gas. Additional side effects include upper respiratory tract infection, pancreatitis, allergic reaction and skin discoloration. More serious and potentially life-threatening risks include liver problems, anemia, lactic acidosis, lipodystrophy, decreased kidney function and metabolic disorders, changes in BMD, hypersensitivity reactions and flare-ups of hepatitis B virus infection in individuals with chronic hepatitis infection who stop study agent. Tests will be done at every study visit to carefully monitor subjects.

In addition, there is some risk that answering questions about some of the topics may be uncomfortable or upsetting. In the event of discomfort or upset, there are counselors at ATN sites with whom subjects can talk and who can provide ongoing support as needed. Subjects do not have to answer any question in the computerized interview that they do not want to answer. Furthermore, subjects will be informed that at any point, they may stop if they do not wish to continue the questionnaire. Every effort will be made to keep the subject's participation in the study and personal information private and confidential, but absolute confidentiality cannot be guaranteed.

Subjects who become HIV-infected while taking PrEP may be at risk for developing resistance to the study agent, FTC/TDF, and therefore, FTC/TDF may not be an effective option as part of the subject's HIV treatment plan. To lower this risk, all subjects will be counseled on the importance of taking the study agent every day as prescribed, having monthly HIV testing done, and using PrEP as part of an overall risk-reduction plan, which includes safer sex practices such as consistent and correct condom use. They will also be informed to immediately contact the study staff if they are experiencing any flu-like symptoms that may be suggestive of acute HIV infection.

14.2.2 Benefits Associated with Participation in This Study

Based on studies that have shown that PrEP reduces the risk of HIV infection in MSM, especially in those most adherent to the medications, the FDA has approved use of Truvada® as PrEP to reduce HIV infection risk. As this is not a randomized, controlled trial of PrEP, the study will not be able to determine the efficacy of PrEP in preventing HIV infection in this population. However, the information learned from this study will assist the ATN 113 Protocol Team in learning about the acceptability of PrEP among youth and in developing acceptable and feasible PrEP studies for the YMSM community. Subjects may benefit from receiving the package of behavioral prevention interventions (3MV, PCC, condoms, STD screening and treatment, referrals for hepatitis B vaccination for those found to be susceptible, and periodic HIV testing and counseling) that are provided along with FTC/TDF (Truvada®). The 3MV and PCC behavioral intervention that subjects will attend have been shown to help reduce risks for HIV infection.

Benefits associated with HIV management for seroconverters. The seroconverters in the study will be provided with HIV-1 viral load test results, CD4+ T cell results, drug resistance testing results, and referrals to primary care and HIV care.

14.3 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent documents, and any subsequent modifications will be reviewed and approved by the IRB responsible for the oversight of the study.

The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Written informed consent will be obtained from the subject for their participation in this study. The signed original consent form will be kept on file at the site and a copy of the signed consent form will be given to the subject. Sample informed consent form is included in **Appendix XIX and the sample addendum to the sample informed consent for study participants is in Appendix XX.**

The enrollment informed consent process will include an assessment of each potential subject's understanding of concepts identified by the Protocol Team members as essential to the informed consent decision prior to the subject signing the informed consent. Subjects who are not able to demonstrate adequate understanding of key concepts after educational efforts will not be enrolled in the study.

Subjects who are able to comprehend the study and want to participate will be asked to sign an informed consent form. Additionally, the study staff member obtaining consent will sign the informed consent form to document the consent process and his/her belief that the subject understands the informed consent form.

14.3.1 Waiver of Signed Informed Consent For the iTouch-Administered Screening Interview and PrEP Opinion Questionnaire

A verbal consent process for the iTouch-administered interviews, i.e., the initial eligibility screening and the PrEP Opinion Questionnaire, is proposed. The introduction to the interviews includes all of the required elements for consent (21 CFR 50.25 and 45 CFR 46.116). No identifying information on subjects will be recorded during the interviews. Therefore, documented consent for these interviews would constitute the only identifying link to subjects. In addition, the interviews present minimal risk to subjects and involve no procedures that would require written consent outside of a research context. Under these conditions the IRB is authorized to modify the requirements to obtain a signed consent form for some or all subjects (21 CFR 56.109 [c] and 45 CFR 46.117 [c]).

14.4 Prisoner Participation

The ATN and NICHD have concluded that this protocol does NOT meet Federal requirements governing prisoner participation in human subject research and should NOT be considered by local IRBs for the recruitment of prisoners.

Enrolled subjects who subsequently become incarcerated or are placed in detention may not continue to participate in study visits during the period of incarceration or detention. A subject may resume participation in the study after being unconditionally released from incarceration, i.e., the subject is not bound by home surveillance, probationary, or any type of required systematic monitoring that keeps the subject actively engaged in some form as a detainee in the social justice system, and as permitted by individual site IRBs.

A subject who continues participation after being released from incarceration must be re-assessed to ensure that the subject fully understands the protocol and is able and willing to adhere to protocol requirements. This assessment should be documented in the subject's source documents and in accordance with the site's IRB requirements.

14.5 45 CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information (“Privacy Rule” Pursuant to the Health Insurance Portability and Accountability Act – HIPAA)

Each site is responsible for adherence to their individual institution's HIPAA policies and procedures.

14.6 Study Discontinuation

This study may be discontinued at any time by the NICHD or the FDA.

15.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ATN policies as outlined in Appendix 1A.6 of the ATN MOGO. The ATN 113 Protocol Team members will make any presentation, abstract, or manuscript available for review by the study sponsors prior to submission.

16.0 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 CDC. These procedures can be found at www.cdc.gov.

ATN specimens will be transported in accordance with Federal and local laws, and in compliance with Occupational Safety and Health Administration (OSHA) blood-borne pathogens standards. This policy includes the samples being transported by ground to the local laboratory. Compliance will be achieved by education of personnel involved with packaging and transporting specimens.

All infectious specimens must be shipped as Diagnostic Specimens according to current IATA Shipping Guidelines for Infectious Substances Class/Div. 6.2. Refer to individual carrier guidelines (e.g., FedEx, Airborne Express) for specific instructions.

All participating sites are also required to follow the specimen management procedures outlined in Chapter 14 of the ATN MOGO in collecting, processing, shipping and storing biological specimens for the study. In addition, sites are required to follow protocol-specific procedures outlined in the protocol.

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APPENDIX I: SCHEDULE OF EVALUATIONS

| Evaluation/Test | Pre-SCR | SCR* | BL* | | Re-SCR! | WK0* | Follow-up Visits ^{#,&} | | | | | | CFM [▲] | HIV Seropositive Visit [#] | | | |
|--|---------|------|-----|--|-----------------|-----------------|-------------------------------------|-----|-------|-----------------|-------|-----------------------|-----------------------|-------------------------------------|------------------|------------------|-----------------|
| | | | | | | | WK4 | WK8 | WK 12 | WK 24 | WK 36 | WK48/ PreHD C % | | SP1 [°] | SP2 [°] | SP3 [°] | |
| Verbal informed consent | X | | | | | | | | | | | | | | | | |
| iTouch Screening Interview ¹ | X | | | | | | | | | | | | | | | | |
| PrEP Opinion Questionnaire for Decliners ² | X | | | | | | | | | | | | | | | | |
| Signed informed consent | | X | | | | | | | | | | | | | | | |
| Contact information | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Demographic information | | X | | | | | | | | | | | | | | | |
| Medical and medications history (self-report) ³ | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Review of signs and symptoms ⁴ | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Full physical exam | | X | | | X | | | | | | | | | | | | |
| Symptom-directed physical exam | | | X | | | X | X | X | X | X | X | X | X | X | X | X | X |
| Tanner Stage | | | X | | | | | | | | | | | | | | |
| Height and weight | | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hepatitis B surface antigen | | X | | | X ¹¹ | X ¹¹ | | | | X ¹¹ | | X ¹¹ | X ^{11,12,13} | | | | |
| Hepatitis B surface antibody | | | X | | | | | | | | | | | | | | |
| HIV test (using an FDA-approved rapid assay) | | X | X | | X | X | X | X | X | X | X | | | | | | |
| Home-based HIV test ⁵ | | | | | | | X | X | X | | | | | | | | |
| Serum chemistries ⁶ | | X | X | | X | | | X | X | X | X | X ¹² | X | X | X | X | X |
| Serum creatinine only | | | | | | X | X | | | | | | | | | | |
| CBC with differential and platelets | | X | X | | X | | | X | X | X | X | X ¹² | X ¹⁴ | X ¹⁴ | X ¹⁴ | X ¹⁴ | X ¹⁴ |
| Syphilis testing ⁷ | | | X | | X ¹⁵ | | | | | | X | X ^{12,13} | | | | | |
| Urine gonorrhea and chlamydia testing ⁸ | | | X | | X ¹⁵ | X | X | X | X | X | X | X ¹² | | | | | |

| Evaluation/Test | Pre-SCR | SCR* | BL* | | Re-SCR ¹ | WK0* | Follow-up Visits ^{#, &} | | | | | | CFM ⁴ | HIV Seropositive Visit [#] | | |
|---|---------|------|-----|---------------------------------------|---------------------|-----------------|--------------------------------------|-----------------|-----------------|-----------------|-----------------|-------------------|------------------|-------------------------------------|------------------|------------------|
| | | | | | | | WK4 | WK8 | WK 12 | WK 24 | WK 36 | WK48/ PremDC % | | SP1 ^o | SP2 ^o | SP3 ^o |
| Rectal swab for central gonorrhea and chlamydia testing | | | X | Behavioral Intervention (3MV or PCC)* | X ¹⁵ | X ¹⁵ | X ¹⁵ | X ¹⁵ | X ¹⁵ | X | X ¹⁵ | X | | | | |
| Spot urine protein to creatinine ratio | | X | | | X | | | | | | | | | | | |
| Urine dipstick for protein and glucose | | X | | | X | X | X | X | X | X | X | X | X ¹² | | | X |
| DXA scan ⁹ | | | X | | X ¹⁶ | | | | | X | | X | | | | X |
| Confirmatory HIV-1 test | | | | | | | | | | | | | X | | | |
| HIV-1 RNA PCR | | | X | | X | | | | | | | X | X | X ¹⁴ | X ¹⁴ | X ¹⁴ |
| CD4+ T cell count | | | | | | | | | | | | | | X ¹⁴ | X ¹⁴ | X ¹⁴ |
| Samples for drug resistance testing ¹⁰ | | | | | | | | | | | | | X | | | |
| Dried blood spot for TFV, FTC, TFV-DP, & FTC-TP | | | | | | | | X | X | X | X | X | X ¹² | | | |
| Hair sample for TFV and FTC | | | | | | | | X | X | X | X | X | X ¹² | | | |
| ACASI | | | X | | | | | X | X | X | X | X | | X | | |
| Study agent supply | | | | | | | X ¹⁷ | X | X | X ¹⁸ | X ¹⁸ | X ¹⁸ | | | | |
| iNSC | | | | | | | X | X | X | X | X | X | | | | |
| Evaluation for PEP | | | X | | | X | X | X | X | X | X | X | | | | |
| Condom distribution with appropriate counseling | | X | X | | | X | X | X | X | X | X | X | X | X | X | X |

*Screening, Baseline, 3MV or PCC, and Week 0 visits all must occur within 30 calendar days, otherwise a **Re-screening visit must be done prior to proceeding with the Week 0 visit**

¹Required **only** if the Week 0 visit cannot be completed within 30 calendar days after the Screening visit.

[#]All other visits must occur within 7 calendar days prior to or after the target visit date.

⁴If an initial reactive HIV antibody test occurs during a routine follow-up study visit, the CFM visit evaluations may be done as additional evaluations at that follow-up study visit. A separate visit is not required.

[&]Subjects that are prematurely discontinued from the study agent will continue to complete all follow-up study visits and complete all evaluations/tests except no study agent will be dispensed, no samples for study agent concentration measurements will be collected, and the ACASI will not include questions related to study pill adherence.

[%]Premature Discontinuation From Study visit is **only** required for subjects who prematurely discontinue study participation after starting study agent (after Week 0).

^oConduct SP1, SP2, and SP3 visits at 4, 12, and 24 weeks, respectively, after HIV infection is confirmed.

¹The iTouch Screening Interview will be administered after verbal consent is obtained.

²Administer to youth found eligible based on the iTouch Screening Interview but declined to participate in the study after verbal consent is obtained.

³At Screening, include lifetime history of bone disease, bone fractures, renal disease, hospitalizations (excluding emergency room visits) and any other clinically significant diagnosis as determined by the site investigator. At all other visits, include interim medical history of the above categories only, but include emergency room visits. At Screening, include 12 month history of all medications listed in Appendix XI, ATN 113 Targeted Medications List and 30 day history of all other medications (including vitamins and herbal/non-herbal supplements). At all other visits, include interim medication history only.

- ⁴At Screening, include signs and symptoms within the past 30 days, including those consistent with acute HIV infection. At all other visits, include interim signs and symptoms only, including those consistent with acute HIV infection.
- ⁵Two HIV home testing kits will be provided at Week 12 (for home testing at Weeks 16 and 20), Week 24 (for home testing at Weeks 28 and 32) and Week 36 (for home testing at Weeks 40 and 44). **Also see Section 10.2.3 of protocol.**
- ⁶Must include Ca, PO₄, BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin.
- ⁷RPR or other FDA-approved diagnostic test.
- ⁸NAAT or other FDA-approved diagnostic test.
- ⁹At baseline (BL), perform at BL visit or anytime between the BL and Week 0 visits. If a repeat scan is required, complete it as soon as possible but no more than 14 calendar days after the first dose of study agent. For subsequent visits, the DXA may be completed within ± 7 calendar days of the corresponding visit. If a repeat scan is required, complete it within 14 calendar days after the previous scan. Subjects whose weight exceeds the weight limit of the local DXA scan machine are exempt from DXA scanning.
- ¹⁰Collect, process and store as two separate plasma aliquots at the site. If HIV-1 positivity is confirmed, send one aliquot to local laboratory for genotype testing. Store the second aliquot for central laboratory testing (genotype and phenotype). If HIV-1 positivity is not confirmed, both aliquots should be discarded.
- ¹¹Perform only for subjects with no documented positive HBsAb result.
- ¹²Complete only if not done at the visit with the first reactive HIV antibody test.
- ¹³Perform only if required to verify infection status.
- ¹⁴May be recorded from clinical care visit.
- ¹⁵Collect only if clinically indicated.
- ¹⁶**Only if 90 calendar days or more has elapsed since the baseline DXA was performed.**
- ¹⁷**Urine dipstick for protein and glucose must be negative or trace before a subject begins the study agent. A result of 1+ or greater for urine dipstick protein or 1+ or greater for urine dipstick glucose in the presence of normal serum glucose (< 120 mg/dL) must be repeated. Refer to section 8.5.3 for important details on evaluations and appropriate management.**
- ¹⁸**If subject has known abnormal sCr, urine protein, and/or urine glucose in the presence of normal serum glucose at the time of the visit, the study agent will be held or only a limited supply (7-10 day supply) will be dispensed, per the discretion of the study clinician, until the abnormal test(s) is/are repeated. Refer to section 8.6.3 for important details on evaluations and appropriate management.**

APPENDIX II: SCHEDULE OF EVALUATIONS FOR EXTENSION PHASE

| Evaluation/Test | EPH1* | EPH2* |
|--|-------|-------|
| Locator information | X | X |
| Medical and medications history (self-report) ¹ | X | X |
| Review of signs and symptoms | X | X |
| Symptom-directed physical exam | X | X |
| Height and weight | X | X |
| HIV test (using an FDA-approved rapid assay, HIV-uninfected subjects only) | X | X |
| Serum chemistries ² | X | X |
| CBC with differential and platelets | X | X |
| Urine dipstick for protein and glucose | X | X |
| DXA scan ³ | X | X |
| iNSC | X | X |
| Condom distribution with appropriate counseling | X | X |

*Extension Phase visits will occur at 24 weeks (EPH1) and 48 weeks (EPH2) after completing the Week 48 visit or the SP3 visit for only those subjects who meet the criteria for the Extension Phase. All visits must occur within 7 calendar days prior to or after the target visit date.

¹Interim history of bone disease, bone fractures, renal disease, hospitalization (including emergency room visits), and any other clinically significant diagnosis as determined by the site investigator.

²Serum chemistries must include Ca, PO₄, BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin.

³Subjects whose weight exceeds the weight limit of the local DXA scan machine are exempt from DXA scanning.

APPENDIX III: LIST OF PARTICIPATING SITES (NEW)

| | | |
|--|---|---|
| Children's Hospital of Los Angeles Los Angeles, CA Site 2 | Marvin Belzer Childrens Hospital of Los Angeles Division of Adolescent Medicine 5000 Sunset Boulevard, 4th Floor Los Angeles, CA 90027 | E-mail: mbelzer@chla.usc.edu Phone: (323) 361-4758 Fax: (323) 913-3614 |
| Children's Hospital of Philadelphia Philadelphia, PA Site 4 | Steven Douglas CHOP-Perelman School of Medicine 34th and Civic Center Boulevard Philadelphia, PA 19104 | E-mail: douglas@email.chop.edu Phone: (215) 590-3561 Fax: (215) 590-3044 |
| Stroger Hospital and the CORE Center Chicago, IL Site 5 | Jaime Martinez Stroger Hospital of Cook County 1900 West Polk Street Administration Building, Room 1110 Chicago, IL 60612 | E-mail: jmartinez@cookcountyhhs.org Phone: (312) 864-3573 Fax: (312) 864-9721 |
| | Lisa Henry-Reid Stroger Hospital of Cook County 1900 West Polk Street Administration Building, Room 1112 Chicago, IL 60612 | E-mail: lhenryreid@aol.com Phone: (312) 864-3582 Fax: (312) 864-9721 |
| Tulane Medical Center New Orleans, LA Site 10 | Sue Ellen Abdalian Tulane University Adolescent Medicine (TW42) 1440 Canal Street New Orleans, LA 70112 | E-mail: sabdali@tulane.edu Phone: (504) 988-3881 Fax: (504) 988-3619 |
| The Fenway Institute Boston, MA Site 21 | Kenneth Mayer Fenway Community Health 1340 Boylston Street Boston, MA 2215 | E-mail: kenneth_mayer@brown.edu Phone: (617) 927-6087 Fax: (617) 267-0764 |
| University of Colorado Denver, CO Site 22 | Elizabeth McFarland University of Colorado The Children's Hospital 13123 East 16th Avenue B-055 Aurora, CO 80045 | E-mail: betsy.mcfarland@ucdenver.edu Phone: (303) 724-3447 Fax: (720) 777-7295 |

APPENDIX IV: SPECIMEN COLLECTION, PROCESSING, STORAGE, AND SHIPPING GUIDELINES

For Local Laboratory Testing

| Test to be Performed | Analyte | Volume | Processing/Testing Instructions |
|--|-------------|--|--|
| HIV-1 test | Oral sample | Not applicable | As recommended in testing kit instructions. |
| | Serum | As recommended by local lab but not to exceed 2 ml. | Perform at site per local site laboratory procedures. |
| HIV-1 Confirmatory test | Serum | As recommended by local lab but not to exceed 5 ml. | Perform at site per local site laboratory procedures. |
| Hepatitis B: surface antigen | Serum | As recommended by local lab but not to exceed 4 ml. | Perform at site per local site laboratory procedures. |
| Hepatitis B: surface antigen and surface antibody | Serum | As recommended by local lab but not to exceed 8 ml. Use same tube collected for syphilis testing, if also being done. | Perform at site per local site laboratory procedures. |
| Syphilis test: RPR or another FDA-approved diagnostic test | Serum | As recommended by local lab but not to exceed 8 ml. Use same tube collected for Hepatitis testing, if also being done. | Perform at site per local site laboratory procedures. |
| Chemistries: Ca, PO ₄ , BUN, sCr, glucose, electrolytes (Na, K, Cl, & CO ₂), amylase and LFTs (AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, and direct bilirubin) | Serum | As recommended by local lab but not to exceed 10 ml. | Perform at site per local site laboratory procedures. |
| Serum creatinine | Serum | As recommended by local lab but not to exceed 4 ml. Use same tube collected for Chemistries, if also being done. | Perform at site per local site laboratory procedures. |
| CBC with differential and platelets | Serum | As recommended by local lab but not to exceed 5 ml. | Perform at site per local site laboratory procedures. |
| Protein to creatinine ratio | Urine | As recommended by local lab. | Perform at site per local site laboratory procedures. |
| Protein and glucose (urine dipstick) | Urine | As recommended by local lab. | Perform at site per local site laboratory procedures. |
| Gonorrhea and chlamydia: NAAT or another FDA-approved diagnostic test | Urine | As recommended by local lab. | Perform at site per local site laboratory procedures. |
| HIV-1 RNA PCR | Plasma | As recommended by local lab but not to exceed 5 ml. | Perform at site per local site laboratory procedures |
| CD4+ T cell count | Serum | As recommended by local lab but not to exceed 5 ml. | Perform at site per local site laboratory procedures. |
| Drug resistance testing (genotypic) - Send for testing if HIV-1 infection is confirmed | Plasma | Use same tube collected for central laboratory drug resistance testing. | Process and store according to instructions for plasma for central laboratory drug resistance testing. If HIV-1 infection is confirmed, send one aliquot for local laboratory testing. |

For Central Laboratory Testing

| Test to be Performed | Analyte | Collection Container and Volume | Processing Instructions | Storage/Shipping Instructions |
|--|----------------|--|---|--|
| Gonorrhea and chlamydia | Rectal swab | 1 swab in swab specimen transport tube | See Appendix VIII. | Store at room temperature. Ship on the 1 st and 15 th of each month. |
| Drug resistance testing (genotypic and phenotypic) – if HIV-1 infection is confirmed | Plasma | 10 ml in EDTA tube | Within 60 min of collection, centrifuge at 1200x g for 10 min at 4°C. Aliquot the plasma into two equal-volume aliquots. Keep in ice bath until frozen. | Maintain frozen at -20°C or lower. If HIV-1 infection is confirmed, send one aliquot for local laboratory drug resistance testing. Store and batch ship the second aliquot at the end of the study for central laboratory drug resistance testing. If HIV-1 infection is not confirmed, discard both aliquots. |
| TFV, FTC, TFV-DP, and FTC-TP | DBS | 4 ml in EDTA tube (purple top) | See Appendix V. | Dry at room temperature, then store in a -20 or -80C freezer until shipment. Batch ship once every two months. |
| TFV and FTC | Hair | At least 100 fibers | Place on aluminum foil, label distal end, and place inside zip-lock bag. See Appendix VII. | Send to local laboratory and store at room temperature. Batch ship at the end of the study. |

The clinical site staff must complete the applicable sections of the *ATN 113 Specimen Tracking Form* pertaining to receipt and processing of the specimens, send it along with the specimens to the local processing laboratory for completion by the local laboratory personnel. The completed form must be returned to the clinical site staff and entered into the ATN 113 OC-RDC database. At the local processing laboratory, all specimens must be logged into the LDMS and labeled with computer labels generated based on the specifications for the ATN LDMS label format.

APPENDIX V: METHOD FOR SPOTTING WHOLE BLOOD FOR QUANTIFICATION OF TFV, FTC, TFV-DP, AND FTC-TP

This method is to be utilized for Dried Blood Spot Sample Collection and Sample Storage for the analysis of tenofovir (TFV), emtricitabine (FTC), tenofovir-diphosphate (TFV-DP), and emtricitabine triphosphate (FTC-TP). Personnel should use universal precautions for blood borne pathogens. This procedure can be done outside a biosafety cabinet if consistent with local regulations.

Supplies

- EDTA Vacutainer Evacuated Blood Collection Tube
- Whatman Protein Saver Card #903 (Whatman 10534612 or Fisher Scientific #NC9307519) (Handle with gloves and do not touch spot areas)
- Whatman Plastic Sample Bag (Whatman 10548232 or Fisher Scientific #50853570) or Whatman Foil-Barrier Sample Bag (Whatman 10534321 or Fisher Scientific #50853569)
- Desiccant pack (Whatman 10548234 or Fisher Scientific #50853571)
- Humidity indicator Card (Multisorb Des Manufacture #MS200032 or Fisher Scientific #NC9511648)
- Whatman card drying rack (VWR catalogue #89015-592)
- Gloves preferably powder free
- Water proof marker (Fisher Scientific #50853571)
- 2 LDMS labels
- 10 - 100 mcL or 20-200 mcL micropipette and appropriate tips with filters (Sites should check with local suppliers for appropriate tips for their micropipettes)

Procedure

1. Whole blood is drawn by venipuncture into a Vacutainer EDTA (purple top) tube. Invert several times and store at room temperature until specimen is processed. If blood is produced from a finger stick, contact the ATN 113 Protocol Team.
2. Samples should be processed within 60 minutes of the time of collection; the actual time should be recorded on the *ATN 113 Specimen Tracking Form*.
3. Label ProteinSaver Card with study protocol#, PID#, SID#, study week, date and time of sample collection. Use a waterproof pen and a non-removable label.
4. Assure the blood tube has been inverted several times. Remove the stopper from the EDTA tube (if not allowable by local regulations, contact the ATN 113 Protocol Team) and spot 25mcL of blood using a pipet onto designated circles on the ProteinSaver Card. Provide at least 2 such spots. Pipet tip should be held approximately 3mm above the spot location and dispense the blood onto the card with one single dispensing from the micropipet. Do not touch, press, or smear the spots. Return the stopper to the tube and process for other lab tests, as appropriate.
5. Complete an *ATN 113 Specimen Tracking Form* with the study protocol#, PID#, SID#, study week, date and time of sample collection and input to the lab database as well.
6. Air dry the card in a card holder for several hours, up to overnight is acceptable.

7. After dried, place DBS card in a low gas-permeability plastic bag with humidity indicator and desiccant pack to reduce humidity.
8. Store bag in a cardboard box at -20°C or -80°C.

Procedural Notes:

If local regulations do not allow removal of blood stopper, a DIFF-SAFE apparatus can be used. Contact the ATN 113 Protocol Team for further instructions.

Shipment of Samples

Place DBS card (in the sample bag) in a freezer box and place box in a zip-lock bag in a **SAF-T-PAK**. The shipment must be packed in sufficient (for 48 hours) dry ice to ensure that samples are frozen upon arrival. Pack, seal, and label the shipping carton according to guidelines for shipping biological agents. Please do NOT ship on a Friday, Saturday, Sunday, or the day before a legal holiday. Please notify the Colorado Antiviral Pharmacology Laboratory at the University of Colorado Denver by FAX (303-724-6135, ATTN: Lane Bushman) prior to the shipment of samples and include the airbill number.

Shipping Address (Fed-Ex)

Lane R. Bushman
Colorado Antiviral Pharmacology Laboratory
Skaggs School of Pharmacy, V20-C238, Room 4410
University of Colorado Denver
12850 East Montview Boulevard
Aurora, CO 80045
Phone: (303) 724-6132
Fax: (303) 724-6135
Email: lane.bushman@ucdenver.edu

APPENDIX VI: LABORATORY ANALYSIS OF DRIED BLOOD SPOT CONCENTRATIONS OF TENOFOVIR AND EMTRICITABINE AND INTRACELLULAR CONCENTRATIONS OF TENOFOVIR-DIPHOSPHATE AND EMTRICITABINE-TRIPHOSPHATE

Analysis of Tenofovir and Emtricitabine in Plasma and Dried Blood Spots

Tenofovir and emtricitabine plasma concentrations will be determined using a validated liquid chromatography-mass spectrometry (LC-MS-MS) assay. Linearity of the method is in the range 10 ng/ml to 1500 ng/ml. The assay has a minimum quantifiable limit of 10 ng/ml when 0.25 ml of plasma is analyzed. Inter- and intraday accuracy and precision are within $\pm 20\%$ at the LLOQ and $\pm 15\%$ at all other concentrations.¹

Analysis of Intracellular Tenofovir-Diphosphate and Emtricitabine-Triphosphate Concentrations

Intracellular tenofovir-diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP) concentrations in human peripheral blood mononuclear cells and TFV-DP in DBS will be determined using a validated liquid chromatography-tandem mass spectrometry (LC-MS-MS assay). This is an indirect method which first isolates TFV-DP and FTC-TP, then dephosphorylates these moieties to form the parent compounds, tenofovir and emtricitabine. Tenofovir and emtricitabine are desalted and concentrated, making it possible for tandem mass spectral detection. The quantifiable linear range for tenofovir is 2.5–2000 fmol/sample, and that for emtricitabine is 0.1-200 pmol/sample. The minimum quantifiable limit is based on the number of cells assayed. Accuracy and precision performance is described in ref 2.²

References for Validated, Published Assays:

1. Delahunty T, Bushman L, & Fletcher CV. Sensitive assay for determining plasma tenofovir concentrations by LC/MS/MS. *J Chromatogr B Analyt Technol Biomed Life Sci* 2006;830:6-12.
2. Bushman LR, Kiser JJ, Rower JR, Klein B, Zheng JH, Ray M, Anderson PL*. Determination of nucleoside analog mono-, di, and triphosphates in cellular matrix by solid phase extraction and ultrasensitive LC/MS/MS detection. *Journal of Pharmaceutical and Biomedical Analysis* 2011;56(2):390-401.

APPENDIX VII: PROCEDURE FOR COLLECTION, STORAGE, AND SHIPPING OF HAIR SPECIMENS

Before collecting hair, proceed with the questionnaire assessing hair product use, coloring and treatment. Scalp hair is preferred; if there is none or not enough scalp hair, facial hair may be collected. Hair from other body parts (e.g., underarm, leg/arm, chest) may be collected only if no scalp or facial hair is available. Pubic hair should not be collected. The procedures described below refer to scalp hair only, please contact Dr. Albert Liu at Albert.Liu@sfdph.org for procedures for other hair locations.

Specimen Collection

Clinicians can find the training on proper hair sampling technique by viewing the scalp hair collection training video at <http://www.youtube.com/watch?v=FI1Fd0b2IIaQ>.

1. Prepare labels (4) with study protocol#, PID#, SID#, visit week, and specimen collection date.
2. Place a label on the outside of a zip-lock bag. Unfold a piece of aluminum foil.
3. Clean the blades of a pair of scissors with an alcohol pad and allow blades to completely dry prior to use.
4. Lift up the top layer of hair from the **occipital** region of the scalp. A hair clip (or an assistant's fingers) can be used to keep this top layer of hair out of the way. Isolate a small thatch of hair (at least 100 fibers of hair) from *underneath* this top layer of hair from the **occipital** region. Two or more scalp locations may be used. If insufficient scalp hair is available, facial hair, which also grows at a steady rate, may be used. A notation will be made for subjects with inadequate hair at either site.
5. Cut the small hair sample off the subject's head *as close to the scalp as possible* (scissors should be gently touching the scalp). As demonstrated in the video, keep track of the directionality of the hair by keeping hair tightly pinched between your fingers.
6. Place hair in aluminum foil and place a small label with the subject's PID over the **distal** end of the hair thatch, taping it to the aluminum foil. The distal end is the portion furthest from the scalp. If the hair is short and the label used to tape the hair to the aluminum foil does not clearly indicate the distal end, place an additional label on the aluminum foil next to the hair thatch with an arrow pointing to the distal end. **It is very important to place the label at the distal end as this will distinguish the scalp (proximal) end from the distal end during hair analysis.**
7. Fold the foil over to completely enclose the thatch of hair. Attach a label so that it appears on the outside.
8. The pair of scissors used to collect the hair samples should be cleaned prior to using on each subject. Reclean the blades of the scissors with an alcohol pad and allow blades to completely dry prior to reuse.
9. Place the labeled folded piece of foil inside a labeled zip-lock bag with a desiccant bag in it and seal the zip-lock bag.
10. Send to site's local LDMS lab.

Storage and Shipment

1. Enter hair specimens into the LDMS using the general instructions for LDMS. Use LDMS code HAR/NON/HAR for primary and derivative. Generate LDMS label.
2. Label the zip-lock bag with LDMS label.
3. Store all hair samples in a dark dry place (for example in a filing cabinet) at room temperature for later shipment. Hair samples are not biohazardous.
4. When shipping to the central laboratory, hair specimens are to be boxed in order of SID and specimen collection date.
5. Specimens should be shipped at room temperature in an insulated container to prevent freezing labeled “ATN 113 Hair Specimen” and shipped with a shipping manifest generated as per instructions for LDMS. Include the shipping manifest with the hair shipment.
6. Shipment will be done **upon request by the protocol team.**

Shipping Address:

Dr. Yong Huang
UCSF, Drug Studies Unit
Medical Science Building
Room S907
University of California, San Francisco
513 Parnassus Avenue
San Francisco, CA 94143
Phone: (415) 476-**9960**
Fax: (415) 476-6770
Email: Yong.Huang@ucsf.edu

APPENDIX VIII: PROCEDURE FOR COLLECTION, STORAGE, AND SHIPPING OF RECTAL SWABS FOR CENTRAL GONORRHEA AND CHLAMYDIA TESTING BY TRANSCRIPTION-MEDIATED AMPLIFICATION (TMA)

Materials

APTIMA Combo 2 Assay Unisex Swab Specimen Collection Kit (Order from the ATN DOC at Westat via the ATN website)

Specimen Collection

1. Insert the small, blue shafted collection swab (NOT the larger white shafted cleansing swab) approximately 3 - 5 cm into the rectum.
2. Rotate swab against the rectal wall at least three times.
3. Withdraw the swab carefully. (Swabs that are grossly contaminated with feces should be discarded and the collection repeated.)
4. Remove the cap from the swab specimen transport tube and immediately place the swab into the transport tube.
5. Carefully break the swab shaft at the score line. Re-cap the swab specimen transport tube tightly.
6. Label transport tube with study protocol#, PID#, SID#, visit week, date of sample collection and send to the local processing lab at room temperature.
7. Place tube in zip-lock bag and label the bag.

NOTE: The swab may be self-collected by the subject if the subject prefers.

Labeling, Storage and Shipment

1. **Enter rectal swab specimens into the LDMS using the general instructions for LDMS. Use LDMS code REC/SWB for primary/derivative. Generate LDMS label and place on specimen.**
2. Store at room temperature until time of shipping.
3. Specimens should be shipped *at room temperature* in a **SAF-T-PAK**. Pack, seal, and label the shipping carton according to guidelines for shipping biological agents.
4. Batch ship to Quest Diagnostics for central testing on the 1st and 15th of each month.

IMPORTANT NOTE: Swab specimens must be sent to Quest Diagnostics within 20 days of collection.

Shipping Address

Quest Diagnostics Incorporated
Department of Virology
Attn: William A. Meyer III, Ph.D.
1901 Sulphur Spring Road
Baltimore, MD 21227
Phone: (410) 536-1593
Fax: (410) 737-1266
Email: William.A.Meyer@QuestDiagnostics.com

APPENDIX IX: ASSESSMENT OF UNDERSTANDING QUESTIONNAIRE

Participant Name: _____ **Date:** _____

INSTRUCTIONS: Circle one response for each question to indicate whether the statement is true or false.

| QUESTION | | RESPONSE | |
|----------|--|----------|-------|
| 1. | I will be asked to participate either in a group-level behavioral intervention called Many Men, Many Voices (3MV) or in an individual-level Personalized Cognitive Counseling (PCC) session. | TRUE | FALSE |
| 2. | I will be able to choose which behavioral intervention I want to be in. | TRUE | FALSE |
| 3. | I must continue to participate in the study even if I feel upset or uncomfortable. | TRUE | FALSE |
| 4. | I will be asked to provide blood, urine and hair samples throughout the study. | TRUE | FALSE |
| 5. | No names or other personal information will be published or used in any way by the study researchers. | TRUE | FALSE |
| 6. | If I give the researchers information that suggests I or someone else might be in danger, state law may require that the researchers report the information to the appropriate authorities. | TRUE | FALSE |
| 7. | The total length of time for my participation in the study is one year. | TRUE | FALSE |
| 8. | I must take the PrEP drug even if it makes me feel not well. | TRUE | FALSE |

Participant Name: _____ **Date:** _____

INSTRUCTIONS TO SITE STAFF: Review the participant’s responses after it is completed. The initial response to each question selected by the participant should be maintained even if the response is incorrect. If the participant has selected the wrong response to any of the questions, review the question and the correct response with the participant until the participant understands the concept. Do not change the initial response on the form. Discuss the concepts as many times as is necessary until you are certain that the participant understands what is correct. Refer to the key below for the correct responses. The teaching points listed below may be used to explain correct concepts to the participants.

Document your discussion and participant’s understanding of each concept in the comments section below and maintain this form as source documentation, together with the signed informed consent forms.

Answer Key:

| | | | | |
|-----|---------|--|-----|---------|
| Q1. | = True | | Q5. | = True |
| Q2. | = False | | Q6. | = True |
| Q3. | = False | | Q7. | = False |
| Q4. | = True | | Q8. | = False |

Teaching Points:

| | |
|-----|--|
| Q1. | You will be asked to participate either in a group-level behavioral intervention called Many Men, Many Voices (3MV) or in an individual-level Personalized Cognitive Counseling (PCC) session. The 3MV will occur in a seminar format and may be conducted over two days. The PCC is a one-hour, individual-level session. |
| Q2. | You will not be able to choose behavioral session in which you want to participate. You will receive whichever intervention is offered at the clinic site where you are participating in the study. |
| Q3. | Taking part in this study is completely voluntary. You may stop participating in the study at any time. If you feel upset or uncomfortable and want to stop participating, you may do so. If you feel upset or uncomfortable when taking the questionnaire, you can choose not to answer specific questions or stop the interview altogether, at anytime. |
| Q4. | You will be asked to provide blood for tests that looks at different minerals and other substances in your blood to see how your body is doing, for HIV testing, and to test the levels of the PrEP drug in your blood to check on how well you are taking the PrEP drug. You will be asked to provide urine for STI testing and to test the different minerals and other substances in your urine to see how your body is doing. You will also be asked to provide a hair sample that will also be used to test the levels of the PrEP drug in your body. |

Participant Name: _____ **Date:** _____

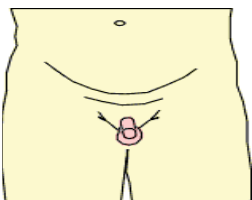
| | |
|-----|---|
| Q5. | No names or other personal information will be published or used by study researchers. Information about the study may be published or used by researchers but names or other personal information will never be used. A certificate of confidentiality has been obtained from the Federal Government for this study to protect your privacy. This means that researchers cannot be forced to give information about your connection to this study, without your written consent. |
| Q6. | If we learn something that would immediately put you or others in danger, the researchers are required by law to take steps to keep you and others safe. This may mean contacting the authorities. |
| Q7. | There are two phases to this study; the Initial Phase and the Extension Phase. All study participants will take part in the Initial Phase of the study. Depending on your bone and kidney tests results at the end of the Initial Phase, you may be asked to continue on the Extension Phase. This means, your participation in this study will be at least 1 year (Initial Phase only), but it could be as long as 2 years (Initial and Extension Phase). If you become HIV infected during the Initial Phase of the study, your participant in this study may be another ½ year longer. |
| Q8. | If at any time you feel the PrEP drug is making you not well and you no longer want to continue taking the PrEP drug, you may stop. You may stop taking the PrEP drug at any time. |

Comments:

| | | |
|-------------------------------|----------------------------|-------|
| _____ | _____ | _____ |
| PI or Designee's Name (print) | PI or Designee's Signature | Date |

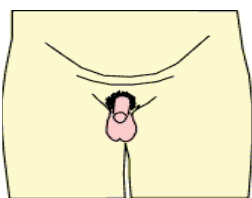
APPENDIX X: SELF-ASSESSMENT OF TANNER STAGE TOOL

INSTRUCTIONS TO THE PARTICIPANT: The drawings below show 5 different stages of how the penis, testicles and pubic hair grow. A male can go through each of the 5 stages as shown. Please look at each drawing and read the sentences that match the drawings. Then, mark an "X" in the box next to the drawing that you think is closest to your stage of penis, testicles, and pubic hair growth.



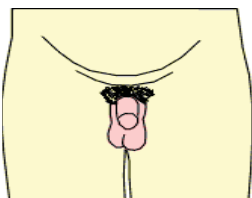
Stage 1

This is the preadolescent stage. There is no pubic hair. The penis and testicles are about the same size as in childhood.



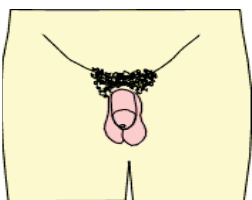
Stage 2

The penis, testicles, and pubic hair start to grow. Sparse and fine pubic hair grows at the base of the penis. The color of the skin around the testicles starts turning red.



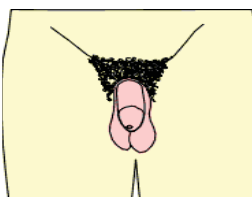
Stage 3

Pubic hair is darker, coarser and curlier, but there isn't very much. The penis is wider as well as longer. The testicles are slightly larger.



Stage 4

Pubic hair is thicker, but does not spread to the thighs. Pubic hair becomes adult type except there is less. The penis is wider and longer. The testicles are larger.



Stage 5

Pubic hair is thick spreading to the thighs. The penis is at its full adult size.

(Adopted from: Morris, NM and Udry, JR (1980) Validation of a Self-Administered Instrument to Assess Stage of Adolescence Development. J of Youth and Adolescence. Vol 9 No 3:271-280).

APPENDIX XI: ATN 113 TARGETED MEDICATIONS LIST

Refer to this list when completing the *ATN 113 Concomitant Medications Form*. This list is not intended to be comprehensive; also record on the form any medications that are of the same categories specified below but not on this list.

| | |
|--|--|
| <p>Lipid Lowering Agents HMG CoA Reductase Inhibitors (“statins”) <u>Atorvastatin</u> (Lipitor[®]) <u>Fluvastatin</u> (Lescol[®]) <u>Lovastatin</u> (Mevacor[®]) <u>Pravastatin</u> (Pravachol[®]) <u>Simvastatin</u> (Zocor[®]) <u>Rosuvastatin</u> (Crestor[®])</p> <p>Other <u>Cholestyramine</u> (Questran[®]) <u>Colestipol</u> (Colestid[®])</p> <p>Systemic Glucocorticoids <u>Prednisone</u> (Orasone[®], Deltasone[®]) <u>Methylprednisolone</u> (Solumedrol[®]) <u>Dexamethasone</u> (Decadron[®]) <u>Hydrocortisone</u> (Solu-Cortef[®])</p> <p>Inhaled Steroids <u>Triamcinolone acetonide</u> (Azmacort[®]) <u>Fluticasone propionate</u> (Flovent[®]) <u>Fluticasone propionate/salmeterol</u> (Advair[®]) <u>Budesonide</u> (Pulmicort[®])</p> <p>Antiepileptics <u>Phenytoin</u> (Di-Phen[®], Dilantin[®], Phenytek[®]) <u>Carbamazepine</u> (Tegretol[®], Carbatrol[®]) <u>Phenobarbital</u> (Solfoton[®]) <u>Valproic acid</u> (Depakote[®], Depakene[®])</p> <p>SSRI Antidepressants <u>Citalopram</u> (Celexa[®], Cipramil[®], Cipram[®], Dalsan[®], Recital[®], Emocal[®], Sepram[®], Seropram[®], Citox[®], Cital[®]) <u>Dapoxetine</u> (Priligy[®]) <u>Escitalopram</u> (Lexapro[®], Cipralext[®], Seroplex[®], Esertia[®]) <u>Fluoxetine</u> (Prozac[®], Fontex[®], Seromex[®], Seronil[®], Sarafem[®], Ladose[®], Motivest[®], Flutop[®]) <u>Fluvoxamine</u> (Luvox[®], Fevarin[®], Faverin[®], Dumyrox[®], Favoxil[®], Movox[®]) <u>Paroxetine</u> (Paxil[®], Seroxat[®], Sereupin[®],</p> | <p>Hormonal Anabolic Agents <i>(Including steroid injections obtained on the street for muscles)</i> Growth hormone <u>Somatropin</u> (Serostim[®], Saizen[®], Nutropin[®], Genotropin[®], Biotropin[®], Norditropin[®], Humatrope CMB[®]) Growth hormone releasing factors <u>Tesamorelin</u> (Egrifta[™])</p> <p>Testosterone and other androgens <u>Testosterone</u> (IM injection (Delatestryl[®]), transdermal patch (Testoderm[®], Androderm[®]) or transdermal gel (AndroGel[®])) <u>Methyltestosterone</u> (Oreton Methyl[®]) <u>Nandrolone decanoate</u> (Deca-Durabolin[®], Nandrobolic[®]) <u>Oxandrolone</u> (Oxandrin[®]) <u>Oxymetholone</u> (Anadrol[®]-50) <u>Stanozolol</u> (Winstrol[®]) <u>Fluoxymesterone</u> (Halotestin[®])</p> <p>Systemic Ketoconazole (Nizoral[®])</p> <p>Hormonal Contraceptives <i>(Including hormones used for feminization)</i></p> <p>Topical or implanted Hormonal Contraceptives: <u>Norelgestromin/ethinyl estradiol</u> (Ortho Evra[®]) <u>Etonogestrel</u> (Implanon[®])</p> <p>Injectable Progestins <u>Medroxyprogesterone</u> (Depo-Provera[®])</p> <p>Oral Progestins <u>Norethindrone</u> (Ortho Micronor[®], Nor-QD[®]) <u>Norgestrel</u> (Ovrette[®]) <u>Progesterone</u> (Prometrium[®]) <u>Medroxyprogesterone Acetate</u> (Provera[®])</p> <p>Oral Progestin and Estrogen Combinations <u>Desogestrel/ethinyl estradiol</u> (Desogen[®],</p> |
|--|--|

Aropax[®], Deroxat[®], Divarius[®], Rexetin[®],
Xetanor[®], Paroxat[®], Loxamine[®], Deparoc[®])
Sertraline (Zoloft[®], Lustral[®], Serlain[®],
Asentra[®])
Vilazodone (Viibryd)

SNRI Antidepressants

Venlafaxine (Effexor[®])
Desvenlafaxine (Pristiq[®])
Duloxetine (Cymbalta[®], Yentreve[®])
Milnacipran (Dalcipran[®], Ixel[®], Savella[®])
Sibutramine (Meridia[®], Reductil[®])

Appetite Stimulants

Megestrol acetate (Megace[®])
Dronabinol (Marinol[®])
Cyproheptadine (Periactin[®])

Herbal Medicine

St. John's Wort
Garlic supplements
Echinacea

Other agents:

Orlistat (Alli[®], Xenical[®])

Over the Counter Agents (sold under a variety of trade names)

Androstenedione
Dhydroepiandrosterone, DHEA
Fish oil (n-3 fatty acids)
GH-releasers (arginine, ornithine, lysine)
B-hydroxy-B-methylbutyrate (betaHMB)

Proton Pump Inhibitors (PPIs)

Dexlansoprazole (Dexilant[®])
Esomeprazole (Nexium[®])
Lansoprazole (Prevacid[®])
Omeprazole (Prilosec[®], Zegerid[®])
Pantoprazole (Protonix[®])
Rabeprazole (Aciphex[®])

Ortho-Cept[®], Mircette[®])
Estrogen/Medroxyprogesterone (Premphase[®],
Prempro[®])
Ethinodiol diacetate/ethinyl estradiol
(Zovia[®])
Levonorgestrel/ethinyl estradiol (Alesse[®],
Levora[®], Nordette[®], Triphasil[®], Trivora[®])
Norethindrone/ethinyl estradiol (Activella[®],
Brevicon[®], Norinyl[®], Estrostep[®] 21,
Estrostep[®] Fe, Femhrt[®], Microgestin[®] Fe,
Modicon[®], Necon[®], Ortho-Novum[®], Ovcon[®],
Tri-Norinyl[®] 28)
Norgestrel/ethinyl estradiol (Lo/Ovral[®], Lo-
Ogestrel[®], Ogestrel[®], Ovral[®])
Norgestimate/ethinyl estradiol (Ortho-
Cyclen[®], Ortho-Prefest[®], Ortho Tri-Cyclen[®])

Other Agents Used for Feminization

Spirolactone (Aldactone[®])
Finasteride (Proscar[®], Propecia[®])
Leuprolide acetate (Lupron[®])
Flutamide (Eulexin[®])
Cyproterone acetate (Androcur[®])
Estrogens (oral, injectable, transdermal,
sublingual)

Other Hormonal Therapy (Thyroid replacement)

Levothyroxine/L-thyroxine (Synthroid[®],
Levothroid[®], Levoxyl[®], Unithroid[®])
Liothyronine (Cytomel[®])
Liotrix (Thyrolar[®])
Methimazole (Tapazole[®])

Drugs that may Interfere with Tenofovir Excretion

Antineoplastics
Penicillins
Adefovir (Hepsera[®])
Cidofovir (Vistide[®])
Cyclosporin A (Neoral[®], Sandimmune[®],
SangCya[®])
Indomethacin (Indocid[®], Indocin[®])
Probenecid (Benuryl[®], Benemid[®], Probalan[®])
Rifampin (Rifadin[®], Rimactane[®])
Sirolimus (Rapamune[®])
Ursodiol (Actigall[®], Urso[®])
(Val)ganciclovir hydrochloride (Valcide[®])

APPENDIX XII: ITOUCH SCREENING INTERVIEW

Potential subjects will be recruited in person at the AMTUs or their collaborative community sites. Potential subjects identified by telephone will be scheduled to complete the iTouch Screening Interview in person. Verbal consent will be obtained from all potential subjects prior to administering the screening interview. When men/**transgender women** present themselves for screening, staff will thank the men/**transgender women** for their time, explain the purpose of the study and obtain verbal consent for completion of the interview. Young men/**transgender women** who screen eligible using the iTouch Screening Interview will be scheduled for a screening visit at the AMTU.

The screening process will be explained as follows:

*Thank you for **your** interest in our PrEP study. PrEP stands for pre-exposure prophylaxis. PrEP is when drugs used to treat HIV/AIDS are given to people before they are exposed to HIV to protect them from getting it. We are doing this study to learn about how safe and practical it is to use PrEP with young men who have sex with men (YMSM) **and young transgender women**. For example, we want to know if it is safe for young men/**transgender women** to be on PrEP, whether it is difficult to recruit and keep young men/**transgender women** in the study, if young men/**transgender women** will stick closely to taking the PrEP medications, and if being in the study will lead to **more** sexual risk behavior. We are asking you to complete a brief **survey** to find out if you **qualify** to be in the study. You will read and answer the questions yourself and I will not be able to see your answers. Some of the questions are personal. The computer will tell you if you **qualify** to be in the study. Answering these questions is voluntary, your responses will be kept private, and you can refuse to answer a question or stop at any time. **If you have trouble understanding a question, please feel free to ask for help.***

Introduction Screen 1:

Thank you for agreeing to **complete this survey**. To learn if you **qualify to join** the study, you will be asked to answer questions about your background, health, and sexual behaviors. Some of these questions may be difficult for you to answer. There **are** no right or wrong answers, so please answer as honestly as possible.

Introduction Screen 2:

Some of these questions **are** very personal but remember, your answers are anonymous. That is, your name will not be associated with any of the information you give me.

Introduction Screen 3:

This interview is going to take about **5** minutes to complete. If you have any questions at any point during the interview, just ask.

To answer the questions in this survey, tap on the box underneath the question. When the screen with the answer options appears, use your finger to scroll down and see all of the choices. To select an option, tap on it. To deselect an option, tap on it again. Answer each question and tap “Done” in the upper right corner of the screen to return to the main question list.

To determine **if you qualify**, please answer all **the** questions.

1. Do you **speak** English?
 Yes
 No (***Ineligible***)

2. How old are you?
|_____| |_____| Years (***If participant is NOT 15-17, inclusive, ineligible for ATN 113***)

3. **What is your gender?**
 Male
 Female
 Transmale/Transman
 Transfemale/Transwoman
 Genderqueer
 Would rather not answer

4. **What sex were you assigned at birth?**
 Male
 Female (***Ineligible***)

5. When was the last time you visited a doctor?
 In the last month
 In the last six months
 A year ago
 More than a year ago

6. Have you ever been tested for HIV?
 Yes
 No (***Go to Q8***)
 Not sure (***Go to Q8***)

7. What were your HIV test results?
 I have HIV (*Ineligible*)
 I do not have HIV
 The test was inconclusive (it couldn't tell me if I had HIV or not)
 I don't know. I never went back for my test results

The next few questions are going to ask about anal sex. When we say anal sex, we mean when you put your penis in someone else's butt or when someone else puts their penis in your butt.

8. **Have you ever had anal sex with a female?**

Yes

No

9. Have you ever had anal sex with a male or a transgender female (transgirl/transwoman)?

Yes

No (*Ineligible*)

10. Are you willing to **consider taking** PrEP (one pill once a day to prevent HIV) if you are enrolled in the study?

Yes

No (*Ineligible*)

11. What is the 5-digit zip code of your current home or place where you sleep?

| | | | | |
|--|--|--|--|--|
| | | | | |
|--|--|--|--|--|

12. Do you plan to move out of the **United States** in the next 12 months?

Yes (*Ineligible*)

No

Not sure

13. Are you currently in school?

Yes

No

14. How often do you exercise?

3 to 4 times a week

1 to 2 times a week

1 to 2 times a month

Less than 1 time a month

You have reached the end of your questions. Thank you for your time.

To finalize and lock your survey, please tap the “Done” button below. Then hand the device to the data collector.

If none of the INELIGIBLE responses are checked, read the ELIGIBLE section below. If any ineligible response is checked, read the INELIGIBLE section.

FOR INELIGIBLE VOLUNTEERS:

Participants for this study are selected based on the questions you were just asked. Based on your answers, it turns out you are not eligible to take part in this study. Thank you for taking the time to complete the interview.

FOR ELIGIBLE VOLUNTEERS:

Thank you very much for the information you provided. Based on your answers to these questions, you are eligible to take part in this study. That means that if you want to take part in the research, you may.

Do you think you might be interested in taking part in this study? Yes No

If NO say: Thank you for taking the time to complete the interview. Would you be interested in answering a few questions about what you think of PrEP so that we can better understand why young people like you are not interested in PrEP studies? If yes, proceed to administer the PrEP Opinion Questionnaire. If no, thank the participant for taking the time to answer the questions.

If YES say: We will need for you to come to _____ (*Name of ATN Site*) to have some tests done to confirm that you are able to participate in the study. We are located at _____ (*Address of Site*). (*Proceed to schedule an appointment date and time.*)

APPENDIX XIII: PREP OPINION QUESTIONNAIRE FOR INDIVIDUALS WHO DECLINED STUDY PARTICIPATION

YOU ARE BEING ASKED TO COMPLETE THIS SURVEY BECAUSE YOU CHOSE NOT TO PARTICIPATE IN A STUDY THAT examines PrEP or Pre-Exposure Prophylaxis. When we say PrEP, we mean when individuals take HIV/AIDS medication in the hope that the medication will prevent them from getting HIV.

Are you willing to complete the PrEP Opinion Questionnaire so that we can better understand why young people like you are not interested in PrEP studies. It takes about 15 minutes to complete this questionnaire and you will receive a gift card for your time.

- Yes
 No (*End of questionnaire. Thank the participant.*)

I: DEMOGRAPHICS/BACKGROUND

1. How old are you?

|____|____| years

2. How do you identify?

- Straight
 Gay
 Queer
 Bisexual
 Trade
 Questioning
 Down Low
 Other, specify: _____

3. How do you describe your race or ethnic background? (*Choose ALL that apply*)

- | | |
|---|---|
| <input type="checkbox"/> Mexican/Mexican-American | <input type="checkbox"/> Black/African American |
| <input type="checkbox"/> Puerto Rican | <input type="checkbox"/> Asian/Pacific Islander |
| <input type="checkbox"/> Central American | <input type="checkbox"/> Native American/Alaskan Native |
| <input type="checkbox"/> South American | <input type="checkbox"/> Multi-Racial/Bi-Racial |
| <input type="checkbox"/> Cuban/Cuban-American | <input type="checkbox"/> White/Caucasian |
| <input type="checkbox"/> Dominican | <input type="checkbox"/> Other, specify: _____ |

4. What is the highest grade you have completed? (*Choose only one*)

- Eighth grade or less
- More than eighth grade but did not complete High School
- GED
- High School Diploma
- Some College/Tech School
- Tech School Graduate
- College Graduate or higher

5. Are you currently working?

- No
- Yes, full time
- Yes, part time

6. In your lifetime, have you received any of the following? (*Choose ALL that apply*)

- I have never received public assistance
- Medical card (such as Medicaid or Medi-Cal, Medicare, etc.)
- Food stamps
- A public aid check
- SSI/Social Security
- Free or reduced priced school lunches

7. Have you ever been “kicked out” or asked to leave the place where you were living by a parent or legal guardian either because you were sexually attracted to other males or because you were having sex with other males?

- No
- Yes

II: BELIEFS RELATED TO HIV RISK

The following are belief statements related to HIV risk with which you may agree or disagree. Below each statement is a scale that ranges from strongly disagree (1) to strongly agree (7). For each item we would like you to choose the number that represents the extent to which you agree or disagree with that statement. The more you agree with a statement, the higher will be the number you select. The more you disagree with a statement, the lower will be the number you select. This is a measure of your personal beliefs; there are no right or wrong answers.

1. I am less threatened by the idea of being HIV positive than I used to be.
2. I am less worried about HIV infection than I used to be.
3. I think HIV/AIDS is less of a problem than it used to be.
4. I think HIV/AIDS is a less serious threat than it used to be because of new HIV/AIDS treatments.
5. I am much less concerned about becoming HIV positive myself because of new HIV/AIDS treatments.
6. I think that condom use during sex is less necessary now that new HIV/AIDS treatments are available.
7. I think that someone who is HIV positive now needs to worry less about condom use.
8. I think that the need for condom use is less than it used to be, because you can always start new treatments for HIV/AIDS, if you get infected
9. I think that someone who is HIV positive and uses new HIV/AIDS treatments can be cured.
10. I think that new HIV/AIDS treatments can eliminate the virus from your body.
11. Now please select from the scale below, how likely do you think you are in becoming HIV positive in your lifetime?

| | | | | | | | | | | |
|--------------------|----|----|----|----|----|------------------|----|----|----|------|
| 1% | 10 | 20 | 30 | 40 | 50 | 60 | 70 | 80 | 90 | 100% |
| Extremely Unlikely | | | | | | Extremely Likely | | | | |

III: MAN WITH MAN SEX

1. In total, how many male sex partners have you had in your whole lifetime?
_____#
2. During the past month, with how many men have you had oral or anal sex?
|_|_|_|_| (If "0", go to Next Section)
3. Of these # (fill from Q2) males, with how many did you have unprotected sex?
|_|_|_|_| partners (If "0", go to Next Section)
4. Of those you had unprotected sex with, how many were known to be HIV positive?
|_|_|_|_|

IV: REASON FOR NOT WANTING TO PARTICIPATE IN THE STUDY TODAY

1. What was the main reason that you chose not to participate in the study today? (*Choose only one.*)
- I'm just not interested
 - The study is too time consuming or demanding
 - I'm worried about the loss of confidentiality
 - I don't want to participate in groups
 - I don't trust the researchers
 - I don't want to feel like a guinea pig
 - I don't see any direct benefit from participating
 - I'm worried about having side effects from medication
 - I'd rather not say
 - Other _____

V: WILLINGNESS TO PARTICIPATE IN FUTURE PrEP STUDIES

1. Please answer the following statements about your willingness to participate in future PrEP studies. (Definitely not = 1; Not likely = 2; Likely = 3; Definitely yes = 4)
- a. I would be willing to enroll in a PrEP study in the future _____
 - b. I would be willing to try PrEP even if there was a slim chance of getting sick from it _____
 - c. I would be willing to enroll in a PrEP study if I didn't have to take medication every day _____
2. What would be most important for you to enroll in a future PrEP study? (*Choose only one*)
- PrEP would have to be proven safe
 - I would be guaranteed medical care for any problems related to the medication
 - I would receive money for being in the study
 - I want to decrease my chances of getting HIV
 - I would have to know that I was helping other people

VI: BELIEFS ABOUT PrEP

1. Please tell me the number which best indicates your answer to the following question:

If PrEP was available, how likely would you be to use it?

| | | | | | | | | | | | |
|-----------------------|---|---|---|---|---|---|---|---------------------|---|----|---|
| ← | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | → |
| Extremely Unlikely | | | | | | | | Extremely Likely | | | |

Please indicate whether you believe the following statements to be true or false for you today. Remember, there is no right or wrong answer

2. If I took PrEP, I would worry less about getting HIV
- True
- False
3. If I took PrEP, I could have more sex partners
- True
- False
4. If I took PrEP, using a condom during sex would not really be necessary
- True
- False
5. If I took PrEP, I would worry that PrEP will hurt my health.
- True
- False
6. If I took PrEP, I would worry that other people will see me taking pills and may think that I am HIV positive
- True
- False
7. PrEP is as effective at preventing HIV as condoms
- True
- False
8. If I took PrEP, I would feel more comfortable having sex with someone who is HIV Positive
- True
- False

9. Which of the following are reasons that you do not wish to take PrEP? (*Choose all that apply*)

- I am concerned about side effects from the pills
- I can avoid HIV in other ways
- I don't like taking pills
- I am concerned that people will think that I am HIV positive because I am taking PrEP
- I am concerned that people will know that I have sex with men and/or trans people because I am taking PrEP
- I fear developing resistance to HIV medications if I became positive
- I don't want to take a pill every day
- None of the above
- Decline to state

APPENDIX XIV: REVISED 3MV INTERVENTION MODULES

| | |
|--|--|
| Session 1. MSM: Dual Identity | <ol style="list-style-type: none"> 1. Warm-up: What have you tried to change? 2. Why we do the things we do? 3. Brainstorming Wheels – Dual Identity 4. Making the connection |
| <u>Session 2. STD/HIV Prevention for MSM: The Roles and Risks of Tops & Bottoms</u> | <ol style="list-style-type: none"> 1. Roles and Risks for Tops & Bottoms 2. What do you know about STDs and HIV in MSM? 3. How do you get an STD or HIV? 4. Sex in the City, followed by Transmission Puzzle Presentation |
| <u>Session 3. STD/HIV Risk Assessment & Prevention Options</u> | <ol style="list-style-type: none"> 1. What are My Chances if...? Building a Menu of Options for STD/HIV prevention 2. Take your own inventory – what would you do with whom? 3. My personal STD/HIV risk behaviors are... |
| <u>Session 4. Intention to Act & Capacity for Change</u> | <ol style="list-style-type: none"> 1. Stage Yourself – how ready are you for change? 2. Choosing to Act 3. Expressing personal ambivalence & barriers 4. Exploring Pros and Cons of chosen option 5. Getting ready for action |
| <u>Session 5. Relationship Issues: Partner Selection, Communication, Negotiation of Roles for MSM</u> | <ol style="list-style-type: none"> 1. The man of my dreams 2. Who’s got power? 3. Why we chose the ones we choose – are you a Top or a Bottom? |
| <u>Session 6. Social Support & Problem-solving to Maintain Change</u> | <ol style="list-style-type: none"> 1. Play your own scene 2. Round robin role plays 3. Group problem-solving 4. Falling off the wagon |
| <u>Session 7. Building Bridges and Community</u> | <ol style="list-style-type: none"> 1. What else do you need? 2. How can I build on this experience? 3. How can we build a community? 4. Writing a <i>Survival Handbook</i> for MSM 5. What else does our agency have for you? |

Adapted from Center for Health & Behavioral Training. Rochester, NY. 2005.

APPENDIX XV: SESSION EVALUATION FORMS

A. PCC SESSION EVALUATION

Please fill out the following information about the session that you just participated in. This information will be helpful in improving the session.

DATE: _____

| | Strongly Agree | Agree | Disagree | Strongly Disagree |
|---|-------------------|-------|----------|----------------------|
| 1. I learned a lot from this session. | 1 | 2 | 3 | 4 |
| 2. I will be able to apply what I learned from this session in my life. | 1 | 2 | 3 | 4 |
| 3. I was given an opportunity to participate and discuss information with others. | 1 | 2 | 3 | 4 |
| 4. The session was well organized. | 1 | 2 | 3 | 4 |
| 5. The topic of this session was interesting. | 1 | 2 | 3 | 4 |
| 6. The counselor stimulated my interest in the material. | 1 | 2 | 3 | 4 |
| 7. The topic of this session was relevant to my life. | 1 | 2 | 3 | 4 |
| 8. The session was enjoyable. | 1 | 2 | 3 | 4 |
| 9. I would recommend this session to others. | 1 | 2 | 3 | 4 |
| 10. I felt comfortable participating in this session. | 1 | 2 | 3 | 4 |

11. Below is a list of activities from today's session. Please circle which activities you liked the most and for each activity you circle please write what about those activities you liked the most.

| |
|---|
| Recall of recent high-risk behavior: |
| Identifying thoughts, feelings, and attitudes that led to the high-risk behavior: |
| Discussion of what led to the decision to engage in high-risk behavior: |
| Discussion of strategies to deal with similar situations in the future: |

12. What would you change about this session?

B. 3MV INTERVENTION GROUP EVALUATION

Please fill out the following information about the workshop that you just participated in. This information will be helpful in improving the session.

DATE: _____

| | Strongly Agree | Agree | Disagree | Strongly Disagree |
|--|----------------|-------|----------|-------------------|
| 1. I learned a lot from this workshop. | 1 | 2 | 3 | 4 |

| | | | | |
|--|---|---|---|---|
| 2. I will be able to apply what I learned from this workshop in my life. | 1 | 2 | 3 | 4 |
|--|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 3. I was given an opportunity to participate and discuss information with others. | 1 | 2 | 3 | 4 |
|---|---|---|---|---|

| | | | | |
|-------------------------------------|---|---|---|---|
| 4. The workshop was well organized. | 1 | 2 | 3 | 4 |
|-------------------------------------|---|---|---|---|

| | | | | |
|--|---|---|---|---|
| 5. The topic of this workshop was interesting. | 1 | 2 | 3 | 4 |
|--|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 6. The presenter(s) stimulated my interest in the material. | 1 | 2 | 3 | 4 |
|---|---|---|---|---|

| | | | | |
|--|---|---|---|---|
| 7. The topic of this workshop was relevant to my life. | 1 | 2 | 3 | 4 |
|--|---|---|---|---|

| | | | | |
|--------------------------------|---|---|---|---|
| 8. The workshop was enjoyable. | 1 | 2 | 3 | 4 |
|--------------------------------|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| 9. I would recommend this workshop to others. | 1 | 2 | 3 | 4 |
|---|---|---|---|---|

| | | | | |
|--|---|---|---|---|
| 10. I felt comfortable participating in this workshop. | 1 | 2 | 3 | 4 |
|--|---|---|---|---|

11. Below is a list of activities from the workshop. Please circle which activities you liked the most and for each activity you circle please write what about those activities you liked the most.

| |
|-----------------------------|
| Why we do the things we do? |
| Brainstorming wheels: |

| |
|---|
| Making the connection: |
| Roles and risks for Tops & Bottoms: |
| How do you get an STD or HIV? |
| Sex in the city: |
| Transmission puzzle presentation: |
| What are my chances if...? Building a menu of options for STD/HIV prevention: |
| Taking your inventory – what would you do with whom? |
| Stage yourself – how ready are you for change? |
| Choosing to act: |
| Exploring pros and cons of chosen option: |

| |
|--|
| The man of my dreams: |
| Who's got power? |
| Why we chose the ones we choose – are you a Top or a Bottom? |
| Round robin role plays: |
| Falling off the wagon: |
| How can we build a community? |
| Writing a Survival Handbook for MSM: |

12. What would you change about this workshop?

APPENDIX XVI: SCHEDULE OF ACASI EVALUATIONS

| | Baseline | Week 4 | Week 8 | Week 12 | Week 24 | Week 36 | Week 48** |
|--|----------|--------|--------|---------|---------|---------|-----------|
| Interviewer Questions | X | X | X | X | X | X | X |
| Introduction | X | X | X | X | X | X | X |
| Timeline | | X | X | X | X | X | X |
| Tutorial | X | X | X | X | X | X | X |
| Demographics | X | X | X | X | X | X | X |
| Study Pill Adherence* | X | X | X | X | X | X | X |
| Sex Life and Pills* | | X | X | X | X | X | X |
| Missed Medication Reasons* | | X | X | X | X | X | X |
| HIV Prevention Readiness | X | | | | | | |
| Risk Behavior and Disinhibition | X | X | X | X | X | X | X |
| Last Sexual Partner | X | X | X | X | X | X | X |
| Beliefs About Condom Use | X | | | | X | | X |
| Beliefs Related to HIV Risk | X | | | | X | | X |
| Sexually Transmitted Infections | X | | | | | | |
| Study-Related Reduced HIV Risk | | X | | | X | | X |
| Substance Use and Abuse Items | X | X | X | X | X | X | X |
| Support from Others | | X | X | X | X | X | X |
| Acceptability Questions | | | | X | | | X |
| PrEP Questions | | | | | | | X |
| Beliefs about PrEP | X | | | | | | X |
| Comments | X | X | X | X | X | X | X |

*Not administered to subjects who discontinue from the study agent.

**Last assessment for subjects who prematurely discontinues from study. Also complete at the SP1 visit for subjects who become HIV positive.

APPENDIX XVII: ACASI INTERVIEW

INTERVIEWER QUESTIONS

SID:

Number will be 8 digits

Participant Type:

2= ATN 113

Round:

Baseline

Week 4

Week 8

Week 12

Week 24

Week 36

Week 48

SP1

Premature Discontinuation

INTRODUCTION

Introduction Screen 1:

“Thank you for agreeing to participate in this very important study about adolescent health. To learn as much as possible about your health, you will be asked to answer questions about your background and your feelings and behavior, including sexual and drug behaviors. We will also ask you some questions about your friends and what you do with your friends. Some of these questions may be difficult for you to answer and dates may be hard to remember. Please take as much time as you need so that you give information that is as accurate as possible.”

Introduction Screen 2:

“Some of these questions may seem embarrassing or very personal but remember, your answers are confidential (that is, your name will not be put on your answers) and there are no right or wrong answers.”

Introduction Screen 3:

“This interview is going to take about one hour to complete. If at any point you need to use the restroom or take a short break, just let the Study Coordinator know. If you have any questions at any point during the interview, just ask.”

TIMELINE

(Participant will complete this section with the help of the interviewer)

Timeline Screen 1:

“Different sets of questions in this survey will be referring to different periods of time--for example, some questions might ask you how you felt about something during the past 14 days, whereas another set of questions might be about the past 30 days. Remember that 30 days is about 1 month.”

Timeline Screen 2:

“It is very important that you really concentrate on the period of time being asked about. The best way to do that is to have a timeline or calendar that you can refer to, to help you remember that exact period as clearly as possible. We need to get some of your personal recent events on a calendar to help you as you get to different sets of questions and the time period changes.”

Timeline Screen Intro:

“The next screen will display a 30-day calendar. If you have any problems with the calendar, please ask the interviewer to help you.”

Timeline Screen 3:

“Please enter any special dates onto the calendar below by touching the date below. Enter as many special dates as you wish. When you are finished or if you do not wish to enter any additional special dates, please select NEXT to continue.”

Calendar Entry:

“Please type in the occasion or reason [insert date]”

“Was a special day. Please note that you are limited to 10 characters including spaces.”

TUTORIAL

Tutorial Screen 1:

“Now we want to teach you how to use this computer. The interviewer will be here to answer any questions you have. The computer will ask you a series of questions. Answer each question by touching your response on the screen. After you answer a question, go to the next question by touching the button marked NEXT in the lower right-hand corner of the screen. Try touching that button now to move on.”

Tutorial Screen 2:

“If you want to go back and change your answer to an earlier question, touch the button marked BACK in the lower left-hand corner of the screen. Touch the BACK button now to return to the last screen. Then touch the NEXT button to return to this screen and again to move on.”

Tutorial Screen 3:

“If you want to change your answer, you can touch the ERASE button and enter a new response. Answer the following question, then touch the ERASE button and enter your answer again. Did you watch television today?”

Tutorial Screen 4:

“You do not have to wait for the computer to read all the choices before selecting your answer. Once you touch the screen, the computer will stop reading. We do request that you keep your headset on throughout the entire interview. Please ask the interviewer for help if needed.”

Tutorial Screen 5:

“To hear a question again, touch the question on the screen once the computer has stopped reading. For example, to hear again what I am saying now, touch the words on the screen.”

Tutorial Screen 6:

“If you skip a question for any reason, the computer will say you didn't answer the question, and will ask whether you really meant to answer, would rather not answer, or don't know the answer. If you choose, “I really meant to answer,” the screen will go back so you can answer the question.”

Tutorial Screen 7:

“To see how this works, push the NEXT button without answering the question below. When the next screen appears, try touching each of the three responses. When you are finished, continue to the next practice screen. Do you like pizza?”

Tutorial Screen 8:

“Sometimes you will be asked a question that refers to a particular time period like the last 14 days, or the last 90 days. Be sure to think only about the specific time period asked in that question. For example: how many days in the past 90 did you eat breakfast?”

Tutorial Screen 9:

“If you answer a question with a response that is not valid, a message will appear on the screen.”

Tutorial Screen 10:

“For example, the question below asks about your activities during the last 90 days. Try answering with a response greater than 90, but less than 100 and then press the NEXT button. A message will appear at the bottom of the screen. Now enter a correct response and press the NEXT button to continue. What you see on the screen is what will be saved as your answer. How many days in the past 90 did you ride the bus?”

For **Tutorial Screen 10**, program to accept answers from 0 to 90. If greater than 90 is entered, show prompt that reads, “The number of days that you enter must be between 0 and 90. Please re-enter.”

Tutorial Screen 11:

“If there is anything that you do not understand, or if you have any problems during the interview, please ask the interviewer to help you. If you are ready to begin the interview, press the NEXT button now.”

DEMOGRAPHICS (BASELINE AND FOLLOW-UP)

DemographicsIntro "The following questions ask about your background, schooling, and living situation. Everything you answer is confidential."

CurrAge "How old are you?"(baseline only)

____|____| Years

Error Message **if participant type = 1:**

If CurrAge is 0-14 or 18-99, display - "I want to confirm your current age. The number you entered is displayed on the screen. Is that correct?"

0 "No"

1 "Yes"

DemID "How do you identify?" (baseline and week 48/SP1/and pre-d/c only)

1 "Straight"

2 "Gay"

3 "Queer"

4 "Bisexual"

5 "Trade"

6 "Questioning"

7 "Down Low"

96 "Other"

When DemID = Other: **DemIDOS** "Please specify:"

DemRace "How do you describe ethnic background? Choose all that apply."(baseline only)

1 "Mexican/Mexican-American"

2 "Black/African American"

3 "Puerto Rican"

4 "Asian/Pacific Islander"

5 "Central American"

6 "Native American/Alaskan Native"

7 "South American"

8 "Multi-Racial/Bi-Racial"

9 "Cuban/Cuban-American"

10 "White/Caucasian"

11 "Dominican"

96 "Other"

When DemRace = Other: **DemRaceOS** "Please specify:"

DemSchool "Are you in school these days? And "school" could mean a school or program where you are working toward a high school diploma, GED, or college/technical degree." (baseline and all follow-ups)

1 "Yes"

0 "No"

2 "No, I have graduated"

3 "Yes, but I am on summer/winter/spring break now"

LastGrade “What is the highest grade you have completed?” (baseline and week 48/SP1/pre-d/c only)

- 1 “Eighth grade or less”
- 2 “More than eighth grade but did not complete High School”
- 3 “GED”
- 4 “High School Diploma”
- 5 “Some College”
- 6 “Tech School Graduate”
- 7 “College Graduate or higher”

DemWork “Are you currently working?” (baseline and all follow-ups)

- 0 “No”
- 1 “Yes, full time”
- 2 “Yes, part time”

DemHealthCare “In your lifetime, have you received any of the following? Choose all that apply.” (baseline only)

- 0 “I have never received public assistance”
- 1 “Medical card (such as Medicaid or Medi-Cal, Medicare, etc.)”
- 2 “Food stamps”
- 3 “A public aid check”
- 4 “SSI/Social Security”
- 5 “Free or reduced priced school lunches”

DemKickOut “Have you ever been “kicked out” or asked to leave the place where you were living by a parent or legal guardian either because you were sexually attracted to other males or because you were having sex with other males?” (baseline and week 48/SP1/pre-d/c)

- 0 “No”
- 1 “Yes”

DemHomeless “Have you ever spent one night or more in an emergency shelter, transitional housing facility, welfare hotel, or a public or private place not designed for sleeping (for example, car, park, etc.) because you were without a regular place to stay?” (baseline and week 48/SP1/pre-d/c)

- 0 “No” (Go to WhereLiveNow)
- 1 “Yes”

DemHomelessNights “Approximately how many total nights have you not had a regular place to stay during your lifetime?” (baseline and week 48/SP1/pre-d/c)

“Nights”

Note: For **DemHomelessNights**, program to accept answers from 1 to 1000. If 0 or a number greater than 1000 is entered, show prompt that reads, “You have entered an invalid response. Please re-enter” If a number greater than 100 is entered, show prompt that reads, “I want to confirm the number of nights that you have not had a regular place to stay during your lifetime. The number you entered is displayed on the screen below. Is this correct?”

- 0 “No”
- 1 “Yes”

WhereLiveNow “Where are you currently living or staying most of the time?” **(baseline only)**

- 1 “Your own house or apartment”
- 2 “At your parent(s) house or apartment”
- 3 “At another family member(s) house or apartment”
- 4 “At someone else’s house or apartment”
- 5 “Foster home or group home”
- 6 “In a rooming, boarding, halfway house, or a shelter/welfare hotel”
- 7 “On the street(s) (vacant lot, abandoned building, park, etc.)”
- 8 “Some other place not mentioned”

When WhereLiveNow = Some other place not mentioned: **WhereLiveNowOS** “Please specify:”

WhereLiveNowPast “Where have you lived or stayed during the past month? Choose all that apply.” **(all follow-ups only)**

- 1 “Your own house or apartment”
- 2 “At your parent(s) house or apartment”
- 3 “At another family member(s) house or apartment”
- 4 “At someone else’s house or apartment”
- 5 “Foster home or group home”
- 6 “In a rooming, boarding, halfway house, or a shelter/welfare hotel”
- 7 “On the street(s) (vacant lot, abandoned building, park, etc.)”
- 8 “Some other place not mentioned”

When WhereLiveNow = Some other place not mentioned: **WhereLiveNowOS** “Please specify:”

PaidSex “Have you ever paid someone for sex in your lifetime?” **(baseline only)**

- 0 “No”
- 1 “Yes”

BeenPaidSex “Have you ever been paid for sex in your lifetime?” **(baseline only)**

- 0 “No” **(Go to WhereStay)**
- 1 “Yes”

BeenPaidSex1Month “In the past month, have you been paid for sex?” **(baseline and all follow-ups)**

- 0 “No”
- 1 “Yes”

WhereStay “In your lifetime, have you ever exchanged sex for a place to stay?” **(baseline only)**

- 0 “No” **(Go to WhoLiveNow at baseline, WhoLiveNowPast at all follow-ups)**
- 1 “Yes”

WhereStay1Month “In the past month, have you exchanged sex for a place to stay?” (**baseline and all follow-ups**)

0 “No” (**Go to WhoLiveNow at baseline, WhoLiveNowPast at all follow-ups**)

1 “Yes”

WhereStayMonth “How many times in the past month have you exchanged sex for a place to stay?” (**baseline and all follow-ups**)

_____ “Times”

Note: For **WhereStayMonth**, allow responses from 1 to 999. If the number entered is greater than 100, then display the response on the screen, along with: “I want to confirm the number of times you have exchanged sex for a place to stay in the past month. The number you entered is displayed on the screen. Is that correct?”

WhoLiveNow “Currently, who do you live with most of the time? Choose all that apply.” (**baseline only**)

1 “Alone”

2 “Birth or adoptive parents”

3 “Foster parents”

4 “Friends”

5 “Other relatives”

6 “Partner, lover, or spouse”

7 “Your children”

8 “Other people not mentioned”

When WhoLiveNow = Other people not mentioned: **WhoLiveNowOS** “Please specify:”

WhoLiveNowPast “Who have you lived with during the past month? Choose all that apply.” (**all follow-ups only**)

1 “Alone”

2 “Birth or adoptive parents”

3 “Foster parents”

4 “Friends”

5 “Other relatives”

6 “Partner, lover, or spouse”

7 “Your children”

8 “Other people not mentioned”

When WhoLiveNow = Other people not mentioned: **WhoLiveNowOS** “Please specify:”

LastDemOutOfRange

If CurrAge is 0-17 or 24-99

“You have reached the end of the final group of questions. Press the NEXT button to end the interview or press the BACK button to check your previous answers.”

LastDem “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

STUDY PILL ADHERENCE (BASELINE AND FOLLOW-UP)

Note: Day of Week, Month, Day = Day the participant entered on the screen in **MedDay**.

FOR BASELINE:

MedAdIntro “The following questions have to do with reminders to take your study pill.” (**Go to MedRemindWill**)

FOR FOLLOW-UP (MedAdIntro-MedTotal):

MedAdIntro “The following questions have to do with how you have been taking your study pills over the past month. We are going to use a calendar to explore what your schedule has been like the past month, when you have taken and when you have missed your study pill, and some of the reasons why you missed taking your study pill on particular days.”

MedAdSpec “Now we would like to ask you about holidays and special events in your life. It is important that you enter all of the special dates from the past month.”

MedAdSig1 “The next screen will display a 30-day calendar. Earlier we asked you to enter special dates from the past month into this calendar. Now, I would like you to review this information and add any additional special dates you may have forgotten about. Please try to remember any days during this period that may have been significant for you, such as holidays, birthdays, anniversaries, parties, illnesses, trips, or changes at work or school.”

MedAdSig2 “Please enter any additional special dates onto the calendar below by touching the date below. Enter as many special dates as you wish. When you are finished, or if you do not wish to enter any additional special dates, please select NEXT to continue.”

Note: Display 1 month calendar reminder during MedAdSig. This is not a calendar reminder- the participant needs to be able to enter text. For each day the participant enters, please ask: **MedAdReason** “Please type in the occasion or reason <Day of Week, Month, Day> was a special day. Please note that you are limited to 10 characters, including spaces.”

MedDoseIntro “The next screen displays a calendar. For all the days on the calendar, we would like to know whether you did or did not take your study pill. We are only interested in the study pill. Do not think about other medications you may take.”

MedDay “This calendar represents the past month. Now please fill in the days you took your study pill. You may want to start with the special days that you entered, but please tap on all the days. Please touch each day on the calendar and answer whether you took your study pill. After you answer whether you took your study pill (PrEP) on each day, you will be asked whether you had sex. After you have answered each of these questions for a day, you will see that the day is labeled “DONE”. Then, tap on another day until all of the days are labeled “DONE”. You will not be able to move on until all days are labeled “DONE”.”

Questions to ask for each day:

Calendar – Please touch each date below...

MedDayX On <day> did you take PreP? No, Yes (Confirmation screen with DK and RF)

MedDaySex On <day> did you have sex? No, Yes (Confirmation screen with DK and RF)

If Yes:

MedDaySexType What type of sex did you have? Select all that apply. (Options Oral, Anal, and Vaginal) (Confirmation screen with DK and RF)

MedTotal “Based on the information you entered, you took the study pill on <Number of days that have an X on the screen> of the past 30 days. If this is not correct, please press the BACK button to review what you have entered. Press the NEXT button to continue.”

MedRemindWill “What will you do to remind yourself to take the study pills? Choose all that apply.”
(baseline only)

- 1 “Set cell phone alarm/reminder”
- 2 “Have friend/family member/partner remind me”
- 3 “Take pill when doing other daily task (brushing teeth, eating dinner)”
- 4 “Nothing”
- 5 “Other”

When MedRemindWill = Other: **MedRemindWillOS** “Please specify:”

MedRemindHave “What have you done to remind yourself to take the study pills? Choose all that apply.” **(all follow-ups only)**

- 1 “Set cell phone alarm/reminder”
- 2 “Have friend/family member/partner remind me”
- 3 “Take pill when doing other daily task (brushing teeth, eating dinner)”
- 4 “Nothing”
- 5 “Other”

When MedRemind = Other: **MedRemindHaveOS** “Please specify:”

MedTake “How sure are you that you will be able to take your study medication as directed every day?”
(baseline only)

- 1 “Not at all sure”
- 2 “Somewhat sure”
- 3 “Very sure”
- 4 “Extremely sure”

Note: If Interview Round = Baseline, go to LastMed, otherwise go to MedShare.

MedShare “During the past month, did you share your study medication with someone else?” **(all follow-ups only)**

- 0 “No” **(Go to LastMed)**
- 1 “Yes”

MedTimes “About how many times have you shared study medication?”

| “Times”

Note: For **MedTimes**, allow responses from 1 to 30. If greater than 30 is entered, show prompt that reads, “You have entered an invalid response. Please re-enter.”

MedWho “Have you shared study pills with any of the following people?”

Note: Use answer options of “yes” or “no” for MedWhoMalePartner through MedWhoOther.

MedWhoMalePartner “Male steady partner (someone with whom you have an emotional bond and with whom you have regular sex such as boyfriend, spouse, significant other, or life partner)”

MedWhoFemalePartner “Female steady partner (someone with whom you have an emotional bond and with whom you have regular sex such as girlfriend, spouse, significant other, or life partner)”

MedWhoCasualPartner “Casual sexual partner (someone that you have sex with but do not consider this person to be a main partner to you. A casual partner is someone with whom you have sex occasionally on a casual basis)”

MedWhoFriend “Friend, colleague, or acquaintance with whom you DON’T have a sexual relationship”

MedWhoOther “Other”

When MedWho = Other: **MedWhoOtherOS** “Who else have you shared study pills with?”

LastMed “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

SEX LIFE AND PILLS (FOLLOW-UP)

PillIntro “The next set of questions will ask whether you ever changed how you took your study pills based on what was going on in your sex life. Please answer this honestly, as there are no right or wrong answers.”

PillChange “Thinking back over the past month, did you ever change how you were taking the study pills based on what was going on in your sex life?”

- 0 “No” (**Go to LastPill**)
1 “Yes”

Note: Use multi-form for PillRisk with response options of “yes” or “no”.

PillRisk “During the past month, did you ever do any of the following?”

- 1 “Take the study pill AFTER, INSTEAD OF BEFORE, having risky sex?”
- 2 “Take more than one study pill at a time AFTER having risky sex?”
- 3 “Take the study pill more than once a day AFTER having risky sex?”
- 4 “Take more than one study pill at a time BEFORE having sex because you thought you might have risky sex?”
- 5 “Take a study pill more than once a day BEFORE having sex because you thought you might have risky sex?”
- 6 “Take more than one study pill AT A TIME because a sex partner asked you to?”
- 7 “Take a study pill MORE THAN ONCE a day because a sex partner asked you to?”
- 8 “Skip ONE OR MORE days of taking the study pill because you had little or no risky sex?”
- 9 “Take the study pill LESS than once a day because a sex partner asked you to?”

LastPill "You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions."

MISSED MEDICATION REASONS (FOLLOW-UP)

ReasIntro “People may miss taking their study pills for various reasons. The following screens have possible reasons why you may have missed taking any study pills within the past month.”

Note to programmer: Display **ReasIntroStem** before each question from **ReasHome** to **ReasSex**.

ReasIntroStem “In the past month, how often have you missed taking your study pills because you:”

ReasHome “Were away from home?”

1 “Never”

2 “Rarely”

3 “Sometimes”

4 “Often”

Note: Use answer options in ReasHome from ReasBusy to ReasSex.

ReasBusy “Were too busy with other things?”

ReasForg “Simply forgot?”

ReasPill “Had too many study pills to take?”

ReasAvoid “Wanted to avoid side effects?”

ReasNot “Did not want others to notice you taking meds?”

ReasRout “Had a change in daily routine?”

ReasTox “Felt like the study pill was toxic/harmful?”

ReasSlept “Fell asleep/slept through dose time?”

ReasSick “Felt sick or ill?”

ReasDepr “Felt depressed/overwhelmed?”

ReasOut “Ran out of study pills?”

ReasSex “Didn’t think you needed it because you weren’t having risky sex?”

LastReas “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

HIV PREVENTION READINESS MEASURE (HPRM) SECTION (BASELINE)

HPRMIntro “The following screens ask questions about how ready you are to take PrEP.”

HPRMReady “I am ready to start taking medication (PrEP) to protect against HIV.”

1 “1=Strongly Disagree

2 “2=Disagree

3 “3=Neither Agree nor Disagree

4 “4=Agree

5 “5=Strongly Agree

Note to Programmer: Use answer options in HPRMReady for HPRMKnow through HPRMTime.

HPRMKnow “Most of the people I live with know that I am taking PrEP.”

HPRMHealthy “I believe taking PrEP can keep me healthy.”

HPRMWish “In the past 3 months, I found myself wishing I hadn't used street drugs so often.”

HPRMBad “Taking PrEP would give me bad side effects.”

HPRMContact “I would know how to contact my pharmacist or medical provider if I had problems or questions about the PrEP medication.”

HPRMStable “I feel like I have a stable place to live.”

HPRMInfect “If I don't take my PrEP medication exactly as instructed, I might get infected with HIV.”

HPRMStrong “I have a strong, trusting relationship with my medical provider.”

HPRMRefill “I would know who and when to call for refills of my PrEP medication.”

HPRMHomeless “Sometimes a homeless shelter is the only place I have to sleep.”

HPRMFamily “Most of my family and friends know I am taking PrEP.”

HPRMNoHelp “Taking PrEP medication would not really help me.”

HPRMMiss “Even when it may be difficult, I will be able to let my medical provider know if I miss doses of my PrEP medication.”

HPRMClinic “I regularly go to the clinic and meet with my medical provider.”

HPRMPoison “PrEP medication would be poison to my body.”

HPRMProtect “I want to start taking PrEP medications to protect against HIV infection.”

HPRMRemember “My household members who know I am on PrEP would help me remember to take my medication.”

HPRMSick “Taking my PrEP medication as prescribed would keep me from getting sick.”

HPRMSupport “I feel supported by my family and friends when times are tough.”

HPRMGoAway “I would take my PrEP medications even if they made me sick at first because the side effects would go away.”

HPRMHelp “My family and friends who know I am on PrEP would help me remember to take my medication.”

HPRMAlcohol “In the past 3 months, I found myself wishing I hadn't drunk alcohol so often.”

HPRMCorrect “I know that I will be able to take my PrEP medication correctly.”

HPRMTime “It would be important to me to take my PrEP medication correctly and on time every day.”

HPRMDrunk “In the past 3 months, I have been drunk...”

- 1 “1=Never”
- 2 “2=Once”
- 3 “3=At least once a month”
- 4 “4=2-3 times per month”
- 5 “5=At least once a week”

Note to Programmer: Use answer options in HPRMDrunk for HPRMMarijuana through HPRMDrugs.

HPRMMarijuana “In the past 3 months, I have used marijuana.”

HPRMDrugs “In the past 3 months, I have used drugs such as crack, meth, or cocaine.”

HPRMStem “In the past month, how often have you...”

Note to Programmer: Display HPRMStem for HPRMSad through HPRMCope.

HPRMSad “Felt lonely or sad.”

- 1 “1=Never”
- 2 “2=Rarely”
- 3 “3=Sometimes”
- 4 “4=Almost Always”
- 5 “5=Always”

Note to Programmer: Use answer options in HPRMSad for HPRMDepress through HPRMCope.

HPRMDepress “Been told you seem sad or depressed.”

HPRMIsolated “Felt isolated or lonely, even when around other people.”

HPRMWay “Felt that things were going your way.”

HPRMConfident “Felt confident in your ability to handle your personal problems.”

HPRMCope “Felt you could not cope with all the things you had to do.”

HPRMTell “I shouldn’t tell the people I live with that I am taking PrEP.”

- 1 “1=Strongly Disagree”
- 2 “2=Disagree”
- 3 “3=Neither Agree nor Disagree”
- 4 “4=Agree”
- 5 “5=Strongly Agree”

HPRMTold “How many people you live with have you told that you are taking PrEP?”

- 1 “1=No one”
- 2 “2=Only one person”
- 3 “3=Some people”
- 4 “4=Most people”
- 5 “5=Everyone”

LastHPRM “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

____|____|____| “Partners”)

If **SexMaleMosFollowUp** is greater than **SexMaleEver**, display “The number that you entered is greater than the number of males that you said you ever had sex with. Please re-enter.”

SexFemaleMosBaseline “During the past month, how many female partners have you had sexual contact with (oral, vaginal, or anal)?” (**baseline only**)

____|____|____| “Partners” (**If “0”, go to LastRisk**)

If **SexFemaleMosBaseline** is greater than **SexFemaleEver**, display “The number that you entered is greater than the number of females that you said you ever had sex with. Please re-enter.”

SexFemaleMosFollowUp “Since the last time you took this survey, how many female partners have you had sexual contact with (oral, vaginal, or anal)?” (**all follow ups only**)

____|____|____| “Partners” (**If “0” AND SexMaleMosFollowUp = 0, go to LastRisk**)

If **SexFemaleMosFollowUp** is greater than **SexFemaleEver**, display “The number that you entered is greater than the number of females that you said you ever had sex with. Please re-enter.”

SexMaleIntro “For the following questions, we would like to focus only on your male partners.”

SexMaleUnprotect “Of these males, how many did you have unprotected oral or anal sex with?”

If **SexMaleUnprotect** is greater than **SexMaleMos**, display “The number that you entered is greater than the number of males that you said you had sex with in the past month. Please re-enter.”

SexMaleHIVPos “Of those you had unprotected sex with, how many did you know were HIV positive?”

If **SexMaleHIVPos** is greater than **SexMaleMos**, display “The number that you entered is greater than the number of males that you said you had sex with in the past month. Please re-enter.”

LastRisk “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

LAST SEXUAL PARTNER (BASELINE AND FOLLOW-UP)

PartnerIntroBaseline “These questions ask you to briefly describe your most recent male sex partner. Remember, for the purposes of this survey “sex” can mean oral or anal. So your most recent male sex partner is the last man you had sex with (oral or anal).

We understand that even if you know this partner well you may not know the answers to all of these questions. If this was a casual partner you may not know the answers to most of them. Please answer the questions to the best of your ability and recollection.

Answer “Don’t know” if you really do not know the answer for this partner. In many cases it is as important for us to learn what information you do not know about this partner as it is to learn the information that you do know.” **(baseline only)**

PartnerIntroFollowUp “These questions ask you to briefly describe your most recent male sex partner since the last time you took this survey. Remember, for the purposes of this survey “sex” can mean oral, or anal. So your most recent male sex partner is the last man you had sex with (oral or anal,).

We understand that even if you know this partner well you may not know the answers to all of these questions. If this was a casual partner you may not know the answers to most of them. Please answer the questions to the best of your ability and recollection.

Answer “Don’t know” if you really do not know the answer for this partner. In many cases it is as important for us to learn what information you do not know about this partner as it is to learn the information that you do know.” **(all follow-ups)**

MostRecentPartner “Have you had oral, or anal, sex with a male since the last time you took this survey?”

0 “No” **(Go to LastSex)**

1 “Yes”

NamePartner “Think about the last time you had sex with a man. This person is your last sexual partner. The following questions are about this person. Enter the partner’s initials. You do not need to write the real initials.”

FirstInitial “What is your most recent sex partner’s first initial?”

“First name initial”

LastInitial “What is your most recent sex partner’s last initial?”

“Last name initial”

ConfirmInitials “The initials that you provided for your most recent sex partner are displayed below. Is this correct?”

0 “No”

1 “Yes”

MostRecentSex “Think about the last time you had sex with this partner. As well as you can remember, when was the last time you had sex with him?”

Range Error Message – “Please enter a month, day, and year.”

IF (Year(MostRecentSex) < derived DemYearBorn OR MostRecentSex > InterDate AND (derived DemYearBorn <> NONRESPONSE) AND (MostRecentSex <> NONRESPONSE) DISPLAY “The date you enter must be after you were born and not after today's date. Please re-enter.”

IF MostRecentSex > InterDate AND (derived DemYearBorn = NONRESPONSE) AND (MostRecentSex <> NONRESPONSE) DISPLAY “The date you enter must not be after today's date. Please re-enter.”

IF YEAR(MostRecentSex) < 1985 AND (derived DemYearBorn = NONRESPONSE) AND (MostRecentSex <> NONRESPONSE) THEN DISPLAY “The date you entered is invalid. Please re-enter.”

MostRecentEdit “In what year did you last have sex with this partner?”

“Don’t know”

IF (MostRecentSexEdit < derived DemYearBorn OR MostRecentSex Edit > CurrentYear) AND (derived DemYearBorn <> NONRESPONSE AND MostRecentSexEdit <> NONRESPONSE) THEN DISPLAY “The year you enter must be after you were born and not after the current year. Please re-enter.”

IF MostRecentSexEdit < 1985 AND DemYearBorn = NONRESPONSE AND MostRecentSexEdit <> NONRESPONSE THEN DISPLAY “The year you entered is invalid. Please re-enter.”

IF MostRecentSexEdit > CurrentYear THEN DISPLAY—“The year you enter must not be after the current year. Please re-enter.”

FirstSex “Think about the FIRST time you had sex with this partner. As well as you can remember, when was the first time you had sex with this partner?”

IF (FirstSex > Interview Date OR FirstSex > MostRecentSex) AND (FirstSex <> EMPTY AND FirstSex <> NONRESPONSE AND MostRecentSex <> EMPTY AND MostRecentSex <> NONRESPONSE) THEN “The date you enter must be after you were born and not after today’s date. Please re-enter.”

Relationship “Which of the following best describes your relationship with this partner?”

- 1 “Fuck buddy”
- 2 “Casual partner (sexual relationship only)”
- 3 “Client (sexual relationship only)”
- 4 “Steady partner (sexual and emotional relationship)”
- 5 “Spouse”

PartBirthGender “What is this partner’s biological sex at birth?”

- 1 “Male”
- 2 “Female”

PartAge “How old is this partner? If you don’t know, please estimate.”

“Years”

Error Message:

If PartAge is 0-14 or 35-99), display — “I want to confirm your most recent partner’s age. The number you entered is displayed on the screen. Is that correct?”

0 “No” (**Go to PartAge**)

1 “Yes”

PartClose “How close to this partner do you feel now?”

- 1 “Not at all”
- 2 “A little”
- 3 “Somewhat”
- 4 “Feel close”
- 5 “Extremely close”

PartLength “How long did you know this partner before you first had sex?”

- 1 “Minutes”
- 2 “Hours”
- 3 “Days”
- 4 “Weeks”
- 5 “Months”
- 6 “Years”

PartOther “Since you first had sex with this partner, has he had other sexual partners?”

- 1 “Don't know”
- 2 “No”
- 3 “Yes, one sex partner”
- 4 “Yes, some sex partners (between 2 and 10)”
- 5 “Yes, probably more than 10”
- 6 “Not sure, but it is very likely”

PartKnowNeg “Does this partner know that you are HIV-negative?”

0 “No” (**Go to PartPos**)

1 “Yes”

PartKnowNegWhen “When did this partner know that you are HIV-negative?”

- 1 “Before your first sexual encounter”
- 2 “After your first sexual encounter”
- 3 “After a few sexual encounters”
- 4 “After many sexual encounters”
- 5 “I really don’t know”

PartPos “Has this partner ever tested positive for HIV?”

- 1 “Yes”
- 2 “No, their most recent HIV test was negative” (**Go to PartPrep**)
- 3 “No, they have never had an HIV test” (**Go to PartPrep**)

PartKnowPosWhen “When did you know that this partner was HIV positive?”

- 1 “Before your first sexual encounter” (**Go to PartInfluence**)
- 2 “After your first sexual encounter” (**Go to PartInfluence**)
- 3 “After a few sexual encounters” (**Go to PartInfluence**)
- 4 “After many sexual encounters” (**Go to PartInfluence**)

PartBelieveNeg “I believe that this partner was HIV negative or he told me they were and I had no reason to doubt it.”

- 1 “True”
- 2 “False “

PartPrep “Is this partner taking PrEP?”

- 0 “No”
- 1 “Yes”

PartInfluence “Thinking about the sex you had with this partner, did what you know about his HIV status influence what you did sexually?”

- 0 “No”
- 1 “Yes”

SexDetailIntro “For the questions on the following screens, if you do not know the answer exactly, please give your best estimate.”

SexReceptiveTimesBaseline “In the last month, how many times did you have receptive anal sex with this partner (his penis was in your butt)?” (**baseline only**)

“Times” (**If “0”, go to SexInsertiveTimesBaseline**)

Note to programmer: Range is 0 to 999. If response is greater than 100, display, “I want to confirm the number of times this happened in the past month. The number you entered is displayed on the screen. Is that correct?”

SexReceptiveTimesFollowUp “Since the last time you took this survey, how many times did you have receptive anal sex with this partner (his penis was in your butt)?” **(all follow-ups only)**

____|____|____| “Times” **(If “0”, go to SexInsertiveTimesFollowUp)**

Note to programmer: Range is 0 to 999. If response is greater than 100, display, “I want to confirm the number of times this happened since the last time you took this survey. The number you entered is displayed on the screen. Is that correct?”

SexReceptiveCondomBaseline “Of the times you had receptive anal sex with this partner in the last month, how many times did he use a condom?” **(baseline only)**

____|____|____| “Times” **(If “0”, go to SexReceptiveNoCondEjacBaseline)**

Note to Programmer: If answer to **SexReceptiveCondomBaseline** is greater than **SexReceptiveTimesBaseline**, display “The number that you entered is greater than the number of times that you said you had receptive anal sex with this partner in the last month. Please re-enter.”

SexReceptiveCondomFollowUp “Of the times you had receptive anal sex with this partner since the last time you took this survey, how many times did he use a condom?” **(all follow-ups only)**

____|____|____| “Times” **(If “0”, go to SexReceptiveNoCondEjacFollowUp)**

Note to Programmer: If answer to **SexReceptiveCondomFollowUp** is greater than **SexReceptiveTimesFollowUp**, display “The number that you entered is greater than the number of times that you said you had receptive anal sex with this partner since the last time you took this survey. Please re-enter.”

SexReceptiveCondomBreakBaseline “Of the times this partner used a condom when you had receptive anal sex in the last month, how many times did the condom break or slip off?” **(baseline only)**

____|____|____| “Times” **(If “0”, go to SexReceptiveNoCondEjacBaseline)**

Note to Programmer: If answer to **SexReceptiveCondomBreak Baseline** is greater than **SexReceptiveCondom Baseline**, display “The number that you entered is greater than the number of times that you said you used a condom for receptive anal sex with this partner in the last month. Please re-enter.”

SexReceptiveCondomBreakFollowUp “Of the times this partner used a condom when you had receptive anal sex since the last time you took this survey, how many times did the condom break or slip off?” **(all follow-ups only)**

____|____|____| “Times” **(If “0”, go to SexReceptiveNoCondEjacFollowUp)**

Note to Programmer: If answer to **SexReceptiveCondomBreakFollowUp** is greater than **SexReceptiveCondomFollowUp**, display “The number that you entered is greater than the number of times that you said you used a condom for receptive anal sex with this partner since the last time you took this survey. Please re-enter.”

SexReceptiveNoCondEjacBaseline “Of the times you had receptive anal sex with this partner without a condom (or when the condom broke or slipped off) in the last month, how many times did he ejaculate/cum inside of you?” **(baseline only)**

|_|_|_|_| “Times”

Note to Programmer: If answer to **SexReceptiveNoCondEjacBaseline** is greater than (**SexReceptiveTimesBaseline** less (**SexReceptiveCondomBaseline** less **SexReceptiveCondomBreak**), display “The number that you entered is greater than the number of times that you had receptive anal sex with this partner without a condom (or when the condom broke or slipped off) with this partner in the last month. Please re-enter.”

SexReceptiveNoCondEjacFollowUp “Of the times you had receptive anal sex with this partner without a condom (or when the condom broke or slipped off) since the last time you took this survey, how many times did he ejaculate/cum inside of you?” **(all follow-ups only)**

|_|_|_|_| “Times”

Note to Programmer: If answer to **SexReceptiveNoCondEjacFollowUp** is greater than (**SexReceptiveTimesFollowUp** less **SexReceptiveCondomFollowUp**), display “The number that you entered is greater than the number of times that you had receptive anal sex with this partner without a condom (or when the condom broke or slipped off) with this partner since the last time you took this survey. Please re-enter.”

SexInsertiveTimesBaseline “In the last month how many times did you have insertive anal sex with this partner (your penis was in his butt)? When I say insertive anal sex, I mean when you put your penis into the anus or butt of your partner (i.e., being a “top”).” **(baseline only)**

|_|_|_|_| “Times” **(If “0”, go to SexOralTimesBaseline)**

Note to programmer: Range is 0 to 999. If response is greater than 100, display, “I want to confirm the number of times this happened in the last month. The number you entered is displayed on the screen. Is that correct?”

SexInsertiveTimesFollowUp “Since the last time you took this survey, how many times did you have insertive anal sex with this partner (your penis was in his butt)? When I say insertive anal sex, I mean when you put your penis into the anus or butt of your partner (i.e., being a “top”).” **(all follow-ups only)**

|_|_|_|_| “Times” **(If “0”, go to SexOralTimesFollowUp)**

Note to programmer: Range is 0 to 999. If response is greater than 100, display, “I want to confirm the number of times this happened since the last time you took this survey. The number you entered is displayed on the screen. Is that correct?”

SexInsertiveCondomBaseline “Of the times you had insertive sex with this partner in the last month, how many times did you use a condom?” **(baseline only)**

|_|_|_|_| “Times” **(If “0”, go to SexInsertiveNoCondEjacBaseline)**

Note to Programmer: If answer to **SexInsertiveCondomBaseline** is greater than **SexInsertiveTimesBaseline**, display “The number that you entered is greater than the number of times that you said you had insertive anal sex with this partner in the last month. Please re-enter.”

SexInsertiveCondomFollowUp “Of the times you had insertive sex with this partner since you last took this survey, how many times did you use a condom?” **(all follow-ups only)**

____|____|____| “Times” **(If “0”, go to SexInsertiveNoCondEjacFollowUp)**

Note to Programmer: If answer to **SexInsertiveCondomFollowUp** is greater than **SexInsertiveTimesFollowUp**, display “The number that you entered is greater than the number of times that you said you had insertive anal sex with this partner since the last time you took this survey. Please re-enter.”

SexInsertiveCondomBreakBaseline “Of the times that you used a condom when you had insertive sex with this partner in the last month, how many times did the condom break or slip off?” **(baseline only)**

____|____|____| “Times”

Note to Programmer: If answer to **SexInsertiveCondomBreakBaseline** is greater than **SexInsertiveCondomBaseline**, display “The number that you entered is greater than the number of times that you said you used a condom for insertive anal sex with this partner in the last month. Please re-enter.”

SexInsertiveCondomBreakFollowUp “Of the times that you used a condom when you had insertive sex with this partner since the last time you took this survey, how many times did the condom break or slip off?” **(all follow-ups only)**

____|____|____| “Times”

Note to Programmer: If answer to **SexInsertiveCondomBreakFollowUp** is greater than **SexInsertiveCondomFollowUp**, display “The number that you entered is greater than the number of times that you said you used a condom for insertive anal sex with this partner since the last time you took this survey. Please re-enter.”

SexInsertiveNoCondEjacBaseline “Of the times you had insertive sex WITHOUT a condom (or when the condom broke or slipped off) in the last month, how many times did you ejaculate/cum inside of this partner?” **(baseline only)**

____|____|____| “Times”

Note to Programmer: If answer to **SexInsertiveNoCondEjacBaseline** is greater than **(SexInsertiveTimesBaseline less SexInsertiveCondomBaseline)**, display “The number that you entered is greater than the number of times that you had receptive anal sex with this partner without a condom (or when the condom broke or slipped off) with this partner in the last month. Please re-enter.”

SexInsertiveNoCondEjacFollowUp “Of the times you had insertive sex WITHOUT a condom (or when the condom broke or slipped off) since the last time you took this survey, how many times did you ejaculate/cum inside of this partner?” **(all follow-ups only)**

____|____|____| “Times”

Note to Programmer: If answer to **SexInsertiveNoCondEjacFollowUp** is greater than (**SexInsertiveTimesFollowUp** less **SexInsertiveCondomFollowUp**), display “The number that you entered is greater than the number of times that you had receptive anal sex with this partner without a condom (or when the condom broke or slipped off) with this partner since the last time you took this survey. Please re-enter.”

SexOralTimesBaseline “In the last month how many times did you have oral sex with this partner (his penis was in your mouth or your penis was in his mouth)?” (**baseline only**)

|_|_|_|_| “Times”

SexOralTimesFollowUp “Since the last time you took this survey, how many times did you have oral sex with this partner (his penis was in your mouth or your penis was in his mouth)?” (**all follow-ups only**)

|_|_|_|_| “Times”

SexOralEjacBaseline “Of the times that you had sex with this partner in the last month, how many did he ejaculate/cum in your mouth?” (**baseline only**)

|_|_|_|_| “Times”

Note to Programmer: If answer to **SexOralEjacBaseline** is greater than **SexOralTimesBaseline**, display “The number that you entered is greater than the number of times that you said you had oral sex with this partner in the last month. Please re-enter.”

SexOralEjacFollowUp “Of the times that you had sex with this partner since the last time you took this survey, how many did he ejaculate/cum in your mouth?” (**all follow-ups only**)

|_|_|_|_| “Times”

Note to Programmer: If answer to **SexOralEjacFollowUp** is greater than **SexOralTimesFollowUp**, display “The number that you entered is greater than the number of times that you said you had oral sex with this partner in the last month. Please re-enter.”

SexAlcohol “Did you drink alcohol either before or during sex the last time you had sex with this partner?”

0 “No”
1 “Yes”

SexDrugs “Did you use any recreational drugs either before or during sex the last time you had sex with this partner?”

0 “No”
1 “Yes”

SexRcvExchange “Did this partner give you money, drugs, food, or a place to stay in exchange for sex the last time you had sex?”

- 0 “No”
- 1 “Yes”

SexGiveExchange “Did you give this partner money, drugs, food, or a place to stay in exchange for sex the last time you had sex?”

- 0 “No”
- 1 “Yes”

ReduceRisk “Did you do anything to try to reduce your risk of HIV infection with this partner the last time you had sex?”

- 0 “No” (**Go to LastSex**)
- 1 “Yes”

HowReduceRisk “Which of the following things, if any, did you do to reduce your risk of HIV infection with this partner? Choose all that apply.”

- 1 “Took Truvada for PrEP”
- 2 “Avoided anal sex”
- 3 “Avoided oral sex”
- 4 “Used a condom during anal, or oral sex”
- 5 “Tried to use condoms during anal, oral sex but could not”
- 6 “Was the insertive partner (or the “top,” I penetrated) during anal sex”
- 7 “Tried to be the insertive partner (or the “top,” I penetrated) during anal sex but could not”
- 8 “Avoided my partner ejaculating/finishing inside my rectum”
- 9 “Avoided my partner ejaculating/finishing inside my mouth”
- 10 “Asked partner to disclose his HIV status”
- 11 “Disclosed my HIV status”
- 12 “Chose to have sex with them only because I knew them well”
- 13 “Chose to have sex with them only because of where I met them”
- 14 “Other”
- 15 “None of the above”

When HowReduceRisk = Other: **HowReduceRiskOS** “Please specify:”

LastSex “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

BELIEFS ABOUT CONDOM USE (BASELINE AND WEEKS 24 AND 48/SP1/PRE-DC ONLY)

CondomIntro “There are many different factors that may impact decisions to have sex with or without condoms. Please read the following statements and indicate how often you believe the statement is true for you when are making decisions about condom use: Always, Often, Sometimes, Rarely or Never.”

CondomCauseHIV “Having sex without a condom could cause me to get HIV.”

- 1 “Always”
- 2 “Often”
- 3 “Sometimes”
- 4 “Rarely”
- 5 “Never”

Note to programmer: Use answer options in CondomCauseHIV for CondomIrresp through CondomLove.

CondomIrresp “Having sex without a condom is irresponsible.”

CondomSTI “Using condoms reduces my risk for HIV/STIs.”

CondomSpont “Sex without a condom is more spontaneous.”

CondomBetter “It feels better to have sex without a condom.”

CondomRelax “It is too difficult to relax and enjoy myself when using condoms.”

CondomSayNo “I worry my partner would say no if I suggested using a condom.”

CondomElse “I worry my partner would think I am having sex with someone else if I suggested using a condom.”

CondomDon’tLike “My partner(s) don’t like having sex with a condom.”

CondomConnect “Having sex without a condom makes me feel more connected to my partner.”

CondomTrust “Not using a condom with a partner shows him that I trust him.”

CondomLove “A guy cumming inside of you is an expression of love.”

LastCondom “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

SEXUALLY TRANSMITTED INFECTIONS (BASELINE ONLY)

STIIIntro “The following questions are about your experience with sexually transmitted infections.”

STI12Mos “In the past 12 months, were you told by a health care provider, such as a doctor or nurse that you had any of the following sexually transmitted infections?”

Note: Use response options of “yes” or “no” for STIGonorrhea through STIOther.

STIGonorrhea “Gonorrhea”

- 0 “No”
- 1 “Yes”

STISyphilis “Syphilis”

STIHerpes “Genital herpes”

STIChlamydia “Chlamydia”

STIHPV “Genital Warts (also known as HPV or Human Papilloma Virus)”

STIHepB “Hepatitis B virus”

STIHepC “Hepatitis C virus”

STIOther “Some other STD, but not HIV”

When STIOther = Yes: **STIOtherOS** “Please specify:”

LastSTITest “When was the last time you had a check-up for STDs or were tested for STDs? Do not include an HIV test in this answer. Was it...”

- 1 “Within the past 30 days”
- 2 “More than 1 month ago to 2 months ago”
- 3 “More than 2 months ago to 4 months ago”
- 4 “More than 4 months ago to 6 months ago”
- 5 “More than 6 months ago to 12 months ago”
- 6 “1-3 years ago”
- 7 “More than 3 years ago”
- 8 “I have never had a check-up or been tested for STDs”

LastBeliefs “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

STUDY-RELATED REDUCED HIV RISK (WEEKS 4, 24, AND 48/SP1/PRE-DC ONLY)

StudyIntro “The following are study-related belief statements on reducing HIV risk with which you may agree or disagree. Below each statement is a scale which ranges from strongly disagree (1) to strongly agree (5). For each item we would like you to choose the number that represents the extent to which you agree or disagree with that statement. The more you agree with a statement, the higher will be the number you select. The more you disagree with a statement, the lower will be the number you select. This is a measure of your personal beliefs; there are no right or wrong answers.”

StudyPrep “Because I am in this PrEP study, I am less concerned about becoming HIV positive.”

1 “1=Strongly Disagree”

2 “2=Disagree”

3 “3=Neutral”

4 “4=Agree”

5 “5=Strongly Agree”

Note: Use answer options in StudyPrep from StudyWilling to StudyInfected.

StudyWilling “I am more willing to take a chance of getting infected now that I am in this PrEP study.”

StudySlipping “I am a lot less worried about “slipping up” now that PrEP may be taken prior to unprotected sex.”

StudyAvailable “The availability of PrEP makes me less worried about having unprotected sex.”

StudyUnprotected “I am less concerned about having unprotected anal sex now that I am in this PrEP study.”

StudyInfected “I have already risked getting infected with HIV through unsafe sex while I’ve been in this study.”

StudyExperience “Below are physical symptoms that some people experience. Please let us know if you have experienced any of these in the past month.”

Note: Use response options of “yes” and “no” for StudyExperience through StudyRash.

StudyMuscle “Muscle pain and/or weakness”

StudyDarkUrine “Dark-colored urine”

StudyYellow Eyes “Yellow color in your eyes”

StudyIncreasedFat “Increased fat in your upper back or neck”

StudyDizziness “Dizziness”

StudyDiarrhea “Diarrhea”

StudyNausea “Nausea”

StudyVomiting “Vomiting”

StudyHeadaches “Headaches”

StudyRash “A rash on your skin”

LastStudy “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

SUBSTANCE USE AND ABUSE ITEMS (BASELINE AND FOLLOW-UP)

SubsIntro “Now we are going to ask you some questions about substance use in the past month. These substances can be smoked, swallowed, snorted, inhaled, injected or taken in the form of pills.”

SubsPresc “Some of the substances listed may be prescribed by a doctor (like amphetamines, sedatives, or pain medications). For this interview, we will not record medications that are used as prescribed by your doctor. Please answer using the following: 0 = Never, 1= Once or Twice, 2 = Every Week, or 3 = Every Day or Almost Every Day.”

SubMonth “In the past month, how often have you...?”

SubDrank “Drank alcohol (beer, wine, liquor, etc.)?”

0 “Never”

1 “Once or Twice”

2 “Every Week”

3 “Every Day or Almost Every Day”

Note: Use answer options in SubDrank from SubDrunk to SubAnythingElse.

SubDrunk “Got drunk off alcohol? (By drunk, we mean when you have had enough alcohol to where your mental functioning may be slightly altered and your decisions or action may be different than those when you are not drinking.)”

SubMarijuana “Smoked marijuana (weed, pot, etc.)?”

SubSnorted “Snorted or sniffed cocaine?”

SubSmoked “Smoked crack or rock cocaine?”

SubSwallowed “Swallowed, snorted, bumped, or smoked methamphetamine (crystal meth, tina, crank, dope, etc.)?”

SubNitrates “Used poppers or inhaled nitrites?”

SubClub “Used club drugs (Ecstasy, GHB, Special K, etc.)?”

SubHeroin “Snorted or smoked heroin?”

SubInject “Injected (used needles to inject drugs, hormones or cosmetic applications (i.e., silicon, Botox))?”

SubElse “Used any other substances?”

When SubElse = Yes: **SubElseOS** “What other substances have you used?”

LastSub “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

SUPPORT FROM OTHERS (FOLLOW-UP)

SupportIntro “The following section will ask you about support you may have received from others regarding your participation in this study.”

SupportPart “In the past month, have you talked with this person/these people about your participation in this research study?”

Note: For this group of questions use 0=No, 1=Yes, and 3= N/A as options.

PartPrimaryPartner “Your primary sex partner?”

PartOtherPartners “Other sex partners?”

PartMotherFather “Your mother or father?”

PartSisterBrother “Your sister or brother?”

PartFamilyMember “Other family member?”

PartFriendNeighbor “A friend or neighbor?”

PartNurseClinician “A nurse or clinician or doctor outside of the study?”

PartElderLeader “An elder or community leader?”

PartAnyoneElse “Anyone else?”

When PartAnyoneElse = Yes: **PartAnyoneElseOS** “Please specify:”

LastSupport “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

ACCEPTABILITY QUESTIONS (ONLY DURING WEEK 12, WEEK 48, SP1 OR PRE-DC)

AcceptIntro “The following section will ask you about the study pills and participation in the study.”

AcceptSize “How much did you like or not like the size of the pill?”

- 1 “Did not like it at all”
- 2 “Did not like it”
- 3 “Liked it”
- 4 “Liked it a lot”

Note: Use answer options in AcceptSize from AcceptTaste to AcceptEveryDay.

AcceptTaste “How much did you like or not like the taste of the pill?”

AcceptColor “How much did you like or not like the color of the pill?”

AcceptEveryDay “How much did you like or not like taking the study pill every day?”

AcceptOverall “Overall, how much did you like or not like the following:”

- 1 “Did not like it at all”
- 2 “Did not like it”
- 3 “Liked it”
- 4 “Liked it a lot”

Note: Use answer options in AcceptOverall from AcceptPart to AcceptContact.

AcceptPart “Taking part in the study.”

AcceptGroup “Participating in the group sessions at the beginning of the study.”

AcceptIndividual “Participating in the individual sessions at the beginning of the study.”

AcceptHIVTest “Having an HIV test at every visit.”

AcceptCounseling “Having individual counseling at every visit.”

AcceptBehavior “Being asked questions about your sexual behavior at every visit.”

AcceptExam “Having a physical exam by a doctor.”

AcceptClinic “Coming to a health clinic for study visits.”

LastAccept “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

PREP QUESTIONS (ONLY DURING WEEK 48, SP1 OR PRE-DC)

PrepLearn “Now that you have learned more about PrEP and have participated in a PrEP study, would you...”

PrepDay “Continue to use PrEP every day if it were available?”

0 “No”

1 “Yes”

3 “Don’t Know”

Note: Use answer options on PrepDay from PrepInter to PrepHIV.

PrepInter “Only take PrEP if the dosing were intermittent (like 3 times a week or on weekends only)?

PrepAnal “Use PrEP for all unprotected anal sex?”

PrepMore “Take PrEP if it had to be taken more than once a day?”

PrepHIV “Use PrEP when you knew that your partner was HIV-infected?”

PrepCasual “Use PrEP with casual sex partners?”

PrepReminder “Forget to take PrEP if you didn’t have reminders?”

PrepPrevent “How good do you think PrEP is at preventing HIV infection? 10 means it prevents HIV infection all of the time, 1 means it doesn’t prevent HIV infection at all, and 5 means it prevents HIV half of the time.”

1 “Doesn't prevent at all”

2

3

4

5 “Prevents half of the time”

6

7

8

9

10 “Prevents all of the time”

LastPrep “You have reached the end of the current group of questions. Press the NEXT button to go to the next group of questions or press the BACK button to check your previous answers. Once you press the NEXT button, you will no longer be able to return to these questions.”

BELIEFS ABOUT PREP (ONLY DURING BASELINE, WEEK 48, SP1, AND PRE-DC)

PrepBeliefIntroBaseline “Please indicate whether you believe the following statements to be true or false for you today. Remember, there is no right or wrong answer” **(baseline only)**

PrepBeliefIntroFU Please indicate whether you believe the following statements to be true or false for you today. Remember, there is no right or wrong answer.” **(all follow-ups only)**

PrepBeliefWorryLess “If I took PrEP, I would worry less about getting HIV.”

- 1 “True”
- 2 “False”

Note to Programmer: Use answer options in PrepBeliefWorryLess for PrepBeliefSex through PrepBeliefComfort.

PrepBeliefSex “If I took PrEP, I could have more sex partners.”

PrepBeliefCondom “If I took PrEP, using a condom during sex would not really be necessary.”

PrepBeliefHurt “If I took PrEP, I would worry that PrEP will hurt my health.”

PrepBeliefPills “If I took PrEP, I would worry that other people will see me taking pills and may think that I am HIV positive.”

PrepBeliefEffective “ PrEP is as effective at preventing HIV as condoms.”

PrepBeliefComfort “If I took PrEP, I would feel more comfortable having sex with someone who is HIV positive.”

PrepBeliefReasons “Which of the following are reasons that you do not wish to take PrEP? Choose all that apply.” **(baseline and pre-d/c only)**

- 1 “I am concerned about side effects from the pills”
- 2 “I can avoid HIV in other ways”
- 3 “I don’t like taking pills”
- 4 “I am concerned that people will think that I am HIV positive because I am taking PrEP”
- 5 “I am concerned that people will know that I have sex with men and/or trans people because I am taking PrEP”
- 6 “I fear developing resistance to HIV medications if I became positive”
- 7 “I don’t want to take a pill every day”
- 8 “None of the above”

Note to Programmer: Ask remainder of section at Week 48 and Premature Discontinuation visits only.

PrepBeliefIntro2 “Please indicate whether you believe the following statements to be true or false for you today. Remember, there is no right or wrong answer.” **(week 48 and pre-d/c)**

Prep2WorryLess “When I take PrEP, I worry less about getting HIV.”

- 1 “True”
- 2 “False”

Note to Programmer: Use answer options in Prep2WorryLess for Prep2Sex through Prep2Comfort.

Prep2Sex “When I take PrEP, I can have more sex partners.”

Prep2Condom “When I take PrEP, using a condom during sex would is not really necessary.”

Prep2Hurt “When I take PrEP, I worry that PrEP will hurt my health.”

Prep2Pills “When I take PrEP, I worry that other people will see me taking pills and may think that I am HIV positive.”

Prep2Effective “PrEP is as effective at preventing HIV as condoms.”

Prep2Comfort “When I take PrEP, I feel more comfortable having sex with someone who is HIV positive.”

PrepNoTake “Which of the following are reasons that you do not wish to take PrEP? Choose all that apply.”

- 1 “I am concerned about side effects from the pills”
- 2 “I can avoid HIV in other ways”
- 3 “I don’t like taking pills”
- 4 “I am concerned that people will think that I am HIV positive because I am taking PrEP”
- 5 “I am concerned that people will know that I have sex with men and/or trans people because I am taking PrEP”
- 6 “I fear developing resistance to HIV medications if I became positive”
- 7 “I don’t want to take a pill every day”
- 8 “None of the above”

PrepGen “If PrEP becomes available for general use, people taking PrEP may have HIV testing done at home. Please indicate whether you would be willing to do each of the following as part of a home HIV testing program while on PrEP.”

Note: Use multi-form for PrepGenA through PrepGenK with response options of “yes”, “no”, and “maybe”.

PrepGenA “Prick your finger to get a drop of blood to test for HIV.”

PrepGenB “Swab your mouth with a Q-tip to collect cells from your cheek to test for HIV.”

PrepGenC “Read your HIV test results yourself.”

PrepGenD “Mail your specimen and call a clinic for your HIV test results.”

PrepGenE “Test yourself for HIV every month at home.”

PrepGenF “Test yourself for HIV every 3 months at home.”

PrepGenG “Test yourself for HIV only when you think you were exposed to HIV.”

PrepGenH “If you test positive for HIV, receive your results by mail.”

PrepGenI “If you test positive for HIV, receive your results by phone.”

PrepGenK “If you test positive for HIV, receive your results by going to a clinic.”

PrepComm “If PrEP is provided to the community, it will require regular HIV testing, counseling and health.”

1 “From my regular doctor/health care provider”

2 “From a community health clinic”

3 “From an STI (sexually transmitted infection) clinic”

4 “Through local community organization/ non---governmental organization (“NGO”)

5 “From a pharmacy”

6 “Through an outreach worker”

7 “Other”

When PrepComm = Other: **PrepCommOS** “Please specify:”

LastPrepBelief “You have reached the end of the final group of questions. Press the NEXT button to end the interview or press the BACK button to check your previous answers.”

COMMENTS (BASELINE AND FOLLOW-UP)

CommentsIntro “We’ve asked you a lot of questions. Now we’d like to give you an opportunity to write anything you want about yourself that you think we may have missed, and/or anything regarding your participation in this study, HIV/AIDS, the gay scene, or about this survey, that you think we should understand.”

ThankYou “Thank you for your participation. Please let the interviewer know that you are finished.”

APPENDIX XVIII: INTEGRATED NEXT STEP COUNSELING

Overview of Integrated NEXT STEP Counseling (iNSC)

Integrated Next Step Counseling is a strengths -based discussion focused on the identification of sexual health protection and PrEP adherence needs and tailored strategies that might help individuals to meet those needs. iNSC was developed for and is presently in use in iPrEX OLE. The approach is based on a situated application of the Information, Motivation, Behavioral Skills (IMB) model of health behavior adoption (Fisher, Fisher & Shuper, 2009), which predicts that adopting a given behavior is a function of behavior specific information (e.g., accurate information about a regimen and adherence requirements or sexual risk and health protection strategies), motivation (personal and social attitudes and beliefs about the consequences of adopting or not adopting a given behavior), and behavioral skills (requisite skills and confidence in using those skills to execute the behavior). The IMB model has been used successfully in characterizing both HIV-risk reduction practices and adherence to ART for treatment, and was articulated to both study product use and comfort in reporting of product use in the iPrEx RCT. This model is “explanatory” in that it identifies what the core “drivers” of behavior are but does not specify how to change or influence these factors. iNSC is a basic guided approach for eliciting the kinds of interactions that are intended to promote high levels of information, motivation and skills relevant to sexual health promotion and PrEP use that uses motivational interviewing and several kinds of general counseling/communication strategies.

In iNSC, the kinds of information, motivation and skills most relevant to a given individual are assumed to be determined by their current life-situation, resources and constructions of sexual health and PrEP that are highly influenced by culture, community and previous experiences. iNSC uses a general process to guide discussions that seek to articulate a given participant’s experiences with sexual health promotion in his/her current life-context and perceived needs for sexual health promotion to be as manageable as possible in that context, which is then used to brainstorm possible strategies to use to meet those needs and culminates in a concrete agreement or goal for using one or more of the identified strategies prior to returning again for a study visit. There are two parts to the iNSC conversation- first a brief discussion focused on strategies used or under consideration for sexual health protection via behavioral strategies (not including PrEP use) which is then followed by a brief discussion focused on PrEP-use for prevention specifically. Thus, the first part of the conversation focuses on eliciting perceived needs for facilitating sexual health promotion (e.g., needs to feel confident in discussion of strategies with partners, have more social support, have consistent access to condoms, feel committed to self-protection) through behavioral strategies (e.g., condom use, HIV testing, disclosure discussions, reduction in number of partners); the second part focuses on experiences with PrEP, adherence-related needs (perceived factors, feelings, events or situations that would promote integration of PrEP taking into daily life), and strategizing on ways that those needs could be addressed in given one’s current life-context (e.g., using an alarm, carrying an extra dose when going out, dosing before starting to drink, so on). While the content for each part of the discussion is different, the process of the conversation (explore, identify, strategize, select a goal) is the same. By looping the two conversations together, the unique needs and strategies for each set of behaviors are well represented while still promoting the continuity of these strategies as unified to protect one’s sexual health and to model a ‘compendium of prevention’ approach.

Table 1. iNSC basic dialogue

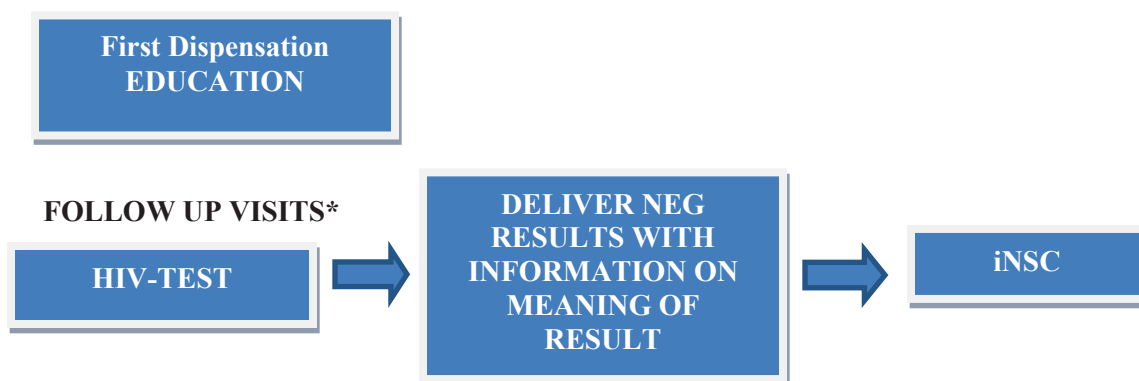
| |
|--|
| Explore experiences |
| Identify needs |
| Strategize on how to meet needs |
| Agree on an actionable goal |

iNSC in context

iNSC is anticipated to be implemented after an education session on first dispensation of PrEP that explains the regimen, potential side-effects, correction of common mis-information and building individual skills sets on anticipated facilitators and barriers. A check sheet for this kind of education session is provided here as an example.

iNSC is recommended to be provided in the context of a person-centered standard of care. If participant product use is demanded and reported or estimated use/non-use is targeted by study team members through directive persuasion, negative or positive reinforcement, punishment or other non-person centered approaches, it will be very difficult for implementers of iNSC to build the kind of rapport and social alliance with participants that are essential ingredients. Further, where possible, it is recommended that sexual health promotion strategies and PrEP use, in terms of facilitators, barriers, needs and strategies be the focus of one conversation with one team member at a given visit. Separate risk-reduction counseling or additional messaging on PrEP use is not recommended as it can diffuse the conversation and can be experienced as excessive by participants. The sexual health promotion part of the iNSC discussion was developed to include post-test counseling requirements most health care agencies must address, however this should be confirmed on a site by site basis. Pre-test counseling that explains HIV-testing and the information on limitations of HIV-test results typically delivered at pre and post-test must be added to the iNSC steps. Although iNSC can be implemented pre- or post-HIV testing, it is likely most efficient as a post-test procedure, immediately following the delivery of a negative HIV-test result.

FIRST DISPENSATION FOR SELF-ADMINISTERED PREP



*It is recommended that iNSC be initiated as early as possible in the visit but in conjunction with delivery of HIV-negative test results. Implementing iNSC as the last part or near last part of a study visit is not recommended.

Education Session Check List

Provide clear instructions on product and for product use

- Explain PrEP (how it works, how well it works, what is known, what is not known).
- Explain regimen (dos and don'ts).
- Explain dosing windows: while it is recommended to take at about the same time every day, if a dose is missed it can be taken when the participant remembers that day. If the dose is missed for a given day, do not take two doses the following day.

Provide information about special situations

- Describe common side-effects, anticipated duration, and suggested management strategies.
- Distinguish between common side-effects and reactions that would cause concern or require the participant call the study site.
- Explain procedures for what to do if the participant runs out of tablets or anticipates not being able to get refills in time.
- Provide information about doses being able to be taken when drinking alcohol or using drugs or planning to do so.

Frame as-recommended PrEP Use

- Provide reasons for requested daily use.
- Normalize natural variability in patterns of PrEP-use (we anticipate that daily use may be challenging and simply not possible to do every day from time to time).
- Position accurate reporting as critical (because of this, we are asking all participants to please do the best that they can but we are also requesting that no matter what happens to feel OK reporting back to us whatever actually happens).

Confirm understanding and elicit questions/concerns

- Perform an information check (ask participant what he or she understood from discussions).
- Elicit additional questions or concerns.

Promote personal relevance of information/education provided

- Ask participant about how the information provided is the same or different than he or she expected.
- Ask participant how he or she sees daily dosing fitting in (or not) with daily life.

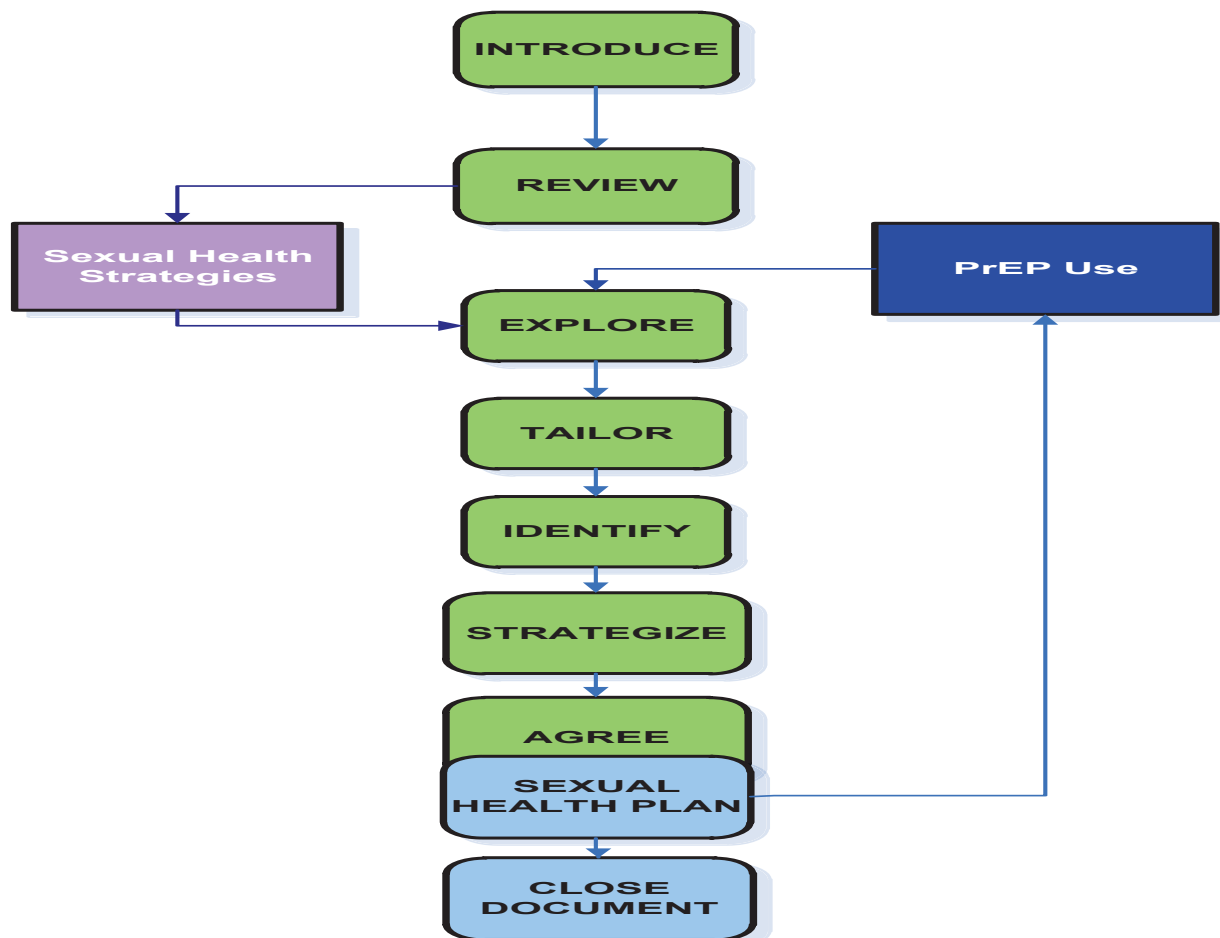
Build skills

- Ask participant about creating a schedule:
 - Given that many people find medication taking easier when it is done at about the same time each day or in conjunction with a regularly occurring event - ask participant if there is a time of day that might be optimal for study medication taking.
- Identify facilitators (ask about what might help with this; reminders, social support).

Close discussion

- Thank participant and remind participant that someone will be checking in with him/her to see how things went at their next visit.

iNSC Steps



GOAL: Create a comfortable environment to talk about experiences and foster motivation and skills.

CLIMATE: Supportive, non-judgmental, neutral, reinforcing of open discussion/efforts, avoidance of “fixing” or direct persuasion, recognition of limited role, and emphasis on participant as a whole person.

METHOD: Exploration of context (experiences, thoughts, beliefs, feelings, skills) to elicit needs-what would need to happen or continue happening for the behavior to be most integrated, manageable or “easy.”

ASSUMPTIONS: Participants choose whether or not to do something based on feeling well informed, motivated and skilled. Direct appeals to persuade someone adopt a behavior will distance participants; joining participants in their exploration of facilitators and barriers without pushing an agenda for perfect protection or perfect PrEP use will better promote motivation by matching the participant’s level of readiness and speak to factors they consider most personally relevant and meaningful at a given point in time.

APPENDIX XIX: SAMPLE INFORMED CONSENT FOR STUDY PARTICIPANTS

ADOLESCENT TRIALS NETWORK

REMINDER TO STUDY SITES: Do not use the preamble in local consents.

NOTE FROM **THE** OFFICE OF HUMAN RESEARCH PROTECTION (OHRP) TO SITES ENROLLING PARTICIPANTS IN THIS STUDY:

Please note that this sample language does not preempt or replace local **Institutional Review Board (IRB)** review and approval. Investigators are required to provide the local IRB with a copy of this sample language along with the language intended for local use. Local IRBs are required to weigh the unique risks, constraints, and population considerations as a condition of any approval. Any deletion or substantive change of information concerning risks or alternative treatment must be justified by the investigator, approved by the local IRB, and noted in the IRB minutes. Justification and IRB approval of such changes must be forwarded to Westat, the ATN **Data and Operations Center (DOC)**, for any NICHD-sponsored trial, or as may be otherwise specified. Sponsor-approved changes in a protocol must be approved by the local IRB before use unless intended for the elimination of apparent immediate hazard. New information shall be shared with existing participants at next encounter, with all new participants prior to involvement, or as the local IRB may otherwise additionally require.

TITLE OF STUDY:

ATN 113 Version 2.0

Project PrEPare – An Open Label Demonstration Project and Phase II Safety Study of Pre-Exposure Prophylaxis Use among 15- to 17-Year Old Young Men Who Have Sex with Men (YMSM) in the United States

Principal Investigator: _____

Telephone Number: _____

INTRODUCTION

We are going to tell you about a research study on PrEP for HIV/AIDS. PrEP is short for Pre-Exposure Prophylaxis. Pre-exposure means before being exposed to the agent that causes the disease. Prophylaxis is the way people who do not have the disease stop the disease from infecting them. With PrEP for HIV, drugs used to treat HIV/AIDS are given to individuals without HIV before they are exposed to HIV. Taking HIV drugs in this way may prevent HIV infection. We are doing this study in young men who have sex with men (YMSM), including transgender women, who are at risk for HIV infection. We want to know if it is safe for YMSM to take an HIV drug called emtricitabine/tenofovir (FTC/TDF (Truvada®)) as PrEP. FTC/TDF (Truvada®) was recently approved by the Food and Drug Administration (FDA) for use as PrEP in adults who are at high risk of becoming HIV infected. However, using FTC/TDF (Truvada®) as a PrEP drug has not been FDA approved for younger people, so it is experimental. This study will help find out if it is safe for younger people to take the drug as PrEP.

We also want to know if it is acceptable and practical for YMSM to use a PrEP drug.

Some of the questions we want to answer are: 1) what makes young men want to join and stay on a PrEP study, 2) will young men take a PrEP drug as they are supposed to, and 3) will young men on a PrEP drug change their sexual behavior because they believe the PrEP drug protects against HIV infection.

This study is funded by the *Eunice Kennedy Shriver* National Institute for Child Health and Human Development (NICHD) through the Adolescent Trials Network (ATN), and will take place in clinics across the U.S. About 100 HIV negative YMSM between the ages of 15 and 17 will take part in the study.

PARTICIPATION IN THIS RESEARCH STUDY IS VOLUNTARY

The purpose of this consent form is to give you the information you will need to help you decide if you want to be in the study. We will tell you the purpose of the study, what you will be asked to do in this study, the possible risks and benefits, and your rights as a volunteer. We want you to ask any questions you may have about this study. When all of your questions are answered, you can decide if you want to be in the study. This process is called “informed consent.” Once you understand the study and all of your questions have been answered, if you still want to take part then you will be asked to sign this consent form. You will be given a signed copy of this form to keep.

DO I HAVE TO JOIN THIS STUDY?

Your participation in this study is completely voluntary. You decide if you want to be in this study. Refusing to join the study will not change your usual health care. You will not lose any benefits that you otherwise could get. There will be no penalties. You may decide not to take part in this study. You may also stop taking part in the study at any time without penalty or losing your medical benefits.

WHAT IS THIS STUDY ABOUT?

In the U.S., it is estimated that at least one-third of all new HIV infections are among people 13 to 29 years of age. Most of these infections occur through sexual activity. YMSM is the largest group of males between the ages of 13 and 24 who are living with HIV /AIDS in the U.S. Rates of HIV infection among this group are increasing rapidly. Prevention methods to lower HIV risk among YMSM are urgently needed. YMSM can be hard to reach. Many live in communities with poverty, high unemployment and poor access to health care. These communities have high levels of street and domestic violence, drug use and alcoholism, and shame toward MSM. The high rates of HIV infections among YMSM tell us we need more **ways to help protect these young men.**

You are being asked to take part in this study because you are between 15- and 17-years of age and may be at risk of becoming infected with HIV.

This study combines two **behavioral interventions** (HIV-prevention programs) that provide education and skills on how to lower HIV risk with a PrEP drug. Before you are given the PrEP drug, you will first take part in one of two HIV prevention programs, Many Men, Many Voices (3MV) or Personalized Cognitive Counseling (PCC). You will not be able to choose the prevention program in which you want to take part. You will receive whichever program is offered at the clinic site where you are participating in the study. After completing the program, you will be provided the PrEP drug, FTC/TDF (Truvada®), which you will need to take daily as PrEP and be followed for 48 weeks (about a year). This study is also trying to see if it is safe to give FTC/TDF (Truvada®) in individuals who are HIV negative.

HOW LONG WILL THE STUDY LAST?

There are two phases to this study, the Initial Phase and the Extension Phase. The Initial Phase will have 10 study visits: Screening visit; Baseline visit; Behavioral Intervention visit; and Weeks 0, 4, 8, 12, 24, 36, and 48 Follow-up visits. If you become HIV infected during the course of the Initial Phase, you will complete 3 HIV Seropositive visits over 24 weeks. The Extension Phase will have two additional visits at 24 and 48 weeks after the end of Initial Phase. All study participants will take part in the Initial Phase of the study. Depending on your bone and kidney tests results at the end of the Initial Phase, you may be asked to continue on the Extension Phase. This means, if you do not become HIV infected, you will be in the study at least 1 year (Initial Phase only), but it could be as long as 2 years (Initial and Extension Phase). If you become HIV infected, you could in the Initial Phase of the study as long as 1 ½ years, and if you are also asked to continue on the Extension Phase, you could be in the study as long as 2 ½ years.

WHAT WILL I HAVE TO DO IN THE STUDY?

If you decide that you would like to be in this study, you will be asked to sign this consent form before you begin the study. Below is the schedule of study visits and the evaluations to be done at each visit.

Screening Visit

The Screening visit must be completed to find out if you are eligible to be in the study.

- We will ask for your address and contact information so that the study staff will be able to get in touch with you. This information will be stored under double locks, separate from all other study records and only the study staff will have access to it.
- We will ask questions about your age, background, and sexual history. We will also ask about your medical history, including any medical conditions you have, medications you are taking and any signs or symptoms you have.
- You will have a complete physical exam.
- About 4 teaspoons of blood will be drawn for tests that measure the different minerals and other substances in your blood to see how your body is working and to test for HIV and hepatitis B infection. **Hepatitis B is a virus that causes your liver to become inflamed (swollen) and is spread the same way as HIV.**
- Urine will be collected **for tests to make sure it is safe for you to take the PrEP drug, Truvada.**
- At the end of the visit, you will receive condoms with counseling.
- The Screening visit will take about two hours to complete.

Baseline Visit

If you meet the criteria to be in the study, you will be asked to come back for the Baseline visit.

- We will give you the results of the tests done at the Screening visit. Your medical history since the Screening visit will be reviewed. You will have a physical exam **done based on how you are feeling and whether you have any symptoms or complaints.** If you are **still** eligible to be in the study, you will be enrolled in the study.
- After enrollment, your contact information will be reviewed to make sure it is up to date.

- You will complete a Tanner Stage Tool to find out your stage of **pubertal** development. This tool shows drawings of five different stages of how pubic hair and genitals grow. You will be asked to mark an "X" in the box next to the drawing that you think is closest to your stage of **pubertal** growth. If you prefer **not to do this yourself**, the study **clinician can examine** your genitals to determine the stage of your **pubertal** development.
- About 6 teaspoons of blood will be drawn for tests that measure the different minerals and other substances in your blood to see how your body is working, to see if you need the hepatitis B vaccine, to test for HIV infection and syphilis, and for an HIV-1 viral load test. Urine will be collected to test for gonorrhea and chlamydia. A rectal swab sample will also be collected to test for gonorrhea and chlamydia.
- You will have Dual-energy X-ray Absorptiometry (DXA) scans of your hip, spine, and whole-body. DXA is a special X-ray that looks at your bones. For these scans, you will be asked to lie down on a table with your hand palms down alongside the body. The scans will take approximately 25 minutes, but may take up to 45 minutes for some people. The DXA scans will not cause you any pain. On rare occasions, it may be necessary to repeat the DXA scans.
- You will complete an interview on a computer in private called ACASI (Audio Computer-Assisted Self-Interview). The interview will take about one hour to complete. ACASI uses a computer and voice recordings so you can hear (through headphones) and see (on the screen) each question and the answers for that question. You will enter your answer right into the computer. When the interview is complete, the computer “locks in” your information so no one at the clinic can see your answers. The interview will ask you to give some information about your thoughts and feelings, health status, substance use, sexual activity, and relationships. You will also be asked about PrEP to find out how much you know about it and your feelings about it. You will not be asked your name, phone number, birth date, address, social security number or any other information that could identify you. Some of the questions may be very personal, such as questions about sexual activity and substance use. You do not have to answer any question that you do not want to, and you can end the interview at any time if you do not want to continue. However, we hope that you will answer all the questions because we can learn much more about young men like yourself if all the questions are completed.
- You will be asked about **recent activities that may have placed you at a high risk for exposure to HIV**. The **study clinician** may recommend that you start PEP if **he or she thinks** that you were at high risk of exposure to HIV in the previous 72 hours. PEP stands for **Post-Exposure Prophylaxis**. Post-exposure means after being exposed to the agent that causes the disease.
- At the end of the visit, you will receive condoms with counseling.
- The Baseline visit will take about three hours to complete.

Behavioral Intervention

After the Baseline visit, you will come back for the behavioral intervention, the intervention being offered here is (*insert 3MV or PCC*).

Include only for sites doing the 3MV: The 3MV is a 2-day group program. From 5 to 10 participants like you will be in the group session. The session includes talks about identity, STD/HIV prevention options, and how you can use those options in your own life. The session will be recorded using a digital voice recorder. The digital recording will be kept private. We will not use your name during the session and you and other participants will be reminded not to use names. The digital recording will be destroyed once the study team has reviewed it for adherence to the protocol.

Include only for sites doing the PCC: The PCC is a one-hour session with just you and a counselor. You and the counselor will talk about a recent high risk behavior you had. The two of you will then talk about the thoughts, feelings, or attitudes that might have led to this behavior and ways to deal with similar situations in the future. The session will be recorded using a digital voice recorder. The digital recording will be kept private. We will not use your name during the session and you will be reminded not to use names. The digital recording will be destroyed once the study team has reviewed it for adherence to the protocol.

After you finish the behavioral intervention, you will be asked to complete a session evaluation form to let the study staff know about your experience.

Re-Screening Visit

If you are unable to complete the Week 0 visit within 30 days after completing the Screening visit, you will need to complete a Re-screening visit before you can move on to the Week 0 visit. This is to make sure that you are still eligible and it is safe for you to take the PrEP drug, Truvada. The Re-screening visit will take about an hour to complete. You will repeat many of the same tests and procedures that were done at the Screening and Baseline visits, with the following exceptions:

- **Hepatitis B testing will be done only if the test done at the Baseline visit showed that you were not protected against this virus.**
- **Depending on how you are feeling and whether you have any symptoms or complaints, blood may be collected to test for syphilis, and urine and/or a rectal swab sample may be collected to test for gonorrhea and chlamydia.**
- **A DXA scan will be done only if 90 days (about 3 months) or more has passed since your baseline DXA scan was done.**

You will be asked about recent activities that may have placed you at a high risk for exposure to HIV. The study clinician may recommend that you start PEP if he or she thinks that you were at high risk of exposure to HIV in the previous 72 hours.

Week 0 Visit

This visit can occur on the same day you finish the behavioral intervention or on a day shortly after, but no more than 30 days after the Screening visit or the Re-screening visit if you had to complete one.

- Your contact information will be reviewed to make sure it is up to date.
- You will have a physical exam. What will be done will depend on how you are feeling and whether you have any symptoms or complaints.
- Your medical history since the Baseline Visit (**or the Re-screening visit if you had to complete one**) will be reviewed.
- Blood (less than 1 teaspoon) will be drawn to test for HIV infection and Hepatitis B infection.
- Urine will be collected to test for gonorrhea and chlamydia, and **for tests to make sure it is safe for you to take the PrEP drug.** A rectal swab sample may be collected to test for gonorrhea and chlamydia depending on how you are feeling and whether you have any symptoms or complaints.
- You will then have a counseling session called Integrated Next Step Counseling (iNSC). During the session, you will be able to talk with a counselor about PrEP and ways you can protect yourself from HIV and sexually transmitted infections.

- You will be asked about **recent activities that may have placed you at a high risk for exposure to HIV**. The **study clinician** may recommend that you start PEP if **he or she thinks** that you were at high risk of exposure to HIV in the previous 72 hours.
- At the end of the study visit, **the study staff may ask you to return to repeat some lab tests if they have concerns about your lab results. If your lab tests show that it is safe for you to take the PrEP drug**, you will receive a bottle of it. The study staff will give you instructions on how to take the PrEP drug and answer any questions you may have.
- *(Include only for sites using the Wisepill device)* Some participants will use the Wisepill device for their PrEP drug. If you are selected, your PrEP drug will be placed into the device container. The study staff will help and show you how to fill the container with the PrEP drug. Each time you open the Wisepill container, a signal will be sent to a central computer to let the researchers know that you are taking your pill. This information will allow the researchers to learn about patterns of PrEP drug use.
- The Week 0 visit will take about one hour to complete.

Follow-up Visits (Weeks 4, 8, 12, 24, 36, and 48)

Follow-up visits will begin 4 weeks after the Week 0 visit. The visits will occur once every 4 weeks until Week 12 and then every 12 weeks until Week 48.

- Your contact information will be reviewed to make sure it is up to date.
- You will have a physical exam **done based on how you are feeling and whether you have any symptoms or complaints**.
- Your medical history since the previous visit will be reviewed.
- Blood will be drawn for tests that measure the different minerals and other substances in your blood to see how your body is working, to test for hepatitis B infection and HIV infection. Depending on the visit, the amount of blood that will be drawn at the visit will range from 2 teaspoons to 6 teaspoons.
- Blood and a hair sample will be collected to test medications levels in your body to check on how well you are taking the PrEP drug. **About one teaspoon of blood will be drawn.**
- Urine will be collected to test for gonorrhea and chlamydia, and **for tests to make sure it is safe for you to take the PrEP drug**. A rectal swab sample will also be collected to test for gonorrhea and chlamydia at the Weeks 24 and 48 visits. It may be collected at other study visits depending on how you are feeling and whether you have any symptoms or complaints.
- DXA will be done at the Week 24 and 48 visits only.
- You will complete the follow-up ACASI. The interview is similar to the ACASI completed at the Baseline visit except there will be additional questions asking about how your behaviors and beliefs may have changed since you started the study and what you have told others about the study. The interview will include questions on beliefs related to HIV risk, sexual behaviors, STIs, drug and alcohol use, and reasons for missed medications. The ACASI at the final visit at Week 48 will have additional questions on acceptability of the PrEP drug, the study, and PrEP in general.
- You will take part in an iNSC session.

- You will be asked about **recent activities that may have placed you at a high risk for exposure to HIV**. The **study clinician** may recommend that you start PEP if **he or she thinks** that you were at high risk of exposure to HIV in the previous 72 hours.
- HIV testing will be done every four weeks. At the Weeks 12, 24, and 36 study visits, you will receive HIV home testing kits so that you could do HIV testing at home at Weeks 16, 20, 28, 32, 40 and 44. For the home test, you will have to prick your finger, collect the blood, and mail it to the company that does the testing. The results of the test will be given to the study staff. The study staff will contact you to give you the test results. If you rather not do the home test, you can come into the clinic to have the test done.
- A one-month supply of the PrEP drug will be provided at the end of the Weeks 4 and 8 visits. A three-month supply of the PrEP drug will be provided at the end of the Weeks 12, 24 and 36 visits. No PrEP drug will be provided at the Week 48 visit. **If the study staff have any concerns about whether it is safe for you to continue taking the PrEP drug, they may “hold” the PrEP drug or provide a limited supply until additional tests are done.**
- If at anytime during the study, you have trouble taking the PrEP drug as you’re supposed to, you will be asked if you would like daily text message reminders sent to your cell phone. The text messages will not contain any personal information or information that will tell others that you are on this study. If you are interested, the study staff will explain how it works and help set it up.
- Each follow-up visit will take about two hours to complete. At Weeks 24 and 48 where the DXA is needed, the visit will be about three hours.

Permanent Discontinuation from Study Agent Visit

If you permanently stop taking the PrEP drug for any reason, you will continue to be seen for your follow-up study visits, unless you want to stop being in the study altogether. The first study visit that is done after you stop taking the PrEP drug will be exactly the same as the follow-up visits described above. All follow-up study visits after that will be similar to the follow-up visits described above, except for the following differences: 1) blood and hair to test PrEP drug levels in your body will not be collected; 2) the ACASI will not include questions on how you take the PrEP drug; and 3) PrEP drug will not be given to you at the end of the visits.

Premature Discontinuation from Study Visit

If you stop taking part in the study **after the Week 0 visit (after starting PrEP), but before the Week 48 visit**, you will be asked to return to complete **one final study visit**. The evaluations scheduled at the Week 48 visit will be done at this visit. **If you stop participating in the study before you start the PrEP drug, you will not be asked to return for a study visit.**

HIV Confirmatory Testing Visit

If **any of** your HIV tests show that you may be HIV infected, you will be contacted **by the study staff** and asked to stop taking the PrEP drug until you can return to the clinic for the HIV Confirmatory Testing Visit to see if you really are HIV infected.

- Your contact information will be reviewed to make sure it is up to date.
- You will have a physical exam **done based on how you are feeling and whether you have any symptoms or complaints.**

- Your medical history since the previous visit will be reviewed.
- About 5 teaspoons of blood will be drawn for tests that measure the different minerals and other substances in your blood to see how your body is working, to help confirm whether you are HIV-infected and to test for hepatitis B and syphilis, if your infection status is not known.
- About 3 teaspoons of blood and a hair sample will be collected to test medications levels in your body.
- An additional 2 teaspoons of blood will be drawn and saved in case you are confirmed HIV infected and we need to figure out which medications will be best for you.
- Urine will be collected to test for gonorrhea and chlamydia, and **for tests to make sure the PrEP drug you took has not harmed your body.**
- At the end of the visit, you will receive condoms with counseling.
- The HIV Confirmatory Testing visit will take about one hour to complete.

If the HIV confirmatory test result is uncertain, you will be asked to return weekly to repeat HIV testing until it can be confirmed that you are HIV infected or not HIV infected. During that time you will continue to stay off the PrEP drug. If you are confirmed HIV infected, you will permanently stop taking the PrEP drug and complete HIV Seropositive visits as described in the next section. You will be referred for primary HIV care outside of the study. If you are confirmed not HIV infected, you will resume taking the PrEP drug and return to your original Follow-up Visits schedule.

HIV Seropositive Visits

You will complete three HIV Seropositive visits (**SP1, SP2, and SP3**) at 4, 12, and 24 weeks, respectively, **if HIV infection is confirmed.**

- Your contact information will be reviewed to make sure it is up to date.
- You will have a physical exam **done based on how you are feeling and whether you have any symptoms or complaints.**
- Your medical history since the previous visit will be reviewed.
- About 5 teaspoons of blood will be drawn for tests that measure the different minerals and other substances in your blood to see how your body is working, for HIV-1 viral load test to see how much HIV virus is in your blood) and CD4+ T cell count to see how your immune system is working.
- Urine will be collected **for tests to make sure the PrEP drug you took has not harmed your body.**
- At the SP3 visit only, you will have a DXA scan done.
- At the SP1 visit only, you will complete the final ACASI that includes additional questions on acceptability of the PrEP drug, the study, and PrEP in general.
- You will take part in an iNSC session that focuses on ways you can protect yourself from **other STIs, as well as protect your partners from HIV** at each visit.
- At the end of each visit, you will receive condoms with counseling.
- The SP1 and SP3 visits each will take about two hours to complete. The SP2 visit will take about one hour to complete.

Extension Phase Visits (24 and 48 weeks after the end of the Initial Phase)

Depending on your bone **and/or** kidney tests results at the end of the Initial Phase (Week 48 or the SP3 visit), you will be asked to take part in the Extension Phase. The Extension Phase will have two visits at 24 and 48 weeks after the end of Initial Phase. The study staff will contact you when those test results are back to let you know whether you need to return for the Extension Phase visits.

- Your contact information will be reviewed to make sure it is up to date.
- You will have a physical exam **done based on how you are feeling and whether you have any symptoms or complaints.**
- Your medical history since the previous visit will be reviewed.
- About 4 teaspoons of blood will be drawn to test for HIV infection (if you are not infected) and to measure the different minerals and other substances in your blood to see how your body is working.
- Urine will be collected **for tests to make sure the PrEP drug you took has not harmed your body.**
- You will have a DXA scan done.
- You will take part in an iNSC session that focuses on ways you can protect yourself from HIV and other STIs. **If you have HIV infection, the iNSC session will focus only on ways you can protect yourself from other STIs.**
- At the end of each visit, you will receive condoms with counseling.
- The Extension Phase visits each will take about two hours to complete.

WHAT ARE THE RISKS IN TAKING PART IN THIS STUDY?

Taking Truvada for PrEP cannot guarantee that you will not get infected with HIV. If you become HIV infected while taking PrEP, the drug may not be able to fight as well against the HIV in your body. This is called drug resistance. If the HIV virus that you are infected with becomes resistant to Truvada, you may not be able to use it as part of your treatment for HIV infection. Although studies have shown that PrEP does reduce the risk of HIV infection, especially in those who follow the prescription directions closely, it does not protect everyone.

You can lessen the chance of resistance to Truvada. Take the drug every day as prescribed and use other ways to lower your risk for getting HIV, such as consistent and correct condom use. Also tell the study staff of any flu-like symptoms that may suggest that you recently became infected with HIV. These symptoms include fever, headache, joint pain, muscle pain, throat pain, vomiting, diarrhea, rash, night sweats and swollen glands.

You may experience side effects from taking the PrEP drug, FTC/TDF (Truvada®). The most common risks and side effects from the PrEP drug include dizziness, fatigue, difficulty sleeping, depression, abnormal dreams, diarrhea, nausea (upset stomach), vomiting, headache, rash and gas. Skin discoloration (small spots or freckles) may also occur.

Less common but more serious and potentially life-threatening risks include:

- liver problems;
- inflammation of the pancreas;
- anemia (low red blood cells);

- lactic acidosis (a buildup of a chemical called lactate in the body that can cause symptoms of unexplained weight loss, stomach discomfort, nausea, vomiting, fatigue, cramps, muscle pain, weakness and shortness of breath);
- lipodystrophy (changes in fat distribution in your body such as an increase in fat around the waist, back of the neck and breast areas, and thinning of the face, legs and arms);
- decreased kidney function;
- metabolic disorders (changes to lipid and sugar levels in your blood);
- changes in bone mineral density (thinning bones);
- allergic reactions (symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue); and,
- if you are also infected with hepatitis B, flare-ups of this infection may occur.

This list of risks and discomforts may be incomplete, and does not include risks and discomforts that we do not yet know about.

At every visit, tests will be done to carefully monitor you. The study **clinician** will ask you about any side effects you have experienced. If you have any problems, you should let the **study clinician** know right away.

The blood draws needed for the lab tests may cause discomfort, bleeding, or bruising where the needle enters the body. A small clot may form and there may be some swelling where the needle enters the vein. There is a small risk of minor infection occurring at the blood draw site. In rare cases, lightheadedness and fainting may occur.

Collection of the rectal swab samples require that a small cotton swab be inserted into the anus. This may cause some discomfort. If you prefer, instead of the study staff collecting it, you may collect it yourself.

It is possible that providing a hair sample may briefly affect the appearance of your hair. However, the amount of hair collected is small and study staff has been trained to collect the hair in a way that has the least effect on the appearance of your hair. **If there is not enough scalp hair, facial hair or hair from the under arm, leg/arm, or chest may be collected.**

The amount of radiation you will be exposed to during DXA scanning is rather small. Such doses of radiation may be potentially harmful, but the risks are so small that they are difficult to measure. If you have already had many x-rays, you should discuss this with the study staff before agreeing to be in the study.

In addition, there is some risk that answering questions about some of the topics may be uncomfortable or upsetting. If it is, there are counselors at (*insert ATN site's location*) with whom you can talk. You do not have to answer any questions in the ACASI that you do not want to answer. You may stop at any point if you do not wish to continue with the interview.

We will make every effort to protect your confidentiality, but there is a small possibility that your name and test results could become known to others.

Include for only sites doing 3MV: By taking part in the group sessions, you will be discussing sexual behavior in a group so the group may know your sexual orientation. Each participant will be asked not to discuss what is stated during the group sessions with others outside the group, but we cannot promise that everyone will keep the information confidential (private).

WHAT ARE THE BENEFITS IN TAKING PART IN THIS STUDY?

You will receive laboratory results from tests for HIV and other STIs. The behavioral intervention you will take part in has been shown to help reduce risks for HIV infection. You will also receive counseling and condoms at every visit to help reduce your risk for HIV and other STIs. Additionally, some studies have shown that PrEP does reduce the risk of HIV infection in MSM especially in those who most closely follow taking the medications as told. Finally, the information learned from this study will help the study staff in learning about acceptability of PrEP among youth and in developing acceptable and possible PrEP studies for the YMSM community.

ARE THERE ANY COSTS TO ME FOR TAKING PART IN THIS STUDY?

You will not be charged for anything we do that is part of this study. You will not be charged for the study visits, the physical exams, and laboratory tests done in this study and the PrEP drug. You or your insurance company will have to pay for any medical care that is not part of this study.

WHAT ARE THE ALTERNATIVES TO TAKING PART IN THIS STUDY (WHAT OTHER CHOICES DO I HAVE)?

You may choose not to join this study or stop taking part in this study at any time. It will not change your regular health care benefits. Nor will it change your ability to be in other studies in the future or to get services from (*insert ATN site's location*). There may be other studies going on here or in the hospital that you may be eligible for. If you wish, we will tell you about other studies that we know about. Please talk to the study staff about these and other choices that may be available to you. You will be told about actions that can be taken to avoid becoming HIV infected. The FDA recently approved Truvada® for the prevention of HIV, so you may also speak with your doctor about prescribing this for you.

WHAT WILL HAPPEN WITH THE SAMPLES COLLECTED FROM ME?

- Any blood, urine or hair samples that remain at the end of the study after all study-specified analyses are done will be destroyed.
- If you are shown to have become HIV infected, genetic testing of the virus will be done using some of the blood that was collected to test medications levels in your body. This testing will be completed within three years after the end of the study.

WILL I BE TOLD OF THE RESULTS OF MY TESTS?

There will be local (**routine**) laboratory tests and research laboratory tests done in this study. **You will receive your results from the HIV and STI testing that is done in this study.** You will not receive results of research laboratory tests done specifically for this study. We will be monitoring your health while you are on this study and if there are test results that show you should stop taking the PrEP drug, TDF/FTC (Truvada®), or if there are other concerns, you will be informed right away.

WILL I BE TOLD IF THERE ARE NEW FINDINGS?

You will be told of any new information learned during the course of the study that might cause you to change your mind about being in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

ARE THERE ANY REASONS WHY I MAY BE ASKED TO STOP TAKING PART IN THE STUDY?

Although you may choose to stop taking part in this study at any time, the following are reasons your study doctor may have to stop your participation in the study without your permission:

- You are unable to complete the Week 0 Visit within 30 days after completing the Screening Visit **and are also unable to complete a Re-screening visit.**
- **You complete a Re-screening visit, but do not complete the Week 0 visit within 30 days after that visit.**
- You are unable to attend the study visits as scheduled or complete study evaluations as required.
- Your doctor decides that continuing on the study would be harmful to you
- You develop a health problem and needs treatment that would interfere with the study.
- You become very upset or angry during an interview.
- You become detained or are sent to prison.
- The study is stopped by the National Institutes of Health (NIH), the government agency sponsoring this study, the FDA or by the site's Institutional Review Board (IRB). An IRB is a committee that watches over the safety and rights of research participants.
- The study has to be stopped for other administrative reasons.

ARE THERE ANY REASONS WHY I MAY BE ASKED TO STOP TAKING THE PrEP DRUG?

The following are reasons why your study doctor may ask you to stop taking the PrEP drug:

- You experience side effects from taking the PrEP drug and your doctor decides that continuing to take the PrEP drug would be harmful to you;
- You experience vomiting or diarrhea from taking the PrEP drug;
- You begin taking a medication that is not allowed while you are on the study;
- You become HIV infected;
- You become infected with hepatitis B;
- You develop acute hepatitis B infection; or
- You have a new illness that, in the opinion of your doctor, requires you to stop taking the PrEP drug.

Even if you stop taking the PrEP drug, you will still continue with your study visits, unless you want to stop taking part in the study.

WHAT WILL I GET FOR TAKING PART IN THIS STUDY?

You (will/will not) be given money for your time. Food (will/will not) be provided. Transportation costs will be paid. *(Insert site-specific details of compensation.)*

HOW WILL MY PRIVACY BE PROTECTED?

Your participation in this study will be kept confidential (private) as allowed by law. This includes the information you provided on the ACASI and your lab test results. You will be assigned a special code number that will be used only for this study on the ACASI, your blood and urine samples **that are tested in the special study laboratories**, and all study forms. **Any other samples that are collected from you and tested in our local hospital laboratory will only have your name, not your assigned study code.** The list that links your name with the special code number will be kept in a locked cabinet in a locked room at the clinic. Study staff involved in this study **are** required to sign a form stating that they will protect your information.

Your information from the study will be coded and stored at the ATN Data and Operations Center (DOC) in Rockville, MD. The ATN DOC will provide the study staff with limited coded information for analysis. Information about the study may be published in a scientific magazine, presented at a scientific meeting, or used by other researchers, but names or other personal information will never be used.

Every effort will be made to keep your participation and the personal information of your research record private and confidential, but absolute confidentiality cannot be guaranteed. For example, if we learn something that would immediately put you or others in danger, the study staff is required by law to take steps to keep you and others safe. This means that we have to report to the authorities (hospital, police, or social services) any information you tell us that suggests that you might be in danger such as if you tell us that you plan to hurt or kill yourself, hurt or kill someone else, or if you tell us that someone is abusing or neglecting you. This includes reporting infectious diseases to health authorities as required by local law.

Also, if you are injured as a result of being in this research study, the cost of treatment will be charged to your insurance company. In such a situation it is possible that your parents or legal guardian may find out about your participation in this study.

In addition, your records may be reviewed, under rules of the Federal Privacy Act, by the Food and Drug Administration, the sponsoring agency at the National Institutes of Health (NIH), staff at the ATN DOC acting on behalf of NIH and by *(name of IRB)* to make sure that the study staff are doing what they are supposed to and you and others in the study are protected. If your study records are reviewed, your identity could become known to them. By signing this form, you are allowing such access.

To help further protect your privacy, the ATN has obtained a Confidentiality Certificate from the U.S. Department of Health and Human Services (DHHS). With this Certificate in place, the study staff cannot be forced (for example by court subpoena) to turn over research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings. However, as mentioned above, your record may be reviewed by the NIH to make sure that the study is being conducted the way it is supposed to.

You should understand that a Confidentiality Certificate does not prevent you from giving information about your involvement in this research if you want to. This means that if someone (like an insurer or employer) finds out about your laboratory samples or research information, asks you for it and you say it is okay for them to have it, then the study staff here cannot use the Certificate to keep your information private. Your research information would have to be given to them. This means that you must also

protect your own privacy. You have to be careful about who you allow to look at your research information.

A description of this clinical trial (study) will be available on <http://clinicaltrials.gov>, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can access this Website at any time.

WHAT HAPPENS IF I AM INJURED?

If you are injured from being in this research study, you will receive immediate, short-term treatment as determined by (*name of hospital*) for the injury. The cost of the treatment will be charged to you or your insurance company, as would normally be done for your medical care. You will then be told where you could receive additional treatment for injuries. Your insurance carrier may or may not pay for treatments for injuries that are caused by taking part in this study. No monetary compensation (payment to you) or other forms of compensation for such injuries will be provided by the hospital or sponsoring agency.

WHAT IF I WANT TO STOP TAKING PART IN THIS STUDY?

Taking part in this study is completely voluntary. You may choose not to take part in this study or may leave this study at any time or for any reason without penalty or loss of benefits. You will be treated the same no matter what you decide. Information and laboratory samples collected from you prior to you deciding to stop taking part in the study may be used in the study analysis.

If you are thinking of or if you have already decided to stop taking part in the study, you should tell the study doctor or nurse at the clinic and they can explain to you how to do it in a safe way. If you stop taking the PrEP drug, you can still come to your study visits for HIV testing and continued to be followed.

WHO DO I CONTACT IF I HAVE PROBLEMS OR QUESTIONS ABOUT THE STUDY?

The doctor in charge of this study at (*name of hospital*) is Dr. (*name of PI*). The study nurse is (*name of study coordinator*). You may call them at (*telephone number*) if you ever have questions about this study or in case of research-related injuries. In addition, if you have any questions about your rights as a study participant, you may call (*IRB contact person name and title*) at the (*name of hospital's*) Institutional Review Board at (*telephone number*).

STATEMENT OF CONSENT

The purpose of this research study, what you will be asked to do, and the risks and benefits of the study have been explained to you. You have been given the time to ask any questions you might have about this study. You have been told that participation in this study is voluntary. You may be a participant in it only if you wish, and you may refuse to take part or may stop taking part in the study at any time without in any way compromising your future treatment at this hospital/clinic, or your future relations with the hospital or its employees.

(NOTE: This is only a suggested signature format. Sites may use their own signature page.)

By signing this consent document, you are agreeing to take part in the study described to you. You will be given a copy of this signed consent form to keep.

Participant's Name (print)

Participant's Signature

Date

Principal Investigator (PI) or Designee's statement:

I have reviewed this study and the consent form with the participant. To the best of my knowledge, the participant understands the purpose, procedures, risks, and benefits of the study.

PI or Designee's Name (print)

PI or Designee's Signature

Date

NOTE: This consent form with the original signatures MUST be retained on file by the principal investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record, if applicable.

**APPENDIX XX: SAMPLE ADDENDUM TO SAMPLE INFORMED CONSENT FOR
STUDY PARTICIPANTS (NEW)**

ADOLESCENT TRIALS NETWORK

REMINDER TO STUDY SITES: Do not use the preamble in local consents.

**NOTE FROM THE OFFICE OF HUMAN RESEARCH PROTECTION (OHRP) TO SITES
ENROLLING PARTICIPANTS IN THIS STUDY:**

Please note that this sample language does not preempt or replace local IRB review and approval. Investigators are required to provide the local IRB with a copy of this sample language along with the language intended for local use. Local IRBs are required to weigh the unique risks, constraints, and population considerations as a condition of any approval. Any deletion or substantive change of information concerning risks or alternative treatment must be justified by the investigator, approved by the local IRB, and noted in the IRB minutes. Justification and IRB approval of such changes must be forwarded to Westat, the ATN DOC, for any NICHD-sponsored trial, or as may be otherwise specified. Sponsor-approved changes in a protocol must be approved by the local IRB before use unless intended for the elimination of apparent immediate hazard. New information shall be shared with existing participants at next encounter, with all new participants prior to involvement, or as the local IRB may otherwise additionally require.

TITLE OF STUDY:

ATN 113

**Project PrEPare – An Open Label Demonstration Project and Phase II Safety Study of Pre-
Exposure Prophylaxis Use among 15 to 17 Year Old Young Men Who Have Sex with Men (YMSM)
in the United States**

Principal Investigator: _____

Telephone Number: _____

INTRODUCTION

You have been participating in ATN 113, the PrEP Study. The informed consent you previously signed is current and valid, but there is some new information we would like to share with you. Once we review the new information and all of your questions have been answered, you will be asked to sign this addendum if you want to continue participating in the study. You will be given a signed copy of this addendum to keep.

HOW WILL MY STUDY VISITS CHANGE?

At every visit:

You will be asked about recent activities that may have placed you at a high risk for exposure to HIV. The study clinician may recommend that you start PEP if he or she thinks that you were at high risk of exposure to HIV in the previous 72 hours.

At the Weeks 24 and 48 visits:

The amount of blood that will be drawn at the Weeks 24 and 48 visits for tests to see how well you are taking the PrEP drug will decrease from about 3 teaspoons to about one teaspoon.

If you have not yet completed the Week 0 visit:

If you are unable to complete the Week 0 visit within 30 days after the Screening visit, you will need to complete a Re-screening visit before you move on to the Week 0 visit. This is to make sure that you are still eligible and it is safe for you to take the PrEP drug, Truvada. The Re-screening visit will take about an hour to complete. You will repeat many of the same tests and procedures that were done at the Screening and Baseline visits, with the following exceptions:

- Hepatitis B testing will only be done only if the test done at the Baseline visit showed that you were not protected against this virus.
- Depending on how you are feeling and whether you have any symptoms or complaints, blood may be collected to test for syphilis, and urine and/or a rectal swab sample may be collected to test for gonorrhea and chlamydia.
- A Dual-energy X-ray Absorptiometry (DXA) scan will be done only if 90 days (about 3 months) or more has passed since your baseline DXA scan was done.

You will be asked about recent activities that may have placed you at a high risk for exposure to HIV. The study clinician may recommend that you start PEP if he or she thinks that you were at high risk of exposure to HIV in the previous 72 hours.

If the study staff have concerns about your lab results:

While you are on the study, the study staff may ask you to return to repeat some lab tests if they have concerns about your lab results. If the study staff have any concerns about whether it is safe for you to continue taking the PrEP drug, they may “hold” the PrEP drug or provide a limited supply until additional tests are done.

If you permanently stop taking the PrEP drug for any reason:

If you permanently stop taking the PrEP drug for any reason, you will continue to be seen for your follow-up study visits, unless you want to stop being in the study altogether. The first study visit that is done after you stop taking the PrEP drug will be exactly the same as the follow-up visits described above. All follow-up study visits after that will be similar to the follow-up visits described above, except for the following differences: 1) blood and hair to test PrEP drug levels in your body will not be collected; 2) the ACASI will not include questions on how you take the PrEP drug; and 3) PrEP drug will not be given to you at the end of the visits.

If you stop participating in the study:

If you stop participating in the study after the Week 0 visit (after starting PrEP), but before the Week 48 visit, you will be asked to return to complete one final study visit. The evaluations scheduled at the Week 48 visit will be done at this visit.

If you stop participating in the study before you start taking the PrEP drug, you will not be asked to return for a study visit.

If there is not enough hair on your head for the hair sample collection:

There are study visits where a small hair sample will be taken from the hair on your head. If there is not enough hair on your head, a small sample of hair may be taken from your face, underarm, leg, arm or chest instead.

ARE THERE ANY CHANGES IN THE RISKS IN TAKING PART IN THIS STUDY?

Taking Truvada for PrEP cannot guarantee that you will not get infected with HIV. If you become HIV infected while taking PrEP, the drug may not be able to fight as well against the HIV in your body. This is called drug resistance. If the HIV virus that you are infected with becomes resistant to Truvada, you may not be able to use it as part of your treatment for HIV infection. Although studies have shown that PrEP does reduce the risk of HIV infection, especially in those who follow the prescription directions closely, it does not protect everyone.

You can lessen the chance of resistance to Truvada. Take the drug every day as prescribed and use other ways to lower your risk for getting HIV, such as consistent and correct condom use. Also tell the study staff of any flu-like symptoms that may suggest that you recently became infected with HIV. These symptoms include fever, headache, joint pain, muscle pain, throat pain, vomiting, diarrhea, rash, night sweats and swollen glands.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT CONTINUED PARTICIPATION IN THIS STUDY OR MY RIGHTS AS A RESEARCH SUBJECT?

The doctor in charge of this study at (*name of hospital*) is Dr. (*name of PI*). The study nurse is (*name of study coordinator*). You may call them at (*telephone number*) if you ever have questions about this study or in case of research-related injuries. In addition, if you have any questions about your rights as a study participant, you may call (*IRB contact person name and title*) at the (*name of hospital's*) Institutional Review Board at (*telephone number*).

STATEMENT OF CONSENT

The new information in this addendum has been explained to you. You have been given the time to ask any questions you might have about continuing participation in this study. Your continued participation in this study is voluntary. You may refuse to take part or may stop taking part in the study at any time without in any way compromising your future treatment at this hospital/clinic, or your future relations with the hospital or its employees.

(NOTE: This is only a suggested signature format. Sites may use their own signature page.)

By signing this consent document, you are agreeing to continue your participation in the study.

| | | |
|----------------------------|-------------------------|-------|
| _____ | _____ | _____ |
| Participant's Name (print) | Participant's Signature | Date |

Principal Investigator (PI) or Designee's statement:

I have reviewed the new information in this addendum with the participant. To the best of my knowledge, the participant understands the purpose, procedures, risks, and benefits of the study.

| | | |
|-------------------------------|----------------------------|-------|
| _____ | _____ | _____ |
| PI or Designee's Name (print) | PI or Designee's Signature | Date |

NOTE: This addendum form with the original signatures **MUST** be retained on file by the principal investigator. A copy must be given to the participant. A copy should be placed in the participant's medical record, if applicable.