

HPTN 082

**Uptake and adherence to daily oral PrEP as a primary prevention strategy for young
African women: A Vanguard Study**

A Study of the HIV Prevention Trials Network (HPTN)

Sponsored by:

Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious
Diseases (NIAID)
US National Institute of Mental Health (NIMH)
US National Institutes of Health (NIH)

Non-IND Study

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LIST OF ABBREVIATIONS AND ACRONYMS

ADAPT	Alternative Dosing to Augment PrEP Pill Taking/HPTN 067 Study
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ATN	Adolescent Trial Network
CAB	Community Advisory Board
CASI	Computer assisted self-interview
CBC	Complete blood count
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence intervals
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximum plasma concentration that a drug achieves after dosing
CMC	Clinical Management Committee
CPQA	Clinical Pharmacology Quality Assurance
CRF	Case Report Form
CRM	Clinical Research Manager
CRPMC	(DAIDS) Clinical Research Products Management Center
CRS	Clinical Research Site
CT	<i>Chlamydia trachomatis</i>
CTA	Clinical trials agreement
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DBS	Dried Blood Spots
DHHS	US Department of Health and Human Services
DNA	Deoxyribonucleic Acid
EAE	Expedited Adverse Event
EC	Ethics Committee
EQA	External Quality Assurance
FACTS	Follow-on African Consortium for Tenofovir Studies
FDA	(United States) Food and Drug Administration
FTC/TDF	Emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF); Truvada®
GBV	Gender Based Violence
GC	<i>Neisseria gonorrhoeae</i>
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
HBV	Hepatitis B virus
HepBsAg	Hepatitis B surface antigen
HepBsAb	Hepatitis B surface antibody
HIV	Human Immunodeficiency Virus
HPRM	HIV Prevention Readiness Measure
HPTN	HIV Prevention Trials Network

HTRM	HIV Treatment Readiness Measure
IATA	International Air Transport Association
IB	Investigator Brochure
ICF	Informed consent form
IND	Investigational New Drug
INR	International normalized ratio
IoR	Investigator of Record
iPrEx OLE	(iPrEx) Open Label Extension
IQA	(DAIDS) Immunology Quality Assurance
IQR	Interquartile range
IRB	Institutional Review Board
ITT	Intention to treat
IUD	Intrauterine device
LC	(HPTN) Laboratory Center
LDMS	Laboratory Data Management System
LL	Local laboratory
LOC	Leadership and Operations Center
MSM	Men who have sex with men
MTN	Microbicides Trial Network
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
PBM	PrEP Beliefs Measure
PEP	Post Exposure Prophylaxis
PK	Pharmacokinetics
PMTCT	Prevention of Mother-to-Child Transmission
PrEP	Pre Exposure Prophylaxis
PRO	Protocol Registration Office
pSMILE	Patient Safety Monitoring and International Laboratory Evaluation
RE	Regulatory entity
RHI	(Wits) Reproductive Health and HIV Institute
RNA	Ribonucleic acid
ROC	Receiver Operating Characteristic
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SDMC	(HPTN) Statistical and Data Management Center
SMC	Study Monitoring Committee
SMS	short message service
SOC	standard-of-care
SOP	Standard Operating Procedures
SSP	Study Specific Procedures
STI	Sexually transmitted infection
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TDF-DP	Tenofovir disoproxil fumarate diphosphate
TFV	Tenofovir
TV	<i>Trichomonas vaginalis</i>
UK NEQAS	United Kingdom National External Quality Assessment Service
UK	United Kingdom
US	United States
VOICE	Vaginal and Oral Interventions to Control the Epidemic (Trial)
VQA	(DAIDS) Virology Quality Assurance

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US National Institute of Mental Health (NIMH)

US National Institutes of Health (NIH)

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

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Site Investigator of Record

Signature of Site Investigator of Record

Date

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Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study SCHEMA

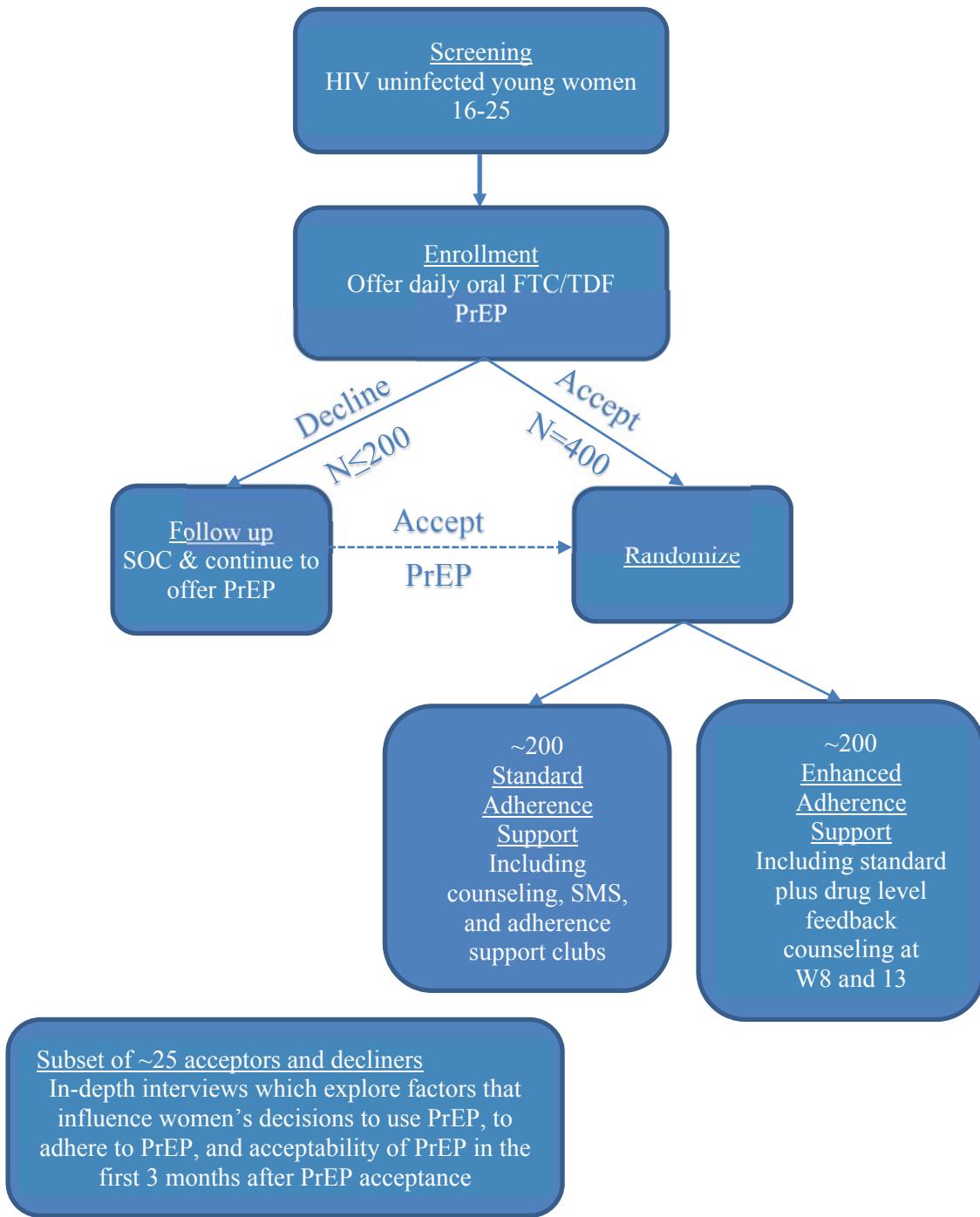
Purpose:	To assess the acceptance rate, adherence, acceptability, and continuation of oral pre-exposure prophylaxis (PrEP) among young southern African women.
Design:	A Phase IV randomized multi-site prospective study to assess PrEP acceptance and adherence among HIV-uninfected young women. All women who accept open-label daily oral PrEP will be randomized 1:1 to receive enhanced adherence counselling based on feedback from observed drug levels or standard adherence support. A subset of up to ~25 women per site (maximum 75), will participate in qualitative assessments of facilitators and barriers for PrEP acceptance, adherence and continuation.
Study Population:	HIV-uninfected women ages 16-25.
Study Size:	400 young women who accept PrEP at enrollment and up to 200 young women who decline PrEP at enrollment.
PrEP Regimen:	All participants will be offered once daily oral emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (FTC/TDF).
Study Duration:	Approximately 24 months, including submissions to Institutional Review Boards (IRBs) and national drug regulatory authorities, recruitment, and 12 months of follow-up per participant.
Primary Objectives:	<ul style="list-style-type: none">• To assess the proportion and characteristics of young HIV-uninfected women who accept versus decline PrEP at enrollment.• To assess the difference in PrEP adherence using drug levels in young women randomized to the enhanced versus standard arms.
Secondary Objectives:	<ul style="list-style-type: none">• To assess the timing of PrEP acceptance among women who initially decline PrEP at enrollment but elect to accept PrEP during follow up.• To assess correlates of early and delayed acceptance of PrEP, including sociodemographic factors, individual-level and partner-level characteristics, and risk practices.• To assess correlates of PrEP adherence at Weeks 13, 26, and 52, after adjusting for study arm, such as adherence at prior study visits, sociodemographic factors, individual-level and partner-level characteristics, exposure to study-based adherence support, and risk practices.• To assess the proportion of young women who discontinue PrEP, timing of discontinuation, and factors associated with PrEP discontinuation.• To assess the specificity and predictive value of a PrEP readiness tool [based on the HIV Prevention Readiness Measure (HPRM) and PrEP Beliefs Measure (PBM)] to predict uptake and adherence to oral PrEP.• To explore qualitative factors that influence women's decisions to use PrEP, to adhere to PrEP, and acceptability of PrEP in the first 3 months after PrEP acceptance.• To compare adverse events between young women taking PrEP and young women who are not taking PrEP.• To assess HIV incidence in those who accept PrEP compared to those who do not, and to assess the association with detectable TFV in PrEP users who acquire HIV infection during the study.
Exploratory Objectives:	<ul style="list-style-type: none">• To determine the uptake and continuation of modern contraceptive methods, and the association of contraception use with PrEP uptake and adherence.

	<ul style="list-style-type: none"> • To describe antiretroviral (ARV) drug resistance among women who acquire HIV infection. • To estimate the potential impact of PrEP use on HIV acquisition in young African women through mathematical modeling. • To perform exploratory laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or sexually transmitted infections (STIs); ARV drug use; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives.
Study Sites:	Spilhaus Clinical Research Site in Harare, Zimbabwe, the Emavundleni Research Centre in Cape Town, South Africa and Wits Reproductive Health and HIV Institute (RHI) in Johannesburg, South Africa.

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OVERVIEW OF STUDY DESIGN



1.0 INTRODUCTION

1.1. Background and Prior Research

Young African women (15-24) are an important population for PrEP implementation, representing three of the four million young people living with HIV in subSaharan Africa, and with high annual HIV incidence rates of 5-6% in recent HIV prevention trials, in the context of monthly risk reduction counseling, treatment of sexually transmitted infections (STIs), and provision of condoms.^{1,2} The rationale for PrEP being the core biomedical intervention for this population is that the highest efficacy for primary HIV prevention strategies has been observed with daily oral PrEP, when adherence is high. Four of six daily oral PrEP trials have demonstrated efficacy among HIV serodiscordant couples from Kenya and Uganda, young men and women in Botswana, men who have sex with men (MSM) in a multi-country trial, and injection drug users in Thailand.³⁻⁶ Efficacy of daily oral tenofovir disoproxil fumarate (TDF) or TDF co-formulated with emtricitabine (FTC) (FTC/TDF) ranged from 44% to 75%, and was strongly related to adherence, which ranged from 52% to 82% based on plasma tenofovir (TFV) testing in a subset of participants.³⁻⁶ In the active arms of these trials, the presence of TFV in plasma was estimated to provide 85-92% protection against HIV acquisition; pharmacokinetic (PK) modeling indicates that plasma TFV levels >10 ng/mL were highly associated with efficacy.⁷ Efficacy of daily oral PrEP among young African women was high in the Botswana TDF-2 study (although with limited power for gender sub-analysis)⁶ and in the Partners PrEP Study, in all women, women <30 years old, and all subgroups of women.⁸ In the FEM-PrEP and Vaginal and Oral Interventions to Control the Epidemic (VOICE) trials which enrolled young African women, overall adherence was too low to observe efficacy, with TFV detected in ~30% of plasma samples; however, a subset of women showed consistent adherence to PrEP based on longitudinal TFV detection in plasma.^{1,2,9} In the VOICE trial, overall HIV incidence was 6% and risk factors that predicted HIV acquisition, including age <25 years, also predicted lower risk of TFV detection.¹⁰

The differential uptake and sustained use of PrEP in the populations enrolled in these placebo-controlled efficacy trials in part reflects several factors, including: population differences in terms of levels of uncertainty about risk for HIV infection; ambivalence about using antiretroviral (ARV) drugs for HIV prevention; concerns about side effects; stigma; reactions of others; partner support; disclosure of study participation, and special concerns related to participating in a placebo-controlled trial (e.g., concerns about randomization to placebo or a product of uncertain efficacy, motivation to obtain access to health care and other services rather than testing candidate products).¹¹⁻¹³ Notably, randomized clinical trials (RCTs) of microbicides and oral PrEP differ substantially from real-world settings, as participants may be motivated to take part in HIV prevention trials for a variety of reasons, including access to quality health services and monetary reimbursement for study visits. Trial participants are also reminded on a monthly basis that they may be in a placebo arm and not receiving active product, and that the active product has not been determined to be effective—all factors that may influence adherence behavior. Qualitative data from FEM-PrEP participants who acquired HIV infection indicate that these young women underestimated their risk, and rationalized their risk behavior; quantitative analyses indicated that perceived risk of HIV was associated with improved PrEP adherence.¹⁴ Qualitative data from a subset of VOICE participants in the VOICE C sub-study indicated that individual, social, and structural factors were barriers to PrEP use.¹³ Use of pictorial feedback of TFV drug levels in the VOICE D sub-study indicated that a pictorial tool was an effective way to provide semi-quantitative feedback about drug levels, and facilitated discussion of drug adherence patterns and behaviors.¹⁵

PrEP uptake and adherence among participants in RCTs who are randomized to placebo or active product and are counseled about unknown product efficacy may not predict PrEP uptake and adherence among at risk participants who are offered open-label product and counseled about known efficacy of

the product and the importance of adherence to achieve protection. Encouragingly, a study of daily oral PrEP among MSM in the United Kingdom (UK) indicated high effectiveness among the immediate PrEP arm,¹⁶ this was also seen using intermittent, event-driven dosing of oral FTC/TDF when compared to the placebo arm in a study conducted in France and Canada.¹⁷ These studies indicate that adherence to oral PrEP among MSM who have self-identified as being at high risk of acquiring HIV, is high in the context of known efficacy when delivered in clinical settings provided by non-research staff with quarterly visits and brief adherence counseling. The Partners Demonstration Project is an ongoing, open-label, demonstration project among African heterosexual HIV serodiscordant couples that is evaluating daily oral PrEP in HIV-uninfected individuals as a bridge to ART initiation among their HIV-infected partners. An empirically-derived risk score was used to recruit 1,013 research-naïve high-risk couples,¹⁸ 20% of whom are <25 years old. Notably, PrEP uptake was high (95% at enrollment), PrEP adherence was high (86% with detectable TFV), ART initiation was high (80% by 12 months with 90% viral suppression), and HIV incidence was reduced by 96% compared to a counterfactual HIV incidence.¹⁹

These demonstration projects indicate that persons at-risk are motivated to use PrEP when counseled about efficacy and are able to use PrEP effectively, achieving higher effectiveness than has been observed in placebo-controlled trials. However, as PrEP demonstration projects are being conducted in other populations, there remains a gap in how to deliver PrEP to young African women with a focus on maximizing adherence. Encouragingly, PrEP adherence was high among African women in the context of open label use in the Cape Town site in HPTN 067/ADAPT study of varying PrEP dosing strategies, where half of the participants were ≤25 years; adherence was highest in the daily dosing arm (92.5% of women at week 10, 79.3% at week 30 who had reported sex in the week prior had detectable tenofovir in plasma).²⁰ Most recently, data from the TDF2 open label PrEP study found that 87% of women enrolled in the study had detectable drug in plasma over time. Also encouraging was the statistically significant association ($p<.001$) between self-reported adherence and drug detection.²¹

PrEP is an important prevention method that must be evaluated for its utility in young African women. The hypothesis that PrEP is biologically ineffective in women has been proven false, and additional studies are needed to determine the characteristics of women who choose to use PrEP, their adherence levels, and strategies to support PrEP adherence, in the context of known PrEP efficacy. Notably, the qualitative research through the VOICE C and D protocols did not indicate that women were rejecting biomedical HIV prevention, but that they encountered barriers to use and desired more direct feedback on adherence.¹³ Oral PrEP has the potential to significantly reduce HIV incidence among young African women, if delivered with clear information about its efficacy and the importance of high-level adherence; counseling and risk assessments to determine women's perceived risks and benefits of PrEP; and tailored cognitive behavioral counseling with SMS reminders adapted to this specific population.

The impact will be greatest if the subset of young women who are at highest risk of HIV infection are motivated to use PrEP, and are able to establish daily pill-taking habits and sustain high adherence, while they remain at risk. A risk score for HIV incidence was developed based on data from the VOICE trial that has high predictive ability, which includes age <25, not married or living with a primary partner, partner providing financial or material support, primary partner with other partners, curable STIs, and alcohol use.²² The risk score from VOICE could identify young African women with the highest risk of HIV acquisition in the next year, and will be adapted for use in HPTN 082 to determine eligibility at Screening.

1.2. Rationale

1.2.1. PrEP adherence support for young African women

The goal of this study is to evaluate whether HIV-uninfected sub-Saharan African women ages 16-25 who are at high risk for HIV infection will accept PrEP and achieve sufficient adherence using scalable adherence support interventions to achieve HIV prevention benefits from this promising biomedical prevention intervention. The objective is to offer oral PrEP to a subset of sexually-active young women in high HIV prevalence and incidence settings who perceive themselves to be at risk of HIV infection and are motivated to use daily oral PrEP to reduce their risk. Women who recognize their risk may be more highly motivated, although young women may not always accurately perceive risk. Accordingly, we will counsel women about their risks of HIV infection based on the risk factors that were identified from analyses of seroconverters in the VOICE study.²² Women may be more motivated to use PrEP if they are not able to use other prevention modalities (e.g., inability to negotiate condoms in relationships with unequal power, fear of violence, relationship dissolution, or other factors). Daily oral PrEP is the regimen selected for HPTN 082 because there is insufficient evidence to support intermittent oral PrEP use in women,²⁰ and because PK data indicate that levels of TFV and FTC are lower in vaginal than rectal tissue.²³

Oral PrEP has the potential for significant reduction in HIV incidence among young African women, if young women are motivated to initiate PrEP in the context of known efficacy, and if their adherence is high, particularly during periods when they are at highest risk. The population-level impact will be significant if young women who are at highest risk of HIV are motivated to use PrEP and are able to establish daily pill-taking habits and sustain high adherence while they remain at risk.

Ultimately, young women may benefit from a choice of PrEP formulations, similar to contraceptive choices, including longer-acting vaginal rings and injectable formulations. While awaiting efficacy data on longer-acting formulations, it is important to assess young African women's uptake and adherence to daily oral PrEP, as well as motivators and barriers to use, some of which may also be relevant to their use of longer-acting PrEP formulations in the future, when those products are available.

1.2.2. Adherence to open-label PrEP

Randomized, placebo-controlled PrEP efficacy trials have demonstrated that adherence to PrEP is crucial for protection against HIV infection, and that many participants struggled to use product daily. PrEP adherence in the VOICE trial was negatively associated with age <25 years.² However, it is important to note that adherence to oral PrEP may be higher when participants are counseled about its known efficacy, as has been observed in demonstration projects among MSM from the iPrEx Open Label Extension (OLE), with greater PrEP use observed during periods of higher HIV risk (e.g., among men reporting condomless receptive anal sex), and no evidence of risk compensation.²⁴ Data from the US MSM Demo Project show high rates of adherence with 75-85% of participants achieving protective levels of PrEP in dried blood spots at any given study visit.^{25,26} The Proud Study among MSM offered PrEP in STI clinics in the UK showed high levels of TFV detection in the subset tested, and importantly showed an 86% reduction in HIV incidence in the immediate PrEP arm.¹⁶ High adherence to PrEP (83%) and effectiveness (96% reduction in HIV transmission) were demonstrated in the Partners Demonstration Project with open-label oral PrEP among research-naïve, high-risk HIV serodiscordant couples in Kenya and Uganda, who were seen quarterly and received brief adherence counseling.²⁷ Relevant to the HPTN 082 study population of young southern African women, adherence to open label daily oral PrEP was high among young women in the Cape Town site of the HPTN 067/ADAPT study with detectable tenofovir among 92.5% at week 10 and 79.3% at week 30 among women assigned to the daily arm who had reported sex in the prior week; notably, PrEP coverage was achieved for 75% of sex acts for women assigned to daily PrEP.²⁰

Among young women who enrolled in the VOICE and FEM-PrEP trials, problems with product use included: failure to initiate PrEP use; difficulty with forming habits of daily pill-taking; and failure of sustained use in the face of other social, environmental, and cognitive demands. We hypothesize that younger women may have greater adherence challenges with daily pill-taking than older women. There may be a biologic basis for adherence challenges in younger persons; neurocognitive research shows that cognitive development continues through adolescence and into the early 20s.²⁸ Studies of medication adherence among adolescents with a range of chronic illnesses, primarily conducted in the United States (US), have shown rates of medication adherence ranging from 20-60%.²⁹⁻³² Although treatment adherence may differ from preventive adherence, a recent global meta-analysis of ARV treatment (ART) adherence in HIV-infected youth found that adherence was highest among youth in Africa and Asia (84%) and lowest in North America (53%), and Europe (62%).³³ Psychological difficulties and/or social barriers are often significant predictors of non-adherence among youth living with chronic illness. Young people in sub-Saharan Africa often suffer from trauma, depression, gender-based violence (GBV), and lack of social support,³⁴⁻³⁹ all of which have been linked to poor ART adherence.⁴⁰⁻⁴³ Depression and anxiety have been associated with non-adherence to medications in a range of illnesses, including HIV disease.⁴⁴⁻⁴⁶ Lower rates of adherence to oral contraceptives have been observed among adolescent and young adult women at high risk of unintended pregnancy.⁴⁷⁻⁴⁹ Thus, biomedical prevention adherence interventions for adolescents and young adults require careful attention to developmental issues,⁵⁰ including social and sexual relationships, future planning skills, as well as broader contextual issues such as caregiver support, peer relations, and the effects of context on mental health, including depression,⁵¹ past trauma, and GBV.⁵²

Scalable interventions to support adherence in HPTN 082 will be brief counseling sessions based on cognitive behavioral therapy (CBT) approaches, two-way SMS, and peer support-based adherence clubs, which are described below. Data from the phase III PrEP trials (i.e., iPrEx, Partners PrEP, and VOICE) indicate that adherence at early time points (i.e., TFV-diphosphate [TFV-DP] levels in dried blood spots [DBS] or TFV in plasma) predicted adherence over the next 1-2 years.^{10,24,53} Thus, randomization will be used to assess an intervention based on feedback from drug levels occurring promptly after acceptance of PrEP that will improve and solidify PrEP adherence habits.

Recent meta-analyses highlight that cognitive-behavioral problem-solving,^{54,55} and peer support⁵⁶ consistently improve medication adherence among adults in the US and developing countries. CBT is grounded in social cognitive learning theory, which posits that human behavior is based, in part, on previous learning, especially the learning of social and interpersonal behavior and of central or core thoughts and beliefs.⁵⁷ These learning experiences are based on operant conditioning processes, classical conditioning processes, social reinforcement, and observation and modeling of significant others. CBT is one of the most extensively researched forms of psychotherapy.⁵⁸ Cognitive behavioral approaches have been used to treat youth depression⁵⁹ and trauma,⁶⁰ improve adult and youth ART adherence,^{55,61,62} and decrease alcohol use in HIV-infected sub-Saharan African adults.⁶³ CBT is a brief, cost-effective intervention strategy that can be implemented by a wide range of providers, including non-specialists, in both clinical and community-based settings. Research indicates that locally-adapted CBT is feasible, acceptable, and effective in low-resource settings and can be delivered by local staff with little counseling experience.⁶⁴⁻⁶⁷ The South African Department of Health is recommending that primary health care workers be trained in CBT for delivery of brief interventions for substance use and depression, and to support adherence for chronic disease treatment. Thus, our CBT adherence counseling builds on an approach and skills, which will be familiar to southern African health care workers.

The basis for the use of drug level feedback is that women in VOICE qualitative interviews reported a desire for more direct counseling¹⁵. Qualitative findings from the VOICE D sub study indicate that women valued feedback based on drug levels. Given the current cost (approximately \$100 for plasma TFV and \$200 for DBS TFV-DP levels and limited availability of tenofovir drug levels in Africa, it is important to assess whether adherence to oral PrEP is affected by early feedback about drug levels. Point of care urine assays for tenofovir are currently in development.. A randomized assessment of the effect of reported drug levels on adherence in this study will evaluate the potential of this intervention in an important population and region.⁶⁸⁻⁷¹

Two-way text messages are an intervention which is consistent with behavioral models that highlight strengthened communications between patients and providers as a way to improve adherence.⁷² The rapid expansion of access to the internet and social media in the past two decades, even in low and middle income countries, through mobile phone technology, represents a significant opportunity to engage with adolescents. In South Africa, young people have high levels of mobile phone and social media use and there are currently more mobile phone connections in South Africa than people.⁷³ In settings where fixed telephone lines and access to personal computers is limited, mobile phones have become a necessity even among low-income households; in 2014 less than 10% of low-income South African adolescents in one study reported not owning a mobile phone.⁷⁴ The WelTel intervention demonstrated efficacy of weekly text messages asking how patients were doing, with telephone support for side effects and crisis management for participants who responded that they were not doing well.⁷⁵ A recent meta-analysis found that text-messaging can be an effective support for ART adherence, particularly with messaging provided on a less than daily basis, content and timing that is tailored, and platforms designed to evoke a reply from the recipient.⁷⁶ With regard to SMS for preventive behaviors for young women, an RCT in 962 oral contraceptive users showed higher continuation rates at 6 months in those that received daily educational messages by SMS compared to controls, although the effects diminished when the intervention was withdrawn.⁷⁷ Given that some women may benefit from ongoing cognitive reminders, in HPTN 082 women who are taking PrEP will be offered an option to continue weekly SMS reminders after Week 13.

In South Africa, the MAMA program provides information that promotes earlier antenatal care, supports HIV-infected mothers, helps women and caregivers understand how to prevent transmission of HIV to their babies, and encourages healthy household practices during pregnancy and in the baby's first year of life. MAMA South African partners developed four different mobile channels to reach women in a broad range of income groups through a variety of mobile phone technologies that they are already comfortable with and using, including a free SMS program, a dynamic community portal, interactive quiz service and a portal on a popular mobile social network. This program was adopted by the South African National Department of Health and is being taken to scale. The South African Department of Health is planning to launch a youth friendly mobile site using the Young Africa Live service.

In Zambia and Uganda, the U-Report platform has been successfully used to support information sharing, outreach, demand creation and adolescent engagement (on HIV testing and counseling, voluntary male medical circumcision, adolescent sexual and reproductive health services, etc.). U-report is designed to be compatible with very simple mobile phones and operates using simple SMS. It's therefore particularly effective at providing information - to adolescents and from adolescents to providers. "U-Reporters" sign up by sending a simple SMS that then links them to a central server. The U-Reporters then receive regular basic information and polls and their responses go into a central database where responses can be analyzed to customize the basic information that they receive in order to address the knowledge gaps, myths and misconceptions reflected in poll responses. The U-reporters numbers are also linked to geographic location and this has enabled

country programs to get feedback from adolescents and young people on service quality aspects or to get a sense of concerns unique to geographic regions. U-Report can also be used for one-on-one counseling. These systems provide unique opportunities to adapt and test to support PrEP use in young women in sub-Saharan Africa.

Participants will be offered enrollment in adherence support clubs that were pioneered for PrEP adherence in the Follow-on African Consortium for Tenovir Studies (FACTS) 001 trial and were identified spontaneously by participants during in-depth interviews as an important source of adherence support (Delany-Moretlwe, personal communication). In this age group, peer norms play an important role in shaping behaviors.⁷⁸⁻⁸⁰ PrEP adherence clubs have been modeled on the experiences of community-based HIV treatment support groups, which have been widely implemented in South Africa and Mozambique.^{81,82} These clubs were introduced after study initiation after it was indicated in other trials (VOICE, FEM-PrEP, etc.) that individual-level counseling might not be sufficient to encourage adherence. Based on successful ART clubs in South Africa, the notion of the FACTS 001 clubs was to provide a similar forum for peer support outside of the formal clinic environment and to create a space to create a positive group norm around gel use. Participants were encouraged to define activities for the clubs. These activities provided an opportunity to build social bonds and social support. Participants learned from each other and exchanged stories about gel use. In FACTS 001, the clubs provided a forum for trial staff and participants to interact outside of the clinic, and provided a forum for peer-to-peer learning and support. Participant-driven clubs used entertainment, sport, and other activities as a foundation for promoting relationships between staff and participants as well as between participants themselves. Club activities were identified by participants and facilitated by trial staff. Clubs varied in size and comfortably accommodated 20-35 participants. Clubs were monitored and assessed on an on-going basis by trial staff, and lessons learned were shared across sites. These clubs bolstered the standing of the trial sites within the local community, and were found to be feasible and acceptable to trial staff and participants.⁸³ In HPTN 082, a staff member will be present at these clubs to answer questions about PrEP and to facilitate discussions.

In summary, for the HPTN 082 intervention, we will support the formation of effective PrEP adherence habits among all women who accept PrEP through: 1) brief adherence counseling based on CBT for women who accept PrEP at enrollment with monthly visits in the first three months to support adherence habit formation; 2) two-way weekly SMS text messaging to provide cognitive reminders about visits and support for PrEP adherence, using an existing platform for SMS reminders, and 3) peer support through HPTN 082 adherence support clubs;. All of these will be described in more detail in Section 4.3. In addition, we will randomize women in a 1:1 ratio to have counseling about their early plasma TFV levels to assess whether this intervention affects adherence.

2.0 STUDY OBJECTIVES AND DESIGN

2.1. Primary Objective(s)

The primary objectives of this study are:

- To assess the proportion and characteristics of young HIV-uninfected women who accept versus decline PrEP at enrollment.
- To assess the difference in PrEP adherence using drug levels in young women randomized to the enhanced versus standard arms.

2.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the timing of PrEP acceptance among women who initially decline PrEP at enrollment but elect to accept PrEP during follow up.
- To assess correlates of early and delayed *acceptance* of PrEP, including sociodemographic factors, individual-level and partner-level characteristics, and risk practices.
- To assess correlates of PrEP adherence at Weeks 13, 26, and 52, after adjusting for study arm, such as adherence at prior study visits, sociodemographic factors, individual-level and partner-level characteristics, exposure to study-based adherence support, and risk practices.
- To assess the proportion of young women who discontinue PrEP, timing of discontinuation, and factors associated with PrEP discontinuation.
- To assess the specificity and predictive value of a PrEP readiness tool (based on the HPRM and PBM) to predict uptake and adherence to oral PrEP.
- To explore qualitative factors that influence women's decisions to use PrEP, to adhere to PrEP, and acceptability of PrEP in the first 3 months after PrEP acceptance.
- To compare adverse events between young women taking PrEP and young women who are not taking PrEP.
- To assess HIV incidence in those who accept PrEP compared to those who do not, and to assess the association with detectable TFV in PrEP users who acquire HIV infection during the study.

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To determine the uptake and continuation of modern contraceptive methods, and the association of contraception use with PrEP uptake and adherence.
- To describe ARV drug resistance among women who acquire HIV infection.
- To estimate the potential impact of PrEP use on HIV acquisition in young African women through mathematical modeling.
- To perform exploratory laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or STIs; ARV drug use; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives.

2.4. Study Design

This is a Phase IV randomized multi-site prospective study to assess PrEP acceptance and adherence among HIV-uninfected young women who are offered open-label daily oral PrEP with adherence support. Women will be consented (or assented with consent/permission from their parent or legal guardian as applicable) to have up to 12 months of follow-up. PrEP will be offered in conjunction with SOC HIV prevention interventions (HIV testing, counseling, condoms, testing for STIs). Up to 600 women will be enrolled from 3 sites: 400 women who accept PrEP at enrollment and up to 200 women who decline oral PrEP at enrollment but have the option to accept PrEP at any time during follow up. All women will be followed for 12 months.

Participants who accept PrEP will be randomly assigned in a 1:1 ratio to receive *standard* adherence support (counseling, two-way short message service (SMS) communication, and peer support through adherence support clubs **or** *enhanced* adherence support with counseling based on

feedback from drug levels at Weeks 8 and 13, plus the standard adherence support (counseling, two-way SMS communication, and peer support through adherence support clubs).

A subset of up to ~25 women per site (maximum 75), including PrEP decliners and late accepters, will also be recruited to participate in serial qualitative interviews, to explore factors that influence women's decisions to use PrEP, to adhere to PrEP, and acceptability of PrEP in the first 3 months after PrEP acceptance. Refer to the Overview of Study Design and Randomization Scheme for a depiction of the study design.

2.5. Enrollment Targets

A cohort of up to 600 women who meet the inclusion and exclusion criteria described in Section 3 will be enrolled at the Spilhaus Clinical Research Site in Harare, Zimbabwe; the Emavundleni Research Centre in Cape Town, South Africa; and Wits RHI in Johannesburg, South Africa. Enrollment will continue until 400 women are enrolled who agree to accept PrEP at the Enrollment visit, with a target of approximately 133 women per site from three southern African sites. The cohort of 400 young women who accept PrEP will be randomized on a 1:1 basis to receive enhanced versus standard adherence support. Up to 200 women who decline PrEP at enrollment will also be eligible for follow-up.

3.0 STUDY POPULATION

Young women 16-25 years old will be enrolled in this study, with a goal to enroll 125 (31%) of the 400 PrEP users in the 16-20 age range. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. They will be recruited, screened, and enrolled as described in Section 3.3. Issues related to participant retention and withdrawal from the study are described in Sections 3.5 and 3.6, respectively.

3.1. Inclusion Criteria

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

- Female at birth
- Age 16-25 years
- Per participant report, sexually active, defined as having vaginal or anal intercourse at least once in the month prior to screening
- Literate in one or more of the study languages
- Willing and able to provide informed consent or assent (if parental consent is required per local regulations)
- If parental consent is required per local regulations, parent/legal guardian willing and able to consent to all study procedures including HIV testing
- Able and willing to provide adequate locator information, as defined in site Standard Operating Procedures (SOPs)
- Have a score of 5 or greater on the VOICE risk score tool
- Interest in PrEP (ascertained by selected questions from the HPRM and PBM defined in the Study Specific Procedures [SSP] Manual)
- Regular access to a mobile phone with SMS capacity
- Agrees not to participate in other research studies involving drugs or medical devices for the next 12 months
- Hepatitis B virus (HBV) seronegative and accepts HBV vaccination.

3.2. Exclusion Criteria

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

- Planning to relocate in the next 12 months
- Has a job or other obligations that would require long absences from the area (> 4 weeks at a time) for 12 months
- Any health condition that may interfere with participation, including any debilitating or life-threatening conditions
- Currently pregnant or planning to become pregnant in the next 12 months
- Any reactive or positive HIV test at Screening or Enrollment, even if subsequent testing indicates that the person is HIV-uninfected
- Renal dysfunction (Creatinine Clearance < 60 ml/min, Schwartz Equation)
- Any reported PrEP use within the last 12 months
- Concomitant participation in a clinical trial using investigational agents, including placebo-controlled clinical trials using such agents
- Prior participation in the active arm, or current participation in any arm, of an HIV vaccine trial
- Signs or symptoms of acute HIV infection (as described in the SSP Manual)
- Current active and serious infections which could interfere with study participation, including active tuberculosis infection, osteomyelitis, and all infections requiring parenteral antibiotic therapy (other than STIs requiring intramuscular injections of antibiotics); active clinically significant medical problems including poorly-controlled cardiac disease (e.g., symptoms of ischemia, congestive heart failure), or previously diagnosed malignancy expected to require further treatment.
- Current use of ARV drugs for post-exposure prophylaxis (PEP) or completion of a PEP regimen within 4 weeks prior to Screening
- History of pathological bone fracture not related to trauma
- Known allergy/sensitivity to the study drug or its components
- Receiving ongoing therapy with any of the following: investigational ARV agents, interferon or interleukin therapy, agents with substantial nephrotoxic potential, other agents that may inhibit or compete for elimination via active renal tubular secretion (e.g., probenecid), and/or other investigational agents
- Any other condition that, based on the opinion of the site Investigator of Record (IoR) or designee, would preclude provision of informed consent, make participation in the project unsafe, complicate interpretation of outcome data, or otherwise interfere with achieving the project objectives.

3.3. Recruitment and Screening Process

Sites will be responsible for developing appropriate recruitment processes that are geared toward their respective local communities. All advertising materials must undergo approval by each participating site's IRB/Ethics Committee (EC).

Recruitment for HPTN 082 will be conducted as described in Section 4.1. At Screening, the VOICE risk tool will be administered to all participants to identify those women who have a score of 5 or greater who are at higher risk of HIV acquisition. Women who have a score of 5 or greater will then be administered selected questions from the adapted HPRM and PBM tools to identify women who are interested in using PrEP. The SSP Manual will identify appropriate scoring for interest in PrEP.

Up to 200 additional women may be enrolled who are interested in PrEP and are eligible for the study, but decline to accept oral PrEP at Enrollment; these women will continue to be offered PrEP during follow up visits to determine the proportion who subsequently accept PrEP, and the characteristics of early vs. delayed PrEP acceptors and those who do not accept PrEP during follow-up.

Enrollment must occur within 45 days of blood collection for HIV testing at screening.

3.4. Co-Enrollment Guidelines

Participants in this study should not take part in any concurrent research studies that use drugs or medical devices while on follow up. Co-enrollment in observational or other studies may be allowable with approval of the site IoR or designee. Previous participation in the placebo arm of an HIV vaccine trial may be allowable with approval of the Clinical Management Committee (CMC) (see Section 6.1).

3.5. Participant Retention

Once a participant enrolls in this study, the study site will aim to retain her for 12 months of follow-up in order to minimize possible bias associated with loss-to-follow-up. Study site staff are responsible for developing and implementing local SOPs to reach this goal. Components of such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Collection of detailed locator information at the study Screening visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Use of appropriate and timely visit-reminder mechanisms.
- Immediate and multifaceted follow-up for missed visits.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness about HIV/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.

Reminders for upcoming follow up visits for participants who attend monthly adherence clubs may also be utilized.

3.6. Participant Withdrawal

Regardless of the participant retention methods used, participants (or their parents or guardians if under legal age of consent) may voluntarily withdraw from the study for any reason at any time. The site IoR or designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the CMC.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site IRBs/ECs or the SMC terminates the study overall or at a specific site prior to 52 weeks.

Every reasonable effort will be made to complete final evaluations (as described in Section 5.10 and 5.11) for participants who terminate from the study prior to the last study assessment or visit;

study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4.0 STUDY INTERVENTIONS AND PRODUCT

Study recruitment and implementation materials (including measures) will be developed in parallel with site activation and local regulatory approvals at the sites. The study team intends to use Computer Assisted Self Interview (CASI) for behavioral measures, as feasible.

4.1. Development of recruitment materials

Recruitment for HPTN 082 will be conducted through community events, school clinics, primary care and family planning clinics, and through youth centers. At the screening visit, young women will be shown a contextually and culturally-appropriate video about sexual and reproductive health, including contraceptive and HIV prevention options with focused information on PrEP. An informational video will be developed about PrEP similar to what was developed by Amico and colleagues (<http://www.whatispref.org>),⁸⁴ followed by counseling about HIV prevalence and incidence in their community, their intent, need and desire for HIV prevention, and evidence for PrEP efficacy and effectiveness. The 'What is PrEP' video will be used as the beta version of the media, which will then be iteratively refined by the protocol team, key individuals at the sites and medical experts. Acceptability and clarity of the video content will be reviewed by experienced PrEP adherence counselors and community advisory board members at the study sites.

4.2. Adaptation of the PrEP Readiness Questionnaire

In initial PrEP efficacy trials, questions about risk perception were limited to a single item. To build on a more expanded construct to measure readiness to take a medication for HIV prevention, formative research will be conducted with youth community advisory boards at the participating sites. During the formative research, the information about risk factors from the VOICE trial will be incorporated into a risk assessment tool to be used in screening prospective participants and risk reduction counseling messages.

The HPRM (Appendix III) will be shortened, adapted and tailored from a treatment readiness measure⁸⁵ and used in the Adolescent Trials Network (ATN) 110/113 study and PBM (developed for iPrEX OLE and used in ATN 110/113) in order to identify women who are interested in PrEP. The HPRM has been adapted from the HIV Treatment Readiness Measure⁸⁵ (HTRM), which has shown high internal consistency and test-retest reliability along with a strong factor structure when administered to HIV-infected youth. The HPRM was adapted for domestic PrEP trials based on the extant literature on predictors of treatment adherence and medication readiness. The key components of prevention readiness are similar to treatment readiness and include: 1) attitudes toward medication, 2) provider characteristics, 3) support systems, 4) control of life, 5) intentions to adhere to medication, 6) psychosocial issues, such as depression and unstable housing, 7) disclosure, and 8) alcohol and drug use. Responses to the HPRM items will determine those participants who are ready or not for PrEP use (e.g., a yes response to "I am ready to start taking medication [PrEP] to protect me against HIV"), which will be administered at the Screening visit.

Responses to selected HPRM and PBM items administered at the Screening visit will determine those participants who are ready or not for PrEP use [e.g., a yes response to "I am ready to start taking medication [PrEP] to protect me against HIV"]. Other items on the HPRM will highlight potential barriers and facilitators to PrEP uptake and adherence, such as "My family and friends who know I'm on PrEP would help me remember to take my medication," to be used to assist in

the development of a personalized prevention plan. The PBM explores personal beliefs about PrEP as it relates to efficacy, sexual disinhibition, side effects, and participants' reasons for not wanting to take PrEP.

The preparedness phase of HPTN 082 will include a thorough review of sub-Saharan African literature to identify factors associated with treatment and prevention adherence in the local context as well as any locally available assessments of readiness to take PrEP. Questions in the existing HPRM (Appendix III) will then be updated to reflect these factors. Once the HPRM has been updated for local use, we will work with youth community advisory board members and others at the sites to improve the questionnaire prior to using in the field.

In order to determine factors that are associated with PrEP uptake and adherence after additional counseling and experience taking PrEP in the first 3 months, PrEP interest questions adapted from the HPRM will be re-administered to PrEP decliners at each visit and PrEP acceptors at Week 13.

4.3. Adherence Support for PrEP Acceptors

For those women who choose to accept PrEP, the following standard adherence support package will be provided:

- CBT adherence support sessions
- Two-way SMS communications
- Optional monthly adherence support clubs

These are described in greater detail below.

CBT adherence support sessions

The CBT intervention will be guided by existing evidence-based CBT adherence interventions and tailored for use with young women in sub-Saharan Africa. One intervention in particular is called Life Steps,^{86,87} which has been successfully used to improve adherence to ART and PrEP among HIV-serodiscordant couples in the Partners PrEP Study.⁸⁸ Life Steps addresses informational, problem-solving, and cognitive-behavioral steps, in face-to-face intervention sessions in which the participants define the problems impacting adherence, generate alternative solutions, make decisions about the alternatives, and collaboratively decide on a plan regarding how to implement the solutions. In the Partners PrEP adaptation, lay counselors were successfully trained to implement the intervention. For this study, the staff will work with all participants to identify any problems impacting adherence, generate alternative solutions, make decisions about the alternatives, and collaboratively decide on a plan regarding how to implement the solutions. More information will be provided in the SSP Manual with suggested session content based on adapted material from Life Steps and others. The sessions will include: PrEP information review (i.e., why adherence is important); identifying pros and cons to high adherence; exploring motivations for PrEP adherence; discussions on gender dynamics and disclosure of PrEP use; examination of adherence barriers and facilitators, and problem solving and skill building around adherence. All CBT adherence support sessions will be audiotaped to allow for enhanced fidelity monitoring as well as subsequent content analysis of the sessions. Participants who object to audio recording of the session may ask the counselor not to record the session.

Weekly SMS reminders

PrEP acceptors will receive weekly SMS text messaging until Week 13, with the option to continue throughout follow up if desired. There are several "mobi sites" (websites for cell phones) platforms that have been established in sub-Saharan countries to support HIV treatment and prevention

activities that could be adapted to support participants in HPTN 082 (for example WelTel, U-Report and MAMA as described in Section 1.2.2). The team will identify an SMS platform (or more than one) that is most appropriate for the locations selected for study implementation in collaboration with the site teams and youth CABs.

Monthly Adherence Support Clubs

These will be modeled after the FACTS 001 adherence support clubs, as described previously.

Counseling based on drug levels

Women who are randomized to enhanced counselling will have adherence monitoring based on plasma TFV levels obtained 4 and 8 weeks after PrEP acceptance as described in Section 4.6.4. Adherence counseling based on drug levels will be provided at the next visit (i.e., for participants who accept PrEP at enrollment Week 4 levels will be provided at the Week 8 visit, Week 8 levels will be provided at the Week 13 visit). Pictorial tools will be developed in conjunction with the youth CABs in order to provide youth-relevant representations of drug levels (e.g., cell phone bars or wireless signal strength symbols).

4.4. Initial PrEP decliners

Up to 200 women who are interested but decline oral PrEP at enrollment will be actively offered oral PrEP to participants by staff up until Week 13, but participants who request PrEP after Week 13 may begin up until Week 39. Women who are not interested in PrEP initially, but decide to accept PrEP after enrollment will be evaluated for acute HIV symptoms and for HIV infection before PrEP is provided. To avoid participants accepting PrEP because of fear of termination of participation in the study, participants who never accept PrEP will be followed until Week 52 (regardless of PrEP acceptance) and offered the SOC HIV prevention services as described in Section 5.

Late PrEP acceptors will follow the Schedule of Evaluations for PrEP acceptors (Appendix IA) after they begin receiving PrEP without adjustment to their length of follow up. For example, if PrEP is accepted at Week 39, they will only receive 13 weeks of open label PrEP. However, the schedule for PrEP adherence support will be followed according to their acceptance date of PrEP as detailed below.

Standard adherence package	
CBT adherence support sessions	Sessions will follow information included in the SSP with counseling beginning with PrEP acceptance date.
Weekly SMS reminders	Weekly texting will begin at PrEP acceptance and continue for the first 13 weeks with an option to continue until final study visit depending on remaining time on follow up.
Monthly Adherence Support Clubs	All PrEP acceptors can attend support clubs. Although PrEP decliners will not be prohibited from attending Adherence Support Clubs, they will not be encouraged to attend unless they accept PrEP.
Enhanced adherence package (randomization) above components, plus:	
Counseling based on near real-time drug levels	Blood draw for drug level monitoring will occur 4 and 8 weeks after PrEP acceptance. Counseling based on each of these levels will occur at their next visit (Week 8 for the Week 4 level and Week 13 for the Week 8 level).

4.5. Standard of Care

The SOC will be provided to all participants and will include: 1) HIV testing and risk reduction counseling at all visits; 2) counseling and provision of contraception options; 3) STI testing at screening, and quarterly genital exam, STI testing and presumptive syndromic STI treatment, as needed; 4) information on proper use of male and female condoms, including condom demonstrations, and provision of condoms; and 5) discussion of HIV testing and prevention for their sexual partner(s) and referrals to local testing options for their partners. Participants who identify symptoms consistent with an STI during an interim medical history and or symptoms-directed physical exam at regular visits will be referred for or provided treatment as indicated. STI testing will include testing for *Neisseria gonorrhoeae* (GC), *Chlamydia trachomatis* (CT), *Trichomonas vaginalis* (TV) and syphilis. Participants with a lab diagnosis consistent with any of these STIs will be referred for or provided treatment as indicated. Due to the timing of lab testing, this may occur as an interim visit.

4.6. Study Product

Participants opting to take PrEP will be provided with oral once per day PrEP in the form of emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (FTC/TDF) with a sufficient supply for once daily dosing until their next scheduled visit.

4.6.1. Study Product Formulation, Content, and Storage

FTC/TDF is a fixed dose combination tablet containing 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF) in each tablet. It is available as Truvada®, a medication approved by the U.S. Food and Drug Administration (FDA) for treatment of HIV-1 infection and for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. Further information on Truvada® is available in the current package insert, which is located at <http://rsc.tech->

FTC/TDF tablets (30 tablets/bottle) must be stored at 25°C (77°F), with excursions permitted to 15°C-30°C (59°F-86°F) (see USP Controlled Room Temperature). FTC/TDF tablets must be stored in the original container. Each container is packaged with a child-resistant screw cap and contains a silica gel to protect the product from humidity and polyester packing material that cushions it during handling and shipping.

4.6.2. Study Product Regimen, Administration and Duration

After enrollment, participants will accept the study product and will be directed to take FTC/TDF tablet orally once daily with or without food throughout follow up. If a participant forgets to take the study product at the correct time, it may be taken later in the day; however, no more than one tablet of FTC/TDF should be taken on any calendar day. Participants may also decide to discontinue taking FTC/TDF at any time during follow up.

To protect participant confidentiality, sites will provide all participants with locally made purses or handbags to carry study materials including pill bottles. These purses or handbags will not include any clinic identifiers or logos. Site staff will work with youth CAB members to identify the best local source for these items.

4.6.3. Treatment/Product/Intervention Supply and Accountability

Emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg study product tablets are manufactured by Gilead Sciences, Inc. under the trade name Truvada® and will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain study product for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* in the section *Study Product Management Responsibilities*.

The site pharmacist must maintain complete records of all study products received from the NIAID-CRPMC- and subsequently dispensed. All unused supplies must be returned to the NIAID CRPMC after the study is completed or terminated, unless otherwise instructed by the CRPMC. Procedures and relevant forms are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*.

4.6.4. Counseling based on feedback from drug level data

Participants who are randomized to enhanced counseling will have measurements of plasma TFV levels on samples taken 4 and 8 weeks after PrEP acceptance. These will be “convenience” or “untimed” samples with respect to the previous dose. A plasma TFV threshold of >40 ng/mL will be used for counseling women about their adherence; 40 ng/mL represents the lower 95th confidence interval for the TFV trough for daily dosing at steady-state, and it has been associated with PrEP efficacy in the Partner’s PrEP study.⁵³ Additional TFV plasma thresholds (described below) were determined through extensive knowledge of TFV pharmacokinetics from numerous studies including HPTN 066. The adherence counseling based on TFV levels will be provided at the next visit (i.e., Week 4 level will be provided at the Week 8 visit, and Week 8 drug levels will be provided at the Week 13 visit). A semi structured feedback guide will be included for site adaption in the SSP. Women will receive the following counseling during their cognitive behavioral counseling sessions:

- For those with TFV levels >40 ng/mL: Positive re-enforcement, as level suggest that they had dosed in the past 24 hours.
- For those with TFV levels 5-40 ng/mL: Discuss details about their dosing patterns in the past week and encourage greater adherence in order to get optimal protection from PrEP.
- For those with TFV levels <5ng/mL: Emphasize the need for greater adherence and explore barriers to taking PrEP, avoiding punitive language.

4.6.5. Primary Adherence Assessment

For the primary adherence outcome measurement (adherence in the cohort by randomization arm) drug levels will be measured retrospectively. The main adherence assessment will be performed using plasma and/or DBS samples. The testing plan will be determined at a later date, based on evaluations of plasma TFV levels and DBS TFV-DP levels in women that are currently underway.

A plasma TFV level of >40 ng/mL will be interpreted to indicate dosing within the last 24 hours. DBS can be used to detect intracellular levels of TFV-DP, providing a measure of cumulative adherence behavior over the prior 2 months. A threshold of 700 fmol/punch predicted 100% efficacy in iPrEX OLE.²⁴ Given the long half-life for TFV-DP, gradients of cumulative adherence can also be estimated, such as those described in iPrEX OLE as follows: Below limit of quantitation (BLQ, no doses), BLQ to 349 fmol/punch (fewer than two tablets per week), 350–699 fmol/punch (two or three tablets per week), 700–1249 fmol/punch (four to six tablets per week), and ≥ 1250 fmol/punch (daily dosing). Although women may respond to TDF/FTC differently compared with men due to differences in mucosal drug distribution, there are no *in vivo* data to support a specific TFV-DP threshold in women. In the absence of such data, we will use the 700 fmol/punch threshold that suggests consistent dosing and was associated with full efficacy in iPrEx OLE, unless new data become available. Finally, FTC-triphosphate levels in DBS serve as a surrogate for quantifiable plasma TFV (at ≥ 10 ng/mL), which informs dosing within the last 48 to 72 hours.²⁴

4.6.6. Toxicity Management

The site investigator has the discretion to interrupt FTC/TDF at any time if s/he feels that continued medication use would be harmful to the participant or would interfere with treatment deemed clinically necessary according to the judgment of the investigator. Clinical or laboratory abnormalities that require follow-up will be documented, and the research associate or clinician will contact the participant to schedule an interim visit for follow-up and/or repeat laboratory testing if indicated. All participants reporting an adverse event (AE) Grade 3 or higher or any grade for creatinine will be followed clinically until the occurrence resolves (returns to baseline grade, defined as grade at Screening/Enrollment) or stabilizes. Participants enrolled with a Grade 2 creatinine clearance (CrCl between 60 and 90 ml/min) will be followed if CrCl increases in severity from baseline levels. PrEP will be discontinued if the CrCl decreases below 60 ml/min and serum creatinine will be monitored. All participants who discontinue PrEP (either for toxicity reasons or personal choice) will be followed under the procedures identified in Appendix 1B for PrEP decliners.

SAEs designated to be related to PrEP will result in temporary hold of PrEP. In the case of temporary holds, the hold will continue until the event is stabilized or resolved. In such cases, PrEP may be reinitiated at the discretion of the Investigator.

4.6.7. HIV Seroconversion

Frequent testing for HIV acquisition during the study period will allow prompt cessation of study drug in an HIV-infected participant, minimizing the risk that resistant virus will emerge. Therefore, HIV testing will be performed at all scheduled study visits for PrEP acceptors. HIV rapid testing

and specimen collection should be completed prior to administration of study medication. Participants who have any reactive or positive HIV test result after initiating PrEP will be instructed to discontinue study drug immediately, and will have further testing to clarify their HIV infection status, as described in Section 5.13 and the SSP Manual. Any enrolled participant who is confirmed to have acquired HIV infection during the study will permanently discontinue study product and will be transitioned to a local HIV care clinic for appropriate follow-up and clinical management, including resistance testing. Participants who acquire HIV infection will have one additional study visit 3 months after a confirmatory visit. Procedures for participants who acquire HIV infection are described in Section 5.13.

4.6.8. Concomitant Medications

Only concomitant medications contraindicated for Truvada® (see below) reported within 14 days prior to confirmation of eligibility for study Enrollment and throughout the course of that component will be recorded on the case report form (CRF) designated for that purpose. Medications used for the treatment of AEs that occur during study participation will also be recorded on applicable study CRFs. Participants who begin taking any medication during the trial that is listed as an exclusionary medication at Screening will temporarily discontinue study drug as noted below. The exception may be if the use of PEP is indicated for participants already receiving oral PrEP. Based on the WHO Guidelines on Post-exposure Prophylaxis (PEP) for HIV, FTC/TDF should form the backbone of PEP following occupational exposure or sexual assault. If a participant begins a course of PEP through local services, site clinicians should evaluate whether to add a third drug but continue oral PrEP in these situations.⁸⁹ If oral PrEP is halted for any reason, after the exclusionary medication regimen is complete and if the site IoR/designee feels it is safe for the participant to resume PrEP, the CMC must be consulted before study drug may be resumed, and all HIV tests must be non-reactive/negative.

Should participants report use of any of the following medications, they will be required to discontinue use of PrEP: investigational ARV agents, interferon or interleukin therapy, agents with substantial nephrotoxic potential, other agents that may inhibit or compete for elimination via active renal tubular secretion (e.g., probenecid), and/or other investigational agents.

5.0 STUDY PROCEDURES

An overview of the study visit and procedures schedule is presented in Appendices IA-ID. Presented below is additional information on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites will be provided in the study-specific procedures manual.

5.1. Screening Visit

At Screening, women who meet inclusion criteria and agree to study participation will be consented (or assented in the case of a minor with parental consent) for 12 months of follow-up with an option to take oral PrEP. A questionnaire about risk behaviors and PrEP interest will be administered, which will gather information on sexual behavior (partner number, partner's HIV status, vaginal and anal sex with partners), pregnancy history and contraceptive use, HIV prevention self-efficacy, relationship characteristics, past and current experience of GBV, alcohol and drug use, anxiety and depression, and HIV risk perception. Staff will query the women on several characteristics in order to determine a risk score.²²

Participants who would like to accept PrEP but are deemed ineligible at Screening due to a positive/reactive HIV or hepatitis B virus (HBV) surface antigen test are considered screen failures and will be referred for appropriate medical care.

During screening, enrollment and follow up, participants will be queried on the contextual factors, which have been shown to impact differential uptake and sustained use in prior trials. Items from the following domains will be included as noted in Sections 7.2.1:

- Sociodemographic characteristics
 - current living situation
 - household composition
 - private space for product storage
- Partnership characteristics, partner's HIV status,
- Sexual behaviors
- HIV risk perception
- HIV stigma
- PrEP readiness
- Future orientation and aspirations; self-efficacy
- Alcohol and drug use
- Gender-based violence (GBV)
- Post-traumatic stress symptoms
- Disclosure to peers, family members, teachers, and partner(s) about PrEP use and participation in the study

As described in Section 4.2, a youth community advisory board will be recruited at each site for HPTN 082, and members of the youth CABs will play an active role in developing materials for screening, recruitment and data collection materials. As described in Section 5.14, in-depth interviews and the qualitative methods used in this study will allow us to explore many of these contextual issues more deeply in a subset of participants.

Because the decision to accept or decline PrEP is at Enrollment, screening procedures for all participants are the same.

5.1.1. Administrative and Behavioral Evaluations/Procedures

- Informed Consent
- Collect/Update Locator information
- Validate mobile phone number and texting capacity
- HIV risk score determined
- Demographic information
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)
- PrEP interest questions

5.1.2. Clinical Evaluations/Procedures

- Contraceptive assessment and associated counseling as appropriate
- Symptom-directed physical exam
- STI treatment, if indicated*

- Blood collection
- Urine collection (if used for pregnancy testing)
- Urine collection (if used for STI testing)
- Participant vaginal swab collection for STI testing

5.1.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Hepatitis B serology (HepBsAg, HepBsAb)
- Serum creatinine (for creatinine clearance, Schwartz Equation)
- Pregnancy test (urine, plasma or serum)
- STI testing (TV, GC/CT, syphilis)
- Plasma for storage

NOTES: At Screening and at other visits where these assessments are performed: Urine, plasma or serum may be used for pregnancy testing; pregnancy tests and HIV rapid tests (if performed) may be performed in the clinic or laboratory; participant collected vaginal swabs will be used for *Trichomonas vaginalis* (TV) testing; participant collected vaginal swabs will also be used for GC/CT testing, if the site has a validated assay for swab testing – if not, GC/CT testing will be performed using urine samples.

*Based on reported symptoms in accordance with national guidelines.

5.2. Enrollment Visit for PrEP acceptors

At enrollment, women who elect to start PrEP immediately will be counseled about the importance of high PrEP adherence to achieve high levels of HIV protection, frequency, type and timing of side effects with oral FTC/TDF, and strategies for confidential storage and anticipating barriers to adherence. A participant is considered enrolled at the point in time when all enrollment visit procedures are complete. Enrollment must occur within 45 days of blood collection for HIV testing at screening. Note that visit procedures for PrEP acceptors and decliners will be based on whether PrEP is accepted (dispensed), not on measures of adherence. Randomization of PrEP acceptors will occur at the Enrollment visit according to procedures outlined in the SSP Manual.

5.2.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- Standard HIV risk reduction counseling (including providing condoms)
- PrEP interest questions
- Study drug supply
- Randomization (to receive drug level feedback 4 and 8 weeks after PrEP acceptance or not)
- Adherence support (see Section 4.3)

5.2.2. Clinical Evaluations/Procedures

- Complete medical history (including concomitant meds and STI symptoms)
- Contraceptive assessment and associated counseling as appropriate
- Provide HBV vaccine, if susceptible*
- STI treatment, if indicated**
- Blood collection

- Urine collection (if used for pregnancy testing)

5.2.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Pregnancy testing (urine, plasma or serum)
- Plasma for storage

*HBV vaccine will be provided to all participants who are identified as not immune during screening. Two doses will follow the initial dose at 4 and 26 weeks.

**Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.3. Enrollment Visit for PrEP decliners

At enrollment, women who decline to start PrEP immediately will follow procedures below as indicated. A participant is considered enrolled at the point in time when all enrollment visit procedures are complete.

5.3.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- Standard HIV risk reduction counseling (including providing condoms)
- PrEP interest questions

5.3.2. Clinical Evaluations/Procedures

- Complete medical history including concomitant meds and STI symptoms
- Contraceptive assessment and associated counseling as appropriate
- Provide HBV vaccine, if susceptible*
- STI treatment, if indicated**
- Blood collection
- Urine collection (if used for pregnancy testing)

5.3.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Pregnancy testing (urine, plasma or serum)
- Plasma for storage

*HBV vaccine will be provided to all participants who are identified as not immune during screening. Two doses will follow the initial dose at 4 and 26 weeks.

**Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.4. Weeks 4 and 8 for PrEP Acceptors

5.4.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment

- AE assessment
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)
- Study drug adherence assessment
- Study drug supply
- Adherence support (see Section 4.3)

5.4.2.Clinical Evaluations/Procedures

- Contraceptive assessment and associated counseling as appropriate
- Provide HBV vaccine*, if susceptible
- Interim medical history (including concomitant meds and STI symptoms)
- Symptom-directed physical exam
- STI treatment, if indicated**
- Blood collection
- Urine collection (if used for pregnancy testing)

5.4.3.Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Pregnancy testing (urine, plasma or serum)
- Plasma TFV concentration (per randomization)
- Plasma for storage
- DBS for storage

*HBV vaccine will be provided to all participants who are identified as not immune during screening. Two doses will follow the initial dose at 4 and 26 weeks.

**Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.5. Weeks 4 and 8 for PrEP Decliners

Participants who opt to begin PrEP after enrollment should also follow the procedures outlined in Section 5.12.

5.5.1.Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- AE assessment
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)
- PrEP interest questions
- Offer PrEP (if participant accepts, follow procedures outlined in 5.12)

5.5.2.Clinical Evaluations/Procedures

- Contraceptive assessment and associated counseling as appropriate
- Provide HBV vaccine*, if susceptible
- Interim medical history (including concomitant meds and STI symptoms)
- Symptom-directed physical exam

- STI treatment, if indicated**
- Blood collection
- Urine collection (if used for pregnancy testing)

5.5.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Pregnancy testing (urine, plasma or serum)
- Plasma for storage

*HBV vaccine will be provided to all participants who are identified as not immune during screening. Two doses will follow the initial dose at 4 and 26 weeks.

**Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.6. Week 13 for PrEP acceptors

5.6.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- AE assessment
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)
- PrEP interest questions
- Study drug adherence assessment
- Study drug supply
- Adherence support (see Section 4.3)

5.6.2. Clinical Evaluations/Procedures

- Contraceptive assessment and associated counseling as appropriate
- Interim medical history (including concomitant meds and STI symptoms)
- Symptom-directed physical exam
- STI treatment, if indicated*
- Blood collection
- Urine collection (if used for pregnancy testing)

5.6.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Pregnancy testing (urine, plasma or serum)
- Plasma for storage
- DBS for storage

*Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.7. Week 13 for PrEP decliners

Participants who opt to accept PrEP after enrollment will follow the procedures outlined in Section 5.12.

5.7.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- AE assessment
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)
- PrEP interest questions
- Offer PrEP (if participant accepts follow procedures outlined in 5.12)

5.7.2. Clinical Evaluations/Procedures

- Contraceptive assessment and associated counseling as appropriate
- Interim medical history (including concomitant meds and STI symptoms)
- Symptom-directed physical exam
- STI treatment, if indicated*
- Blood collection
- Urine collection (if used for pregnancy testing)

5.7.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Pregnancy testing (urine, plasma or serum)
- Plasma for storage

*Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.8. Weeks 26 and 39 for PrEP acceptors

5.8.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- AE assessment
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)
- Study drug adherence assessment
- Study drug supply
- Adherence support (see Section 4.3)

5.8.2. Clinical Evaluations/Procedures

- Contraceptive assessment and associated counseling as appropriate
- Provide HBV vaccine*, if susceptible
- Interim medical history (including concomitant meds and STI symptoms)
- Symptom-directed physical exam
- STI treatment, if indicated**

- Blood collection
- Urine collection (if used for pregnancy or STI testing)
- Participant vaginal swab collection for STI testing (Week 26 only)

5.8.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Serum creatinine (for creatinine clearance) (Week 26 only)
- Pregnancy testing (urine, plasma or serum)
- STI testing (TV, GC/CT, syphilis) (Week 26 only)
- Plasma for storage
- DBS for storage

*HBV vaccine will be provided to all participants who are identified as not immune during screening. Two doses will follow the initial dose at 4 and 26 weeks.

**Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.9. Weeks 26 and 39 for PrEP decliners

5.9.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- AE assessment
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)
- PrEP interest questions

5.9.2. Clinical Evaluations/Procedures

- Contraceptive assessment and associated counseling as appropriate
- Provide HBV vaccine*, if susceptible
- Interim medical history (including concomitant meds and STI symptoms)
- Symptom-directed physical exam
- STI treatment, if indicated**
- Blood collection
- Urine collection (if used for pregnancy or STI testing)
- Participant vaginal swab collection for STI testing (Week 26 only)

5.9.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Pregnancy testing (urine, plasma or serum)
- STI testing (TV, GC/CT, syphilis) (Week 26 only)
- Plasma for storage

*HBV vaccine will be provided to all participants who are identified as not immune during screening. Two doses will follow the initial dose at 4 and 26 weeks.

** Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.10. Exit Visit (Week 52) for PrEP acceptors

5.10.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- AE assessment
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)
- Study drug adherence assessment

5.10.2. Clinical Evaluations/Procedures

- Interim medical history (including concomitant meds and STI symptoms)
- Symptom-directed physical exam
- STI treatment, if indicated*
- Blood collection
- Urine collection (if used for pregnancy or STI testing)
- Participant vaginal swab collection for STI testing

5.10.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Serum creatinine (for creatinine clearance)
- Pregnancy testing (urine, plasma or serum)
- STI testing (TV, GC/CT, syphilis)
- Plasma for storage
- DBS for storage

*Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.11. Exit Visit (Week 52) for PrEP decliners

5.11.1. Administrative and Behavioral Evaluations/Procedures

- Collect/Update Locator information
- Social impact assessment
- AE assessment
- Behavioral risk assessment
- Standard HIV risk reduction counseling (including providing condoms)

5.11.2. Clinical Evaluations/Procedures

- Interim medical history (including concomitant meds and STI symptoms)
- Symptom-directed physical exam
- STI treatment, if indicated*
- Blood collection
- Urine collection (if used for pregnancy or STI testing)
- Participant vaginal swab collection for STI testing

5.11.3. Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- Pregnancy testing (urine, plasma or serum)
- STI testing (TV, GC/CT, syphilis)
- Plasma for storage

*Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines.

5.12. Procedures for Participants who accept PrEP after Enrollment (Late acceptors)

Participants who decline PrEP at Enrollment but accept PrEP during a later visit will follow these additional procedures at this visit:

5.12.1. Administrative and Behavioral Evaluations/Procedures

- Study drug supply
- Randomization (to receive drug level feedback 4 and 8 weeks later or not)
- Adherence support (see Section 4.3)

5.12.2. Clinical Evaluations/Procedures

- Symptom directed physical exam

5.12.3. Laboratory Evaluations/Procedures

- Serum creatinine (for creatinine clearance)
- Screening for signs of acute HIV infection

Note that these are additional procedures, HIV testing and other procedures should also be completed per their usual visit schedule. If safety evaluations (creatinine clearance or HIV testing) are not available same day at site, drug supply should be held until after results are available. These women will then follow the schedule of evaluations for PrEP acceptors at all subsequent visits, without change to their visit schedule except as noted in Section 4.3 (Adherence Support for PrEP Acceptors). For late PrEP acceptors randomized to receive drug level feedback will be asked to return to the clinic 4 weeks after PrEP is dispensed for a blood draw, 4 weeks after that for counseling and so on.

5.13. Procedures for Participants with Suspected or Confirmed HIV Infection

Participants with a reactive or positive HIV test result identified at any time after study Enrollment will have further testing to confirm infection, as described in the SSP Manual, and will be referred for care. Appendix ID describes procedures for participants with suspected or confirmed HIV infection.

The following procedures will be conducted during a visit to confirm HIV infection:

Administrative Evaluations

- Update locator information
- Linkage to HIV care

Clinical Procedures:

- Symptom-directed physical exam
- Blood collection

Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- CD4 cell count testing
- Additional plasma storage*
- HIV genotyping for resistance testing*

** Stored plasma will be used for Quality Assurance (QA) testing, HIV viral load, and other assessments at the HPTN LC, including resistance testing (see Section 9). These assessments will be performed retrospectively; results will not be returned to study sites or participants (with the possible exception of HIV diagnostic testing, if results obtained at the HPTN LC differ from site results). Additional samples from participants with confirmed HIV infection will be collected and sent to a local laboratory for resistance testing to assist with clinical management; results from resistance testing performed in local laboratories will not be reported to the HPTN SDMC.*

Many of these procedures will be repeated 3 months later at a post-confirmatory visit with the exception of HIV genotyping. See Appendix ID.

If participants have a reactive or positive HIV test after study Enrollment, but further testing indicates that they are not HIV infected the participant may not resume study drug and will be terminated from the study.

5.14. Qualitative data collection

The use of qualitative methods that give young women the opportunity to discuss their decision-making, adherence barriers, and facilitators in their own words will result in a more culturally-sensitive approach to the study of PrEP uptake and adherence among young women in Africa.

In-depth qualitative interviews will be conducted with three distinct groups of women including:

1. Young women who accept and adhere to PrEP (these women will be selected from those who have TFV levels >40 ng/mL at Week 4).
2. Young women who accept but do not initiate, adhere to PrEP, or discontinue (selected among those with TFV levels <40 ng/mL at Week 4), and
3. Young women who do not accept PrEP during the first 3 months.

For PrEP acceptors, these in-depth qualitative interviews will occur at two visits. The first will be after the Week 13 visit. The second will be after their Week 26 visit. The first interview will explore the decision to take PrEP or not, as well as barriers and facilitators to PrEP adherence within the first 3 months of PrEP use. Among women who accepted PrEP, this interview will assess how women incorporated daily pill-taking into their daily routines, where they stored product, and whether they disclosed their PrEP use with family members, peers, and their partner(s). This interview will also assess whether women experienced side effects and/or other barriers to pill-taking and how that influenced their adherence in the first 3 months. This interview will explore whether their risk perception and motivation to use PrEP changed over the first 3 months of use. The second interview will further explore barriers and facilitators to PrEP adherence, and will include a discussion of randomized participant's reaction to counseling about their 4 and 8 week TFV results provided at the Week 8 and 13 visits. When possible, with consent of the participant, the second interview will be conducted at the participant's residence, in order for the interviewer to observe potential environmental and structural influences that may impact PrEP adherence.

For the subset of PrEP decliners recruited for in-depth interviews, the interview guide will assess factors that were associated with not initiating PrEP. The interview will explore the woman's perception of HIV risk and need for PrEP. Personal and community beliefs about PrEP will be explored along with other factors such as stigma or concerns about side effects. Finally, family, peer and partner relationships will be explored as they relate to disclosure of sexual activity and beliefs about PrEP.

Interview guides will be developed using reviews of local literature and community advisory board (CAB) feedback. A primary purpose of this iterative process is developing language with which to ask questions that are accessible to informants and that encourages rather than discourages expression of responses in their own terminology.⁹⁰ At the end of this process, the research staff will be well-versed on the structure of the interview and the appropriateness of probes of differing detail. The semi-structured qualitative interview guide will provide a general structure for discussion but require participants to provide their own definitions of risk, motivations to use PrEP, and adherence. Participants will first be asked to discuss their general experiences with PrEP as well as medications in general. They then will be guided through an in-depth exploration of barriers and facilitators to PrEP adherence using a socio-ecological framework to guide initial areas of inquiry. Local researchers/ethnographers will conduct all qualitative interviews with oversight from the protocol team. All interviews will be audio-recorded and transcribed and translated into English by trained site staff.

When conducting a qualitative exploration, the sampling method should be designed to include a range of possible perspectives on the phenomenon under study, thus ideal qualitative samples are purposive in nature. The proposed study will utilize a stratified purposive sample, which will allow for consideration of the concepts of range, saturation/redundancy, and stratification in the sampling frame.⁹¹ We also took into account feasibility when creating our sample sizes, a factor that is especially relevant in qualitative research with "hard to reach" populations such as youth. We will stratify the sample based on PrEP acceptance and PrEP adherence, as described above. Stratification on these factors will allow for a diverse purposive sample that will include a range of types of young women who may have various experiences with PrEP use. Thus, we will conduct in-depth interviews at two time points with up to 25 young women per site (maximum N=75) or until saturation/redundancy are reached.

In addition to data collection using serial in-depth interviews, ethnographic non-participant observation data will be collected and analyzed from field notes recorded by trained social science interviewers who will observe participant waiting room discussions, adherence support clubs and related events. Non-participant observation has many strengths as a qualitative method and allows researcher to observe participant interactions as a "fly on the wall", but remain as an identified outsider.⁹²⁻⁹⁴ One weakness of overt non-participant observation is the potential that participants may change their behavior because they are aware of being observed. However, this effect (i.e., Hawthorne or observer effect) on participants' behavior has been shown to wane over time, even while observations continue.⁹⁵ Field notes collected by the interviewers will not collect specific participant identifiers, and will be analyzed using qualitative software methods to highlight common narratives about PrEP use and adherence among participants and within the community more generally.

5.15. Contraceptive Use and Pregnancy

Clinical trials of candidate biomedical prevention products, including microbicides and the efficacy trials of PrEP in women, typically have required modern forms of contraception during the trial to minimize diminishing study power due to time off product and also to reduce any potential harm

to the fetus from a product of unproven/unknown efficacy and safety. However, even in trials that required contraception, pregnancy incidence was often high: 8% per year in both VOICE¹⁰ and FACTS 001 (Delany-Moretwe, personal communication), and higher among new users, suggesting that contraception initiated solely for study participation was not used well. For women who become pregnant, PrEP offers a strategy to reduce HIV risk in the peri-conception period, and data from PrEP trials has demonstrated that peri-conception use is safe in terms of pregnancy incidence, pregnancy outcomes, and infant outcomes.⁹⁶ Thus, contraception, while essential in the efficacy trials of PrEP, should not be required in post-efficacy studies such as HPTN 082, since there are clear benefits to PrEP and demonstrated safety in women who become pregnant while using PrEP. Thus, contraception is not a requirement for enrollment in HPTN 082. However, as noted throughout the protocol, contraceptive counseling will be provided to all participants at all visits as well as access to hormonal and barrier methods.

The FDA-approved label for FTC/TDF (Truvada®) summarizes risks and benefits related to use of this medication for PrEP in pregnancy:

TRUVADA has been evaluated in a limited number of women during pregnancy and postpartum. Available human and animal data suggest that TRUVADA does not increase the risk of major birth defects overall compared to the background rate. There are, however, no adequate and well-controlled trials in pregnant women. Because the studies in humans cannot rule out the possibility of harm, TRUVADA should be used during pregnancy only if clearly needed. If an uninfected individual becomes pregnant while taking TRUVADA for a PrEP indication, careful consideration should be given to whether use of TRUVADA should be continued, taking into account the potential increased risk of HIV-1 infection during pregnancy.

Thus, while PrEP can be used in pregnancy, HPTN 082 will not continue women on PrEP if they become pregnant. Given the limited duration of follow-up in HPTN 082 (12 months), limited experience with PrEP use in younger African women and no existing protocols to formally evaluate PrEP use through pregnancy, women in HPTN 082 will be discontinued from PrEP at the time pregnancy is diagnosed. Women will continue to be followed off PrEP until their Exit visit. At each visit after pregnancy is diagnosed, the procedures for PrEP decliners (e.g. SOC, Appendix IB) will be followed per their appropriate visit including STI testing and treatment as determined by the clinician. After their Exit visit, they will be followed clinically for pregnancy outcome.

5.16. Hepatitis

Hepatitis B surface antigen (HepBsAg) and surface antibody (HepBsAb) testing will be conducted at screening for all potential participants. All participants who are not immune based on serology at screening will receive vaccination for hepatitis B. Participants will receive their first dose with their results followed by another dose after 30 days. The final dose will occur at approximately 6 months after the first dose during follow up. Potential participants with positive HBsAg results will be referred for care and treatment of active infection and cannot be enrolled.

If symptoms or signs of clinical hepatitis are present in a participant during the course of the study, the Site Investigator or designee will temporarily hold oral study product and test the participant for hepatitis (including HBsAg plus any other testing indicated by the local standard of care). If hepatitis B infection is confirmed, the participant will be referred for appropriate care.

5.17. Interim Contacts and Visits

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the

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

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff. Interim visits at which no data are collected are not documented on CRFs. Other interim contacts and visits may occur in response to AEs experienced by study participants or if an STI is identified during laboratory testing after a participant's visit. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically, record the event on the CRF, and provide or refer the participant to appropriate medical care.

5.18. Criteria for Early Termination of Study Participation

Participants (or their parents/guardians) may voluntarily withdraw from the study for any reason at any time. Site IoRs may, with the approval of the CMC, withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the OHRP), or site IRBs terminate the study prior to its planned end date. Follow up may also be ended at a site if the interim review of adherence indicates insufficient adherence. Study staff will record the reason(s) for all withdrawals in participants' study records. Participant non-adherence to the intervention or study drug regimen is not a reason for participant withdrawal from the study.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1. Safety Monitoring

Close cooperation between the Protocol Chair, study site Investigator(s), DAIDS Medical Officer, LOC CRM, SDMC Biostatistician, SDMC Clinical Affairs Staff, HPTN Laboratory Center (LC), and other study team members will be necessary in order to monitor participant safety and to respond to occurrences of toxicity in a timely manner.

The study site Investigators are responsible for continuous close monitoring and management of AEs in conjunction with IoRs. Sites are required to have detailed SOPs describing methods for AE reporting and toxicity management to ensure that AEs are reported and managed in accordance with the protocol and for alerting the CMC if unexpected concerns arise.

A sub-group of the Protocol Team, including the Protocol Chair and co-Chair, DAIDS Medical Officer, site clinicians, and the SDMC Clinical Affairs Safety Associate will serve as members of the CMC. The CMC provides support to site clinicians regarding individual participant clinical management (e.g., questions related to eligibility, toxicity management, clinical holds of study drug, permanent discontinuations, etc.).

The HPTN Study Monitoring Committee (SMC) will review all safety data. The SDMC will prepare routine study conduct and safety reports for the SMC, which will meet by conference call approximately every 6 months or as needed.

The SMC will assess PrEP adherence, based on measurement of TFV levels at the Week 13 visit at each site. If <60% of the women assessed during these reviews who accepted PrEP by Week 13 at any one site has plasma TFV levels >40 ng/mL at the Week 13 visit, the SMC may discuss discontinuation of enrollment at the site. Open label access of up to 52 weeks of PrEP to women

participating in HPTN 082 will provide equitable access to this effective prevention strategy, regardless of the adherence of other participants at a site.

6.2. Clinical Data Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the CMC if unexpected concerns arise.

Participant safety data is also monitored by the SDMC Clinical Affairs staff (SMC reviews), who review incoming safety data for completeness and consistency on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer for review.

The SDMC will prepare routine study conduct and safety reports for the SMC as indicated above. A recommendation to stop the trial may be made by the SMC at any such time that the team agrees an unacceptable type and/or frequency of AEs has been observed. If at any time a decision is made to discontinue the study product in all participants, DAIDS will notify appropriate regulatory agencies, as well as the site IoRs, who will notify the responsible IRBs expeditiously.

6.3. Adverse Event Definition and Reporting

An AE is defined as any untoward medical occurrence in a clinical research participant and which does not necessarily have a causal relationship with the product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a study product, whether or not considered related to the product. The term “study product” for this trial refers to the fixed dose oral medication FTC/TDF (described in Section 4.6). For those participants that have not been administered FTC/TDF at any point in the trial, there will be no assessment of relationship to study product.

For the purposes of this study, only serious adverse events (SAEs) and adverse events Grade 3 and above [with the exception of Creatinine Clearance, which will be measured using the Schwartz Equation (detailed in the SSP) and documented at Grade 2 or higher]. All AEs that result in a clinical hold or permanent discontinuation of study product are reported on AE Log CRF regardless of grade.

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

6.4. Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study product. The relationship of all AEs to the study product will be assessed per the clinical judgment of the investigator based on the package insert and investigator’s brochure, and as defined in Version 2.0, January 2010 (or most current version) of the DAIDS EAE Reporting Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. ‘Not related’ will be noted for AEs among participants who do not accept PrEP.

6.5. Grading Severity of Events

All AEs will be graded using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (known as the DAIDS AE Grading Table), Version 2.0, November 2014.

6.6. Serious Adverse Events (SAE)

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 (or latest version) of the Manual for Expedited Reporting of Adverse Events to DAIDS, will be used for this study. Only SAEs deemed related to the study product must be reported in an expedited fashion to DAIDS.

Related SAEs will be defined as AEs occurring at any dose that:

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

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

6.7. Discontinuation of Study Medication

Any participant who prematurely discontinues PrEP (for toxicity, preference, pregnancy or another reason) should be followed according to the procedures in the Schedule of Evaluations in Appendix IB (e.g. they will be offered the SOC provided to PrEP decliners). If PrEP is reinitiated, procedures identified in 5.12 and Appendix IC should be followed if indicated.

6.7.1. AE Grades 1 or 2

Continue FTC/TDF at the discretion of the site investigator.

6.7.2. AE Grade 3

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

6.7.3. Grade 4

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

6.7.4. Creatinine Clearance

Eligibility for enrollment in HPTN 082 mirrors CDC guidelines for starting PrEP.^{97,98} Participants who enroll with a Grade 2 CrCl will discontinue PrEP only if there is an increase in severity (to Grade 3 or 4). Participants who enroll with CrCl >90mL/min who develop a Grade 2 CrCl should discontinue study drug temporarily and be followed clinically until level returns to baseline (screening value).

Estimated CrCl< 60 mL/min (Schwartz Equation)

If the calculated creatinine clearance is <60mL/min, it should be confirmed ideally within approximately one week of the receipt of the results. Study drug should be halted temporarily awaiting confirmatory testing. The CMC should be consulted for further guidance about restarting study drug for participants who fail to have a confirmed test within two weeks of receiving the initial result.

Confirmed CrCl<60 mL/min

If the calculated creatinine clearance is confirmed to be <60 mL/min, the study drug must be temporarily discontinued. The participant will be monitored as deemed clinically necessary in consultation with the CMC until level returns to baseline (screening value) or stabilizes.

Re-testing result is ≥60 mL/min

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

6.8. Expedited Adverse Event (EAE) Reporting to DAIDS

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

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

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

6.9. Reporting Requirements for this Study

The study agents for the purposes of SAE/EAE reporting are part of a fixed dose combination tablet of FTC/TDF (also outlined in Section 4.6).

For each study participant, the SAE/EAE reporting period begins at Enrollment (Day 0) and ends when the participant's follow-up in the study ends (at the Week 52 Visit). All reportable SAEs occurring during the study reporting period will be reported to the principal investigator and for EAEs to the DAIDS RSC Safety Office in an expedited manner, within three reporting days of site awareness of the events (see definition in Appendix D of the DAIDS EAE Manual). After the study has ended, sites must report Suspected Unexpected Serious Adverse Reaction (SUSARs) as

defined in Version 2.0 of the DAIDS EAE Manual if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

Site staff will also report information regarding SAEs to their IRB or other local regulatory agencies in accordance with all applicable regulations and local IRB requirements.

6.10. Social Impact Reporting

It is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. These are social harm events. Social harm events are those negative events that a participant reports as affecting them as a result of being involved in a research study. It is not the researcher's opinion of how they perceive an event has affected a participant. A social harm that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs at least annually, or according to their individual requirements. Social harms which are also AEs will require reporting as both. Social impacts will be reviewed as part of the SMC reviews as described in Section 6.1.

As described in Section 8.4, there are also several potential social benefits for participants that may occur as a result of study participation. All social impacts (benefits and harms) will be collected and reported on CRFs during regular visits. In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SSP Manual. While maintaining participant confidentiality, study sites may engage their Community Advisory Board (CAB) in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

7.0 STATISTICAL CONSIDERATIONS

7.1. Review of Study Design

A randomized multi-site prospective study to assess PrEP acceptance and adherence among HIV-uninfected young women. All women who accept open-label daily oral PrEP will be randomized 1:1 to receive enhanced adherence counselling based on early feedback from observed drug levels or standard adherence support. PrEP will be offered in conjunction with SOC HIV prevention interventions (HIV testing, counseling, condoms, STI testing). Feedback from drug levels will be measured at 4 and 8 weeks, reported at 8 and 13 weeks, respectively.

A subset of up to ~25 women per site (maximum 75), will participate in qualitative assessments of facilitators and barriers for PrEP acceptance, adherence, acceptability and continuation.

7.2. Endpoints

7.2.1. Primary Endpoints

Consistent with the primary study objective to assess the proportion and characteristics of young HIV-uninfected women who accept versus decline PrEP at enrollment the following endpoint(s) will be assessed:

- Acceptance of oral PrEP at the enrollment visit.

Covariate characteristics assessed at baseline will include:

- Sociodemographic characteristics
 - current living situation
 - household composition
 - private space for product storage
- Partnership characteristics, partner's HIV status,
- Sexual behaviors
- HIV risk perception
- HIV stigma
- PrEP interest
- Future orientation and aspirations; self-efficacy
- Alcohol and drug use
- Gender-based violence (GBV)
- Post-traumatic stress symptoms
- Disclosure to peers, family members, teachers, and partner(s) about PrEP use and participation in the study

Consistent with the primary study objective to assess the difference in PrEP adherence using drug levels in young women randomized to the enhanced versus standard arms, the following endpoint(s) will be assessed:

- TFV levels in plasma or DBS at Weeks 13, 26 and 52 after PrEP acceptance among those who accept PrEP and are randomized. This will include young women who accept PrEP after enrollment.
- Drug not dispensed among those who accept PrEP

7.2.2. Secondary Endpoints

Consistent with the secondary study objective to assess the timing of PrEP acceptance among women who initially decline PrEP at enrollment but elect to accept PrEP during follow up, and to assess correlates of delayed acceptance the following endpoint will be assessed:

- Acceptance of PrEP during follow up amongst those who decline at enrollment

Correlates of early and delayed acceptance of PrEP (i.e., acceptance of PrEP after enrollment) will include sociodemographic factors, individual-level and partner-level characteristics, and risk practices, as described for the primary objective, assessed at baseline and at the visit where PrEP is accepted.

Consistent with the secondary study objective to assess correlates of PrEP adherence at Weeks 13, 26, and 52, after adjusting for study arm, such as adherence at prior study visits, sociodemographic factors, individual-level and partner-level characteristics, exposure to study-based adherence support, and risk practices, the following endpoint(s) will be assessed:

- TFV levels in plasma or DBS at Week 13, 26 and 52 amongst those women who accept (based on CRFs) and remain on PrEP (based on drug dispensed)
- Drug not dispensed among those who accept but do not remain on PrEP

Covariates assessed at baseline and follow-up visits will include:

- TFV levels in plasma

- Sexual risk
- Alcohol use
- Number of partners
- Age of partner
- Transactional sex
- Intimate partner violence

Consistent with the secondary study objective to assess the proportion of young women who discontinue PrEP, timing of discontinuation, and factors associated with PrEP discontinuation, the following endpoint(s) will be assessed:

- Date of discontinuation of PrEP during study follow-up
- Factors associated with PrEP discontinuation

Consistent with the secondary study objective to assess the specificity and predictive value of a PrEP readiness tool (based on the HPRM and PBM) to predict uptake and adherence to oral PrEP, the following endpoint(s) will be assessed:

- Acceptance of PrEP at Enrollment or during follow up
- TFV levels in plasma or DBS at Week 13, 26 and 52 amongst those women who accept (based on CRFs) and remain on PrEP (based on drug dispensed)
- Drug not dispensed among those who accept but do not remain on PrEP

Covariates assessed at baseline (PrEP acceptance) will be:

- PrEP readiness based on the HPRM and PBM

Consistent with the secondary study objective to explore qualitative factors that influence women's decisions to use PrEP, to adhere to PrEP, and acceptability of PrEP in the first 3 months after PrEP acceptance, the following endpoint(s) will be assessed:

- Primary themes identified from serial IDIs among up to 25 PrEP users per site about reasons women accepted or declined PrEP; barriers and facilitations to PrEP pill-taking, whether being counseled about their drug levels at Weeks 4 and 8 affected their motivation and ability to subsequently adhere to PrEP (among participants randomized to receive drug level feedback) and acceptability of PrEP.
- Barriers and facilitators to adherence as identified on counseling CRFs

Consistent with the secondary study objective to compare adverse events in women taking PrEP and not taking PrEP, the following endpoint(s) will be assessed:

- Grade 3 and above adverse events will be categorized and compared between the two groups. In addition, any grade adverse event will be evaluated for creatinine clearance in PrEP users.

Consistent with the secondary study objective to assess HIV incidence in those who accept PrEP compared to those who do not, and to assess the association with detectable TFV in PrEP users who acquire HIV infection during the study, the following endpoint(s) will be assessed:

- HIV seroconversion, assessed at Weeks 4, 8, 13, 26, 39 and 52.

Covariates assessed will be:

- Detectable and quantitative concentrations of TFV in plasma and or DBS at Weeks 4, 13, 26 and 52.

7.2.3.Exploratory Endpoints

This study includes several exploratory objectives:

- To determine the uptake and continuation of modern contraceptive methods, and the association of contraception use with PrEP uptake and adherence.
- To describe ARV drug resistance among women who acquire HIV infection
- To estimate the potential impact of PrEP use on HIV acquisition in young African women through mathematical modeling.
- To perform exploratory laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or STIs; ARV drug use; characterization of HIV in infected participants; and evaluation of laboratory assays related to the study objectives.

7.2.4. Mathematical modeling

Using the data from HPTN 082 (risk behavior, PrEP uptake, adherence, observed HIV incidence in HPTN 082), we will use mathematical models to estimate the impact of the proposed intervention on annual HIV acquisition risk among young women in the trial population across settings. A counterfactual simulation will be developed using the HIV risk score from VOICE to predict the expected number of HIV seroconversions in HPTN 082 and compared to the observed HIV incidence over 6 months. We will also model the expected HIV incidence at a range of PrEP adherence levels, bracketing those observed in HPTN 082, and using the relationship of tenofovir levels to HIV incidence in completed oral PrEP trials which showed efficacy in heterosexuals (e.g., Partners PrEP and TDF-2). We will also evaluate the impact of the intervention on short and long term HIV incidence in the overall female and male population, and assess what combinations of the intervention components are sufficient to achieve a predefined percentage (30%, 50%) reduction of population-level HIV incidence over 5 and 10 years.

7.3. Accrual, Follow-up, and Sample Size

A total of 400 women who accept PrEP at enrollment will be enrolled over a period of approximately six months. No more than 200 initial PrEP decliners will be permitted to enroll and will be offered the opportunity to begin PrEP. Enrollment will stop when 400 women have been enrolled who accept PrEP at their enrollment visit.

Given high uncertainty about the levels of adherence we will observe in this trial of young women, the sample size has been selected to have reasonable power under a range of possible adherence scenarios. Given the additional costs and complexity of measuring drug levels, a non-inferiority margin of 15% was selected, that is, assuming adherence (measured by drug levels) in the standard adherence arm is 50%, provided the 95% confidence interval for the difference in adherence between the enhanced and standard arms rules out increased adherence as high as 85%, an increase of 15%, the standard arm will be considered non-inferior. A sample size of 400 will provide better than 80 percent power to assess whether standard adherence counselling is non-inferior to enhanced adherence counselling based on adherence of 50% in the standard arm, as measured by drug levels at each of Weeks 13 and 26; this sample size will also provide better than 80% power over a range of higher and lower adherence (Table 1). The protocol will randomize participants who do not initially accept PrEP; these women are not included in these sample size considerations although they will increase the information available for PrEP adherence. For example, if an additional 100 women are randomized, the power would increase to close to 90%.

Table 1: Sample sizes required to rule out the given non-inferiority margin for different levels of adherence using a one-sided $\alpha = 0.025$. 10% loss to follow-up is assumed.

Adherence in standard arm	Non-inferiority margin	Sample Size for 80% power	Sample Size for 90% power	Observed difference that rules out the non-inferiority margin
40%	15.0%	373	499	4.5%
50%	15.0%	388	519	4.5%
60%	15.0%	373	499	4.5%
70%	15.0%	326	436	4.5%
80%	15.0%	249	333	4.5%
40%	12.5%	536	718	3.8%
50%	12.5%	559	748	3.8%
60%	12.5%	536	718	3.8%
70%	12.5%	469	628	3.8%
80%	12.5%	358	479	3.8%
40%	10.0%	838	1121	3.0%
50%	10.0%	873	1168	3.0%
60%	10.0%	838	1121	3.0%
70%	10.0%	733	981	3.0%
80%	10.0%	559	748	3.0%

This sample size also allows reasonable precision to assess the proportion of women accepting PrEP in a population at high risk of HIV. Assuming the most conservative outcome of 66% choosing to accept PrEP, 600 women will be enrolled and the $\frac{1}{2}$ width of the 95% confidence interval for the proportion will be $+-3.8\%$; for a site with 200 enrolled the 95% CI $\frac{1}{2}$ -width is $+-6.5\%$. If 80% accept, 500 women will be enrolled and the width of the 95% CI will be $+-3.5\%$. With 600 women we have 80% power to detect differences of approximately 7.75% assuming probability of acceptance of 66% and groups of equal size, for example, between younger (ages 16-19) and older women (ages 20-25).

7.4. Data Analysis

7.4.1. Primary Analyses

The proportion of women who accept PrEP at study enrollment, if the cap of 200 is not reached, will be assessed as the proportion of women who choose to accept PrEP at enrollment among the total number of women enrolled, including those who declined PrEP at enrollment. If the limit of 200 declining PrEP is reached, we would assess the proportion who accepted PrEP at enrollment up to the time these 200 enrollments are achieved. Confidence limits will be computed using the binomial distribution. Logistic regression will be used to assess the association of baseline characteristics of young HIV uninfected women between those who accept versus decline PrEP at enrollment.

Amongst those who accepted PrEP and were randomized, we will report average adherence to daily PrEP as the proportion with plasma TFV >40 ng/mL at any visit using TFV levels at Weeks 13, 26 and 52 after accepting PrEP. The difference in proportion adherent at weeks 13, 26 and 52 will be compared between arms using a t-test (assuming the normal approximation to the binomial) at each visit. Women who are missing drug level assessment but did not have drug dispensed at their most

recent visit will be defined as non-adherent. Among all women who accept PrEP, the primary assessment will compare the proportion with TFV levels in plasma >40 ng/mL across all visits between arms using logistic regression accounting for repeated measures. If DBS is used, the above TDF levels will be replaced with a TFV-DP threshold for high adherence of 700 fmol/punch, or determined from ongoing studies when available.

7.4.2. Secondary Analyses

- Timing of PrEP acceptance will be assessed using the number who accept PrEP at enrollment, and those who accept later during follow up.
- Correlates of acceptance of daily PrEP in women who do not accept PrEP at enrollment will be assessed using survival time methods
- Correlates of PrEP adherence at Weeks 13, 26 and 52, after adjusting for study arm, will be assessed using logistic regression with repeated measures amongst those who initiate PrEP at Enrollment and later during follow up. Baseline covariates and time dependent covariates will be used.
- The specificity and predictive value of a PrEP readiness tool to predict acceptance of PrEP will be assessed amongst all women screened with the PrEP readiness tool using ROC methods
- The specificity and predictive value of a PrEP readiness tool to predict adherence to oral PrEP at Week 13 among women who accept PrEP will use ROC methods. The predictive value of a PrEP readiness tool to predict adherence throughout follow-up will use logistic regression methods for repeated measures.
- Qualitative factors that influence women's decisions to use, adhere to PrEP, and acceptability of PrEP for HIV prevention will be explored through analyses of themes from in-depth interviews of a subset of randomly selected participants in the first 3 months after PrEP acceptance. Within approximately 3 days of completing the interview, staff will complete a debriefing summary report to facilitate more rapid "real-time" summary and analysis of qualitative data prior to formal analysis of interview transcripts. A codebook will be created that organizes and defines codes corresponding to key themes from the interviews, and use Atlas-ti or a comparable qualitative analysis software package to code and analyze the qualitative data. A team composed of site staff and team investigators with expertise in qualitative research will code and analyze the qualitative data.
- Adverse events will be compared between young women taking PrEP and young women who are not taking PrEP through the proportion who report SAEs on and off PrEP.
- HIV incidence will be assessed as cumulative incidence (# events/# person years) in those who accept PrEP compared to those who do not. 95% CI will be computed using the Poisson distribution.
- Relative rates of HIV acquisition will use either Kaplan-Meier or exact methods based on the Poisson distribution depending on the number of events observed. The relative risk of HIV acquisition will be compared between women who do versus do not accept PrEP.
- In PrEP users, the risk of acquisition will be compared between visits with and without plasma TFV ≥ 40 ng/mL using time-dependent survival analysis methods. For the same analysis, the value for TFV-DP in DBS will be determined from ongoing studies, or 700 fmol/punch will be used if no additional data are available.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1. Ethical Review

The HPTN Ethics Working Group (EWG) developed the [Ethics Guidance for Research](#), a network-wide ethical principles document, which is suitable for further elaboration and tailoring for each study.

This protocol and the template informed consent forms (ICF) contained in Appendices IIA-C will be reviewed and approved by the HPTN Scientific Review Committee and NIAID Prevention Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

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

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office, in accordance with the current DAIDS Protocol Registration Manual.

8.2. Informed Consent

Written informed consent will be obtained from each study participant (or the parents or legal guardians of participants who cannot legally consent for themselves and assent obtained from the child). Each study site is responsible for developing study ICFs for local use, based on the templates in Appendices IIA-C, which describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template form into local languages, and verifying the accuracy of the translation by performing an independent back-translation. Sites will assess literacy in one of the study languages as described in study specific SOPs.

Literate participants (and their parents or legal guardians, as indicated) will document their provision of informed consent by signing their informed consent forms. Because of the use of computer-assisted self-interview (CASI) and texting, participants who are not literate in a study language will not be eligible for enrollment.

Illiterate parents or guardians of participants will be asked to document their informed consent by marking their ICFs (e.g., with an X, thumbprint, or other mark) in the presence of a literate third party witness. Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants (and their parents or legal guardians as indicated) will be provided with a copy of their ICFs if they are willing to receive them.

If a participant reaches the legal age of research consent during the study, they will be asked to provide independent informed consent (i.e. Re-consent procedures will be followed).

Further details regarding DAIDS requirements for documenting the informed consent process are provided in the DAIDS standard operating procedure (SOP) for Source Documentation. Any other

local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

In many countries, children ages 16 to 18 cannot legally consent to participation in research. In particular circumstances, (for example due to discussion about sexual activities, substance abuse etc.) it may be ethically justified for minors (especially older minors i.e. 16 years and older) to choose independently i.e. without parental assistance, whether to participate in research. In such cases, the local regulatory bodies (research ethics committee or IRB) may grant a waiver for informed consent. If such a waiver is obtained, then minors will provide consent and parental consent will not be sought. If this were to occur at any site, specific requirements would be developed in collaboration with local regulatory authorities.

However, if required per local regulation, parental/guardian consent and adolescent assent for screening and enrollment will be obtained prior to beginning screening procedures. For participants that are eligible for the study, a private informed assent/consent session will be held with each individual potential participant and their parent or legal guardian, during which the study will be explained in an age-appropriate way. The assent/consent process will include a thorough review of any other current knowledge of the safety and protective effects of FTC/TDF pre-exposure prophylaxis. Sites will adapt the consents to clarify for minor participants what information will and will not be shared with parents/guardians based on local regulations.

Even under a consent/assent requirement, minors can consent independently to some procedures in the study depending on local laws, for example, in South Africa they can consent independently to:

- Medical treatment, including STI and HIV treatment
- Contraceptives access and contraceptive advice and information, including emergency contraceptives
- Pregnancy testing and counseling.

8.3. Risks

Phlebotomy

Venipuncture is sometimes associated with discomfort. Phlebotomy may lead to discomfort, dizziness, bruising, swelling, and rarely, an infection at the venipuncture site.

HIV and STI Testing

Sites will instruct women in obtaining self-collected vaginal swabs for STI testing. Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become worried or anxious while waiting for their HIV and STI test results. Individuals who learn that they have an STI or HIV infection may experience anxiety or depression related to their test results. Trained counselors will be available to help participants deal with these feelings.

Sensitive Questions

Participants will be asked questions about their sexual behavior that may make them feel uneasy. Participants do not have to answer any question that they do not want to and can stop answering the questions at any time.

Confidentiality

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (e.g., because participants could become known as at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and communities. This is discussed further in Section 6.10. Participants who are concerned about confidentiality may choose to use a pseudonym when participating in adherence club events and all adherence club attendees will be encouraged to refrain from discussing other participants with friends and families. The challenges of maintaining confidentiality in group settings are described to participants in the ICF templates.

Mobile Phones

As described in Section 4.3, participants will participate in two-way SMS texting to support PrEP adherence where feasible. It is possible that timing or volume of text messages will be inconvenient to participants or may exceed cell phone plan limits and obligate participants' to pay for them. Sites will develop a system to provide compensation for mobile phone charges to participants.

Information entered by participants into mobile phone programs will be maintained on a secure server via a secure, password-protected log-in. However, it is possible that someone who has access to the participant's phone may see this information, revealing participation in the study. To mitigate this risk, staff will develop a password system to verify the identity of the person receiving the text. It will not be possible for the study team to access any private information on participants' mobile phones. Lost or stolen phones are a practical reality. Participants will be trained to secure their phones with a password or PIN and to delete old messages. Messages will not disclose individual level information so that if accessed will not compromise confidentiality around health status or medication use.

HIV Resistance

It is possible that a participant who is taking PrEP and becomes infected with HIV during this study may develop resistance to FTC/TDF. Multiple steps will be taken to minimize the risk of drug resistance. HIV testing will be performed at all study visits for all participants. Persons with acute viral syndromes that may reflect acute HIV infection will not be eligible to accept PrEP. If acute HIV infection is suspected after Enrollment for any participant accepting PrEP, the participant will undergo evaluation using tests described in the SSP Manual. These steps should minimize the risk of drug resistance occurrence by identifying HIV infection in its early stages and stopping study drug. If any participant in HPTN 082 becomes HIV-infected during the study and develops TDF or FTC resistance, an alternative treatment regimen could be used that is not impacted by resistance to these drugs. Resistance testing will be conducted retrospectively at the HPTN LC; those results will not be returned to study sites or participants. If a participant becomes infected during the study, the site will obtain real-time resistance testing for clinical management (see Section 9.5).

Study Drug Side Effects

FTC/TDF may have side effects, some of which are listed below. This list includes the more serious or common side effects with known or possible relationship. Participants taking FTC/TDF will be monitored closely for any side effects, and are asked to report all side effects to the study site clinician.

The following side effects have been commonly associated with the use of FTC/TDF:

- Gastrointestinal intolerance (such as nausea, abdominal pain, diarrhea, or vomiting), most commonly in the first month and typically resolves
- Flatulence (gas), most commonly in the first month and typically resolves
- Headache, dizziness, tiredness, or inability to sleep

Rare, but serious side effects include:

- Rash
- Worsening or new kidney damage
- Bone pain and bone changes such as thinning and softening
- Allergic reaction
- Lactic acidosis (buildup of too much acid in the body). Lactic acidosis can cause shortness of breath, nausea and liver failure.
- Individuals with HBV who suddenly stop taking FTC/TDF may get a “flare” or worsening of hepatitis symptoms.
- Depression and unusual dreams have been reported in HIV infected persons taking Truvada.

Hepatitis B

While TDF has potent activity against HBV, severe acute exacerbations of hepatitis B have been reported in patients who are co-infected with HBV and HIV and have discontinued TDF. Although transaminitis associated with ongoing TDF use is uncommon, it has been reported. For these reasons, several mechanisms for protecting participants against AEs associated with TDF use, particularly in the setting of pre-existing or newly acquired HBV infection, are planned for HPTN 082. All participants undergo screening for active HBV with assessment of HBsAg at the screening visit. Those with active HBV infection receive standardized counseling relevant to natural history and transmission risks of HBV, and are excluded from enrollment.

Those who test negative for HBsAg but are not immune per the algorithm identified in the SSP are offered immunization against HBV and are considered eligible for enrollment. Participants who decline HBV immunization are not eligible for enrollment.

During follow-up, HBV serology may be drawn for suspected HBV infection at the discretion of the investigator of record or designee. Those participants with newly detected HBsAg will have study product discontinued.

8.4. Benefits

There may be no direct benefits to participants in this study beyond the provision of oral PrEP; however, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to prevent HIV and other infections.

In addition, participants will receive up to 52 weeks of open label oral PrEP, HIV counseling and testing as part of the study Screening process, as well as free HBV and STI Screening.

Participants found to be susceptible to HBV will have the vaccination series. Participants found to have STIs will be offered STI treatment. Participants who become pregnant will be referred for or provided antenatal care. Participants with a reactive or positive HIV test result identified at any time after study Enrollment will have further testing to confirm infection, as described in the SSP Manual, and will be referred for care. See Section 5.13.

Compensation

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

8.5. Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link PTID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Staff will use a code word prior to each text message (similar to Weltel) to prevent inadvertent disclosure of study participation in the case of shared mobile phones. Staff will not be able to access any information on participants' mobile phones.

Participants will be told as part of the informed consent process that observers may collect ethnographic data when they are conversing in waiting rooms, adherence clubs, etc. These data will not include identifiable information about participants.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; Gilead Sciences, Inc.; representatives of the HPTN LOC, SDMC, and/or LC; other government and regulatory authorities, and/or site IRBs/ECs.

For minors who must have parental consent to participate, it is further noted that STI results, HIV, and pregnancy test results are given to the adolescents and not their parents. However, minors who acquire conditions with long-term physical and emotional complications will require on-going support, and therefore, it is in their best interests to disclose changes in their health status to a trusted adult within a reasonable timeframe. Accordingly, minors who become HIV positive or pregnant ought to be encouraged to identify and disclose this information to a trusted adult (not necessarily the parent or guardian). The results of any behavioral risk assessments completed by minors as part of the HPTN 082 study (including sexual activity, drug and alcohol use, etc.) also will not be shared with their parents or legal guardians.

8.6. Communicable Disease Reporting Requirements

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

8.7. Reports of Sexual Abuse

Reporting requirements and confidentiality of minor's information should be detailed in site specific consents/assents and SOPs.

8.8. Study Discontinuation

The study also may be discontinued at any time by NIAID, the HPTN, Gilead Sciences, Inc., other government or regulatory authorities, and/or site IRBs/ECs.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described below, in Appendices IA-C, and in Section 5.0; additional tests to be performed at a subsequent visit for participants who have a reactive or positive HIV test result are described in Appendix ID.

9.1. Local Laboratory Specimens

As described in Section 5, the following types of specimens will be collected for testing at the local laboratory (LL):

HIV rapid testing (US FDA cleared assay if an FDA-cleared test is not available, the HIV rapid test must be approved by the HPTN LC)

- HIV testing (see SSP Manual)
- HBV testing (HBsAg, HBsAb)
- Creatinine for creatinine clearance
- Pregnancy testing
- TV testing (vaginal swab)
- GC/CT testing (vaginal swab or urine)
- Syphilis testing (serum)
- Plasma TFV testing*
- CD4 cell count testing (participants who acquire HIV infection)
- Resistance testing (for clinical management for participants who acquire HIV infection)
- Plasma storage
- DBS storage

*Plasma TFV testing for use in counseling will be performed at a centralized laboratory in Africa designated by the HPTN LC; CPQA approval is required for this testing. If this laboratory does not have CPQA approval for plasma TFV testing, this testing will be performed at the HPTN LC.

Local laboratories performing tests will be monitored by Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) and must demonstrate successful participation in the relevant External Quality Assurance (EQA) programs.

Local laboratories may also perform CD4 cell count testing as indicated in Appendix ID. Laboratories performing these tests will be monitored by the Immunology Quality Assurance (IQA) programs and must demonstrate successful participation in the relevant EQA programs.

Each study site will adhere to standards of Good Clinical Laboratory Practice (GCLP), and local standard operating procedures for specimen management including proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the LL will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the study-specific procedures manual.

9.2. Laboratory Center Specimens

As described in Section 5, the following types of specimens will be collected for testing at the HPTN LC or at a designated laboratory:

- HIV QA testing (see below)
- HIV viral load
- Pharmacology testing
- Resistance testing
- Other testing*

* Other testing may include: characterization of HIV (e.g., HIV subtype, expanded resistance testing, and phylogenetic analysis); analysis of the host response to HIV infection; analysis of HIV incidence; analysis of ARV drug use; and characterization of HBV. Samples collected in the study may also be used to evaluate assays related to HIV infection and STIs. In some cases, testing will be performed at a commercial laboratory or other laboratory designated by the HPTN LC. These assessments will be performed retrospectively; results will not be returned to study sites or participants (with the possible exception of HIV diagnostic testing, if results obtained at the HPTN LC differ from site results).

9.3. Quality Control and Quality Assurance Procedures

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

9.3.1. QC for HIV Diagnostic Testing

The HPTN LC will perform HIV diagnostic testing for QC. Before performing HIV diagnostic testing, all sites must have validated their HIV test kits that will be used in the study. Local laboratories will perform testing for HIV diagnosis at Screening, Enrollment, and other scheduled visits. Algorithms for HIV diagnostic testing are provided in the SSP Manual.

Participants who have any reactive/positive HIV test result at Screening or have a reactive/positive HIV rapid test at Enrollment will not be eligible for Enrollment in the study, regardless of subsequent test results. In these cases, HIV infection status will be confirmed using local HIV testing guidelines. Participants who have any reactive/positive HIV test after Enrollment will have their HIV infection status determined using procedures described in the SSP Manual. Additional testing will be performed if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition (see SSP Manual). In all cases, HIV infection following Enrollment must be confirmed using two independent samples collected on different days.

9.3.2. QC for HIV RNA Monitoring

Quantitative HIV RNA (viral load) testing will be performed retrospectively at the LC for participants with confirmed HIV infection. Viral load testing will be performed in HIV-infected participants at the visit when HIV infection is confirmed, and may be at subsequent study visits. Results of this testing will not be returned to study sites or participants.

9.3.3.QC for CD4 Cell Count Determination

For participants who become HIV-infected during the study, CD4 cell count testing will be performed at study sites at the time when HIV infection is confirmed. Laboratories performing CD4 cell count testing must be enrolled in the United Kingdom National External Quality Assessment Service (UK NEQAS) program through the DAIDS IQA program.

9.4. Pharmacology Testing

Assays used to evaluate PrEP adherence must be approved for use in HPTN studies by the cross-network Clinical Pharmacology Quality Assurance (CPQA) program. The quality of the assays will be monitored through a proficiency testing program administered by the CPQA, when available. Laboratories performing this testing will adhere to Good Laboratory Practice (GLP) for processing all samples.

9.5. Resistance Testing

Resistance testing will be performed at the HPTN LC or a laboratory designated by the HPTN LC for all participants who acquire HIV infection. This testing will be performed retrospectively using stored specimens. Results of resistance testing performed at the HPTN LC or an HPTN LC-designated laboratory will not be returned to study sites or study participants. Resistance testing may also be performed at local laboratories in real-time for clinical management using locally-available resistance test methods. Study specimens may not be used for this testing; additional specimens must be collected for this testing.

9.6. Specimen Storage and Possible Future Research Testing

Study site staff will store all plasma, and DBS specimens collected in this study for at least three years after the end of the study (i.e., after completion of the last study visit). In addition, study participants (and their parents/guardians as appropriate) will be asked to provide written informed consent for their specimens to be stored after the end of the study for possible future testing related to the study objectives. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed after all protocol-related testing has been completed; sample destruction must be coordinated with the HPTN LC and HPTN SDMC.

9.7. Biohazard Containment

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

10.0 ADMINISTRATIVE PROCEDURES

10.1. Protocol Registration

Initial Registration of the protocol by the DAIDS Protocol Registration Office (PRO) is required prior to implementation of this protocol. As part of this process, each site must have the protocol and protocol ICF(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO

at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. In the case of Initial Registration, site-specific ICFs **WILL** be reviewed and approved by the DAIDS PRO. Sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

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

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which can be found at <http://rsc.tech-res.com/protocolregistration/>.

10.2. Study Activation

Pending successful protocol registration and submission of all required documents, the HPTN LOC staff will “activate” a site. Study implementation (screening and enrollment) may not be initiated until a study activation notice is provided to the site by the HPTN LOC. In addition, if study “activation” is determined to be necessary for any subsequent amendments, study implementation may not be initiated until a study activation notice is provided to the site by the HPTN LOC.

10.3. Study Coordination

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

Study implementation will be directed by this protocol as well as the SSP manual. The SSP manual — which will contain links to the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials, as well as the DAIDS Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, dated (January 2010) and the DAIDS Toxicity Tables — will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; and other study operations.

Study CRFs and other study instruments will be developed by the protocol team and HPTN SDMC. Data will be transferred to the HPTN SDMC for data entry, cleaning, reporting and analysis. Quality control reports and queries will be generated and distributed to the study sites on a routine schedule for verification and resolution.

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

10.4. Study Monitoring

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

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

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., ICFs, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC, NIAID, site IRBs/ECs, and US regulatory authorities (OHRP). A site visit log will be maintained at each study site to document all visits.

10.5. Protocol Compliance

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

10.6. Investigator's Records

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. Under the US Department of Health and Human Services (DHHS) regulations, the Investigator is required to retain all study records relating to research for at least three [3] years after completion of the research, or longer if needed to comply with local regulations.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g. when all subjects are off study);
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;
- All analysis of identifiable private information described in the IRB/EC-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including ICFs, locator forms, CRFs, notations of all contacts with the participant, and all other source documents.

10.7. Use of Information and Publications

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

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Appendix IA: Schedule of Study Visits and Procedures for PrEP Acceptors

	Screening	Enrollment	Weeks 4 & 8	Week 13	Weeks 26 & 39	Exit visit
Administrative and Behavioral Evaluations/Procedures						
Informed Consent	X					
Collect/Update Locator information	X	X	X	X	X	X
Validate phone number and texting capacity	X					
HIV risk score determined	X					
Demographic information	X					
Social impact assessment		X	X	X	X	X
AE assessment			X	X	X	X
Behavioral risk assessment	X		X	X	X	X
Standard HIV risk reduction counseling (including providing condoms)	X	X	X	X	X	X
PrEP interest questions	X	X		X		
Study drug adherence assessment			X	X	X	X
Study drug supply		X	X	X	X	
Randomization		X				
Adherence support (see Section 4.3)		X	X	X	X	
Clinical Evaluations/Procedures						
Complete medical history (including concomitant meds and STI symptoms)		X				
Contraceptive assessment and associated counseling as appropriate	X	X	X	X	X	
Provide HBV vaccine, if susceptible ³		X ¹	X ¹		X ¹	
Interim medical history (including concomitant meds and STI symptoms)			X	X	X	X
Symptom-directed physical exam	X		X	X	X	X
STI treatment, if indicated ²	X	X	X	X	X	X
Blood collection	X	X	X	X	X	X
Urine collection (if used for pregnancy testing) ³	X	X	X	X	X	X
Urine collection (if used for STI testing) ⁴	X				X ⁵	X
Participant vaginal swab collection for STI testing ⁶	X				X ⁵	X
Laboratory Evaluations/Procedures						
HIV testing (see SSP Manual) ⁴	X	X	X	X	X	X
Hepatitis B serology ⁷	X					
Serum creatinine (for creatinine clearance, Schwartz Equation)	X				X ⁵	X
Pregnancy testing ^{3,4}	X	X	X	X	X	X
STI testing (TV ⁶ , GC/CT, syphilis)	X				X ⁵	X
Plasma TFV concentration (per randomization)			X			
Plasma storage	X	X	X	X	X	X
DBS storage			X	X	X	X

¹ HBV vaccine will be offered to all participants who are identified as not immune during screening. Two doses will follow the initial dose at Weeks 4 and 26.

² Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines. An interim visit for STI treatment may be scheduled if testing performed after the visit indicates that the woman has one or more STIs.

³ Pregnancy testing may be performed using urine, plasma or serum samples.

⁴ Urine pregnancy testing and HIV rapid testing (if performed) may be performed in the clinic or the laboratory.

⁵ Week 26 only.

⁶ Participant collected vaginal swab samples will be used for TV testing; if a site does not have a validated GC/CT assay for vaginal swabs, urine will be used for GC/CT testing.

⁷ Includes HepBsAg, HepBsAb.

Appendix IB: Schedule of Study Visits and Procedures for PrEP Decliners

Because the decision to accept or decline PrEP is at Enrollment, screening procedures for all participants is the same.

	Enrollment	Weeks 4 & 8	Week 13	Weeks 26 & 39	Exit visit
Administrative and Behavioral Evaluations/Procedures					
Collect/Update Locator information	X	X	X	X	X
Social impact assessment	X	X	X	X	X
AE assessment		X	X	X	X
Behavioral risk assessment		X	X	X	X
Standard HIV risk reduction counseling (including providing condoms)	X	X	X	X	X
PrEP interest questions	X	X	X	X	
Offer PrEP		X	X		
Clinical Evaluations/Procedures					
Complete medical history (including concomitant meds and STI symptoms)	X				
Contraceptive assessment and associated counseling as appropriate	X	X	X	X	
Provide HBV vaccine, if susceptible ¹	X ¹	X ¹		X ¹	
Interim medical history (including concomitant meds and STI symptoms)		X	X	X	X
Symptoms-directed physical exam		X	X	X	X
STI treatment, if indicated ²	X	X	X	X	X
Blood collection	X	X	X	X	X
Urine collection (if used for pregnancy testing) ^{3, 4}	X	X	X	X	X
Urine collection (if used for STI testing) ⁶				X ⁵	X
Vaginal swab collection for STI testing ⁶				X ⁵	X
Laboratory Evaluations/Procedures					
HIV testing (see SSP Manual) ⁴	X	X	X	X	X
Pregnancy testing ^{3, 4}	X	X	X	X	X
STI testing (TV ⁶ , GC/CT ⁶ , syphilis)				X ⁵	X
Plasma storage	X	X	X	X	X

¹ HBV vaccine will be offered to all participants who are identified as not immune during screening. Two doses will follow the initial dose at Weeks 4 and 26.

² Based on reported symptoms, previous lab testing and/or examination in accordance with national guidelines. An interim visit for STI treatment may be scheduled if testing performed after the visit indicates that the woman has one or more STIs.

³ Pregnancy testing may be performed using urine, plasma or serum samples.

⁴ Urine pregnancy testing and HIV rapid testing (if performed) may be performed in the clinic or the laboratory.

⁵ Week 26 only.

⁶ Participant collected vaginal swab samples will be used for TV testing; if a site does not have a validated GC/CT assay for vaginal swabs, urine will be used for GC/CT testing.

⁷ Includes HBSAg, HBSAb

Appendix IC: Additional procedures at the PrEP initiation visit for those who accept PrEP after enrollment

Participants who initially decline PrEP at enrollment will be offered PrEP throughout follow up. Participants who discontinue PrEP for any reason should also follow these procedures to ensure they may safely begin PrEP.

Administrative and Behavioral Evaluations/Procedures	
Study drug supply	X
Randomization	X
Adherence support (see Section 4.3)	X
Clinical Evaluations/Procedures	
Symptom-directed physical exam	X
Laboratory Evaluations/Procedures	
Creatinine clearance	X
Screening for signs of acute HIV infection and HIV testing	X

Appendix ID: Schedule of Study Visits and Procedures for Participants with Suspected or Confirmed HIV Infection

	Time of Diagnosis (Confirmatory Visit)	3 Months Post-Confirmatory Visit
Administrative Evaluations/Procedures		
Update locator information	X	X
Linkage to HIV care and associated counseling	X	X
Clinical Evaluations/Procedures		
Symptoms directed physical exam	X	
Blood collection (this must be collected on a date different from the date where an initial reactive/positive test results was obtained)	X	X
Laboratory Evaluations/Procedures		
HIV testing ¹	X	
CD4 cell count testing	X	X
Additional plasma storage ²	X	X
HIV genotyping ³	X	

¹Procedures for HIV testing are provided in the SSP Manual.

²Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC, including resistance testing (see Section 9).

These assessments will be performed retrospectively; results will not be returned to study sites or participants (with the possible exception of HIV diagnostic testing, if results obtained at the HPTN LC differ from site results).

³Real-time resistance testing (HIV genotyping) for clinical management requires that a separate specimen must be obtained and the testing must be arranged locally.

Appendix IIA: Sample Screening/Enrollment Informed Consent Form

HPTN 082

Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study

Final Version 1.0/ 8 December 2015

DAIDS Document ID: 12068

Sponsored by: Division of AIDS, US National Institute of Allergy and Infectious Diseases, US National Institute of Mental Health, US National Institutes of Health.

PRINCIPAL INVESTIGATOR: *[Insert Name]*

PHONE: *[Insert Number]*

INTRODUCTION

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

Before you decide whether you/your child will join the study, we would like to explain the purpose of the study, the risks and benefits to you/your child, and what is expected of you/your child.

If you are under X years, we will also need to obtain the consent of your parent or legal guardian in order for you to participate.

If your child is under X years, you are being asked to allow your child to participate in this research study.

PARTICIPATION IS VOLUNTARY

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

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

- Your participation/your child's participation is voluntary. You do not/your child does have to take part in any of the tests or procedures in the study.
- You/your child may decide not to take part in the study, or you/your child may decide to leave the study at any time without losing your/her regular medical care.
- If you/and your child decide not to take part in the study, you/she can still join another study at a later time if there is one available and you/she qualify.

- You/your child cannot join this study if you are/she is taking part in another study of drugs or medical devices. You are/she is asked to tell the study staff about any other studies you are/she is taking part in or thinking of taking part in. This is very important for your/her safety.

PURPOSE OF THE STUDY

Young women in southern Africa have a high risk of becoming HIV infected. Recent studies make us believe that either between 1 in every 10 or 1 in every 20 young southern African women will become HIV infected every year. Taking medication to prevent becoming HIV-infected is called “pre-exposure prophylaxis” or “PrEP.” Four studies that compared PrEP to placebo (a pill which looks like the regular pill but does not have the real drug) have shown that PrEP works very well in preventing HIV infection, and that the main thing which impacts how much protection PrEP provides is whether someone takes PrEP every day. However two other studies that compared PrEP to placebo in young African women did not show protection against HIV with PrEP because too few women took their pills. Very few women (fewer than 1 out of 3 women) had PrEP drug that could be found in their blood. Now that we know that PrEP works from multiple studies, it is important to understand whether young women in southern Africa are interested in and able to take PrEP.

The purpose of the HPTN 082 study is to find out whether young women in southern Africa at risk of HIV are willing to start and continue to take PrEP every day for up to one year. This study will ask young women what they like and do not like about taking PrEP. We will also ask questions to find out what makes some young women more or less interested in starting PrEP. We also hope to find out if young women find it helpful to hear about how much PrEP drug is in their blood during their first two follow-up visits with counselors.

HPTN 082 is enrolling young women ages 16-25, only women ages 18 and above were included in the PrEP trials we have discussed. Other studies are currently underway of oral PrEP in 16 and 17 year olds.

The name of the pills being used for PrEP in this study is Truvada®. Truvada® is a tablet that contains two medications called “emtricitabine” and “tenofovir” that are commonly used to treat HIV infection. It is not a cure for HIV or AIDS but is generally safe when used as treatment for HIV. Several studies have also shown that Truvada® is safe and effective in preventing HIV when taken by people who are HIV-negative. There are some side effects of Truvada® that sometimes occur. These are described later in this consent form.

Not everyone in this study will decide to start taking Truvada® (their PrEP pills), right away or possibly at any time during this study. This study will enroll 400 women at three sites in southern Africa who are interested in beginning PrEP right away. We will also enroll up to 200 women at these same sites who are interested in PrEP but may not want to begin taking it right away or possibly at any time during follow-up in the study. If you/your child or the study staff decide that you/your child should stop taking PrEP you/your child can still be in this study.

The US FDA recommends taking Truvada® daily. This is because PrEP studies show that the ability of Truvada® to prevent HIV depends a lot on how often people actually take their pills. In PrEP studies among people in Africa, those who took PrEP and PrEP drug was found in their blood were more likely to not get HIV. Remember that PrEP will not protect you/your child from pregnancy or other sexually transmitted infections you/she can get while having sex so it is important to keep using condoms or other means of pregnancy prevention. Condoms will be given to you/your child at every visit.

If you decide/your child decides to start taking PrEP, it is important that you/your child try to take PrEP on a daily basis. This will give you/your child the highest level of protection against HIV and help you/your child build a routine for taking your/her pills. If you are/your child is having problems taking

your/her pills, have/has concerns, or decide not to take your/her pills for any reason, please tell us. We encourage all participants to discuss any concerns about this study, or the safety of Truvada®, with the study staff.

To help young women who decide to take PrEP remember to take their pills, we will ask you/your child to sign up with a special confidential system that will send you/your child a text message every week for the first 13 weeks. We will send you/your child messages that provide information about HIV and pregnancy prevention, to remind you/your child to attend study visits, and ask you/your child about your/her health. We will not refer specifically to your/her health status or your/her use of PrEP. If you have/your child has a problem, we will provide you/her with a 24 hour number to contact study staff messages. We can always call back. We can help you/your child to understand how to delete these message from your/her phone if you are/she is concerned about others seeing them. At 13 weeks you/she can decide to continue to receive the text messages or stop. We will not be able to see any information on your/her mobile phone and any texts you/she send us will not be shared with anyone outside of our research team.

We will also provide counseling about taking PrEP regularly at each visit to learn if you/your child are having difficulty with taking the pill every day and to help find ways to make it easier for you/your child to take PrEP daily. You/your child will be able to come to a monthly peer group club to talk about taking PrEP with other participants on this study as well as have fun.

If you/your child decide to take PrEP and you are/your child is part of this study, we will use a lottery-like system to determine whether you/your child will receive counseling based on how much PrEP drug is in your/her blood. Half of the young women who decide to take PrEP will receive counseling that talks about how much PrEP drug is found in their blood and half of the young women will not. If you are/your child is in the group that gets this type of counseling, we will use the blood sample taken four weeks and again eight weeks after you/your child start PrEP to test for the PrEP drug in your/your child's blood and will give you/your child those results at your/her next visit four weeks later. We will talk to you/your child about your/her PrEP adherence based on the drug levels.

STUDY PROCEDURES

If you decide/allow your child to join the study, you/your child will be asked to come to this clinic for up to one year (52 weeks). After the enrollment visit when most young women in the study will begin taking PrEP, we will ask you/your child to return for a visit every month for three months. Then every three months you/your child will be asked to come in again for no more than six visits after enrollment. We refer to these visits here as your/your child's Week 4, 8, 13, 26, 39 and 52 visits.

Screening Visit

Today is your/your child's screening visit when you/your child will read, discuss, understand, and sign this form. You/your child will be offered a copy of this form to keep. The procedures done at the Screening visit will take about 1-2 hours.

The study staff will first make sure that you are/your child is eligible to participate in this study by:

- Confirming where you/your child live and how to contact you/her.
- Text your/her cell phone to make sure we have the right number on file. Because an important part of this study is sending you/your child text messages, you/she cannot be in this study if you do/she does not have a cell phone that you/she can use regularly.

- Asking you/her questions about yourself/herself including, your/her age, ethnic group, health, your/her interest in using PrEP, people you have/she has sex with and your/her sexual practices, and whether you use/she uses alcohol or drugs.
- Collecting a blood sample [sites to insert amount] to test:
 - The health of your/her kidneys
 - To see if you have/your child has or can get hepatitis
 - For common infections you/she can get when you have/she has sex, including HIV
 - *To see if you are/she is pregnant (depending on site testing protocol)*
 - An extra sample of blood [site to insert amount] will be drawn in case there is a question about your/her lab results
- Collecting a urine sample to test:
 - For common infections you/she can get when you have/she has sex
 - *To see if you are/she is pregnant (depending on site testing protocol)*
- Talking with you/her about HIV and ways to protect yourself/herself from getting it and offer you/her condoms.
- Talk to you/her about ways to keep from getting pregnant. If you are/she is pregnant you/she cannot join this study.
- Showing you/her how to use a swab to test for common infections you/she can get when you have/she has sex.

The results from the HIV testing will be available [*site to insert timeframe of testing*]. You/your child will be contacted about the results of your/her other tests when they are available. If you have/she has gonorrhea, chlamydia, trichomonas or syphilis, you/she will be referred for treatment (*sites to add specifics about this here as necessary*).

No other samples collected at the time of Screening will be kept or used for any other tests other than those listed above.

Confirmation of Eligibility:

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

- You/she will be told your/her HIV test results and what they mean.
- If you have/she has a positive HIV test result, you/she will not be eligible for the study even if additional tests show that you do not/she does not have HIV. If you have/she has a positive HIV test result, you/she will be referred for further HIV testing (if it is not clear whether you have/she has HIV infection) and you/she will be referred for appropriate medical care.
- If your/her HIV test results indicate that you do not/she does not have HIV infection, you/she will be eligible to enroll in the study if there are no other reasons that you/she can't enroll.

- Some people may not be eligible to join the study because of information they provide during the Screening process or because of laboratory test results. If this is the case, we will tell you that you are/her that she is not eligible for the study.
- You/she will be given referrals for other health services, if you need/she needs them.

Enrollment Visit

If you are/she is eligible for this study and decide to take part in the study, you/she will be asked to return for the enrollment visit. This visit will last between 1-2 hours. During the visit, the study staff will:

- Confirm where you live/she lives and how to contact you/her.
- Talk with you/her about HIV and ways to protect yourself/herself from getting it and offer you/her condoms.
- Talk to you/her about your/her medical history and ask you/her about any other medicines you are/she is taking.
- Collect a blood sample *[sites to insert amount]* to test:
 - For HIV
 - *To see if you are/your child is pregnant (depending on site testing protocol)*
 - An extra sample of blood *[site to insert amount]* will be drawn in case there is a question about your/her lab results
- *Ask you/her for a urine sample to see if you are/she is pregnant [site to adjust].* We will also talk to you/her about ways to keep from getting pregnant. If you are/she is pregnant you/she cannot join this study.
- If you/she agree to begin PrEP during this visit and you are/she is eligible for this study, we will give you/her a supply of PrEP pills. We will also discuss any side effects they may cause and develop a plan for remembering to take your/her pill every day at around the same time. We will use a lottery-like system to determine whether you/your child will receive counseling based on how much PrEP drug is in your/her blood 4 weeks and 8 weeks after starting PrEP.
- Give you/her the results of any laboratory tests from your screening visit including tests for common infections you can get when you have sex.
- If your/her screening tests show that you do/she does not have immunity to hepatitis B (immunity means protection against infection), you/she will be given the hepatitis B vaccine at no cost to protect your/her health. You/she will have the hepatitis B vaccine three times total *[sites to insert local guidelines regarding vaccine protocol, if applicable]*.

Follow up visits:

After enrollment, you/she will be asked to come back for visits at one month (Week 4), two months (Week 8), three months (Week 13), six months (Week 26), nine months (Week 39) and one final visit a year later (week 52). During these visits, the study staff will:

- Confirm where you/she live and how to contact you/her.

- Ask you/her questions about yourself/herself, your/her health, people you have/she has sex with, ways that you are/she is keeping yourself/herself from getting pregnant, and sexual practices, and whether you use/she uses alcohol or drugs.
- Talk with you/her about HIV and ways to protect yourself/herself from getting HIV and offer you/her condoms.
- At each visit a blood sample [sites to insert amount] will be taken to test:
 - For HIV
 - To see if you are/she is pregnant [*depending on site testing protocol*] (if you are/she is pregnant you/she cannot continue taking PrEP)
 - An extra sample of blood [site to insert amount] will be drawn at certain visits in case there is a question about your lab results
- At some visits blood samples [sites to insert amount] will also be used to test:
- For common infections you/she can get when you have/she has sex. If your/her blood test from Screening showed that you/she can get hepatitis but do not currently have the disease, we will give you/her all three doses of the vaccine to prevent you/her from getting this disease in the future.
- Ask you/her for a urine sample to test for pregnancy [*site to adjust depending on testing protocol*]. If you are/she is pregnant you cannot continue to take PrEP.
- Show you/her how to use a swab to test for common infections you/she can get when you have/she has sex.
- Ask you/her if you if there have been updates to your/her medical history and any other medicines you/she may have taken recently.
- We will discuss any health problems you/she might be having. If you/she tell us about any health problems you are/she is having we may need to do an exam or additional tests to help us understand what is causing the problem and how to help you/her.
- Give you/her the results of any laboratory tests from your/her last visit including tests for common infections you/she can get when you have/she has sex.

If you **DO**/your child **DOES begin PrEP**:

- You/she will be asked about your/her medical history and any other medicines you are/she is taking.
- Your/her blood will also be tested for:
 - The health of your/her kidneys
 - How much Truvada® is in your/her body
- We will give you/her a supply of PrEP at each follow up visit. We will also discuss any side effects you/she might have experienced and discuss your/her plans for remembering to take your/her pill every day at around the same time. These sessions will be recorded on audiotape so that the researcher does not miss any information that you/she provide. If you do not/she does not want this session taped, please let your/her counselor know.

- Two months after you/she start PrEP, about half of the women will receive counseling based on how much PrEP drug is found in their blood. If you/your child is in this group, we will tell you/your child what we learned about how much Truvada® was in your/her body after one month and again after two months of taking the pills. We will use these test results to talk to you/her about what makes it easier and harder to take your/her PrEP pills.
- We will also send you/her text messages on your/her mobile phone on a regular basis for the first 3 months (13 weeks) after enrollment. These messages will ask you/her if you have/she has had any problems taking your/her pills and offer ideas for how taking pills might be easier.
- You/she will also have the opportunity to attend regular events with other young women who are in this study where you/she can have fun and talk about using the pills.

If you **DO NOT**/she **DOES NOT** begin PrEP at enrollment, you/she will have the opportunity to begin PrEP at every study visit until your/her next to last study visit (Week 39).

If at any of those visits you/she **decide to begin PrEP** we will:

- Talk to you/her about your/her current health, ask you/her questions about your/her medical history and ask you/her about any other medicines you are/she is taking.
- Your/her blood will also be tested for:
 - The health of your/her kidneys
- After we test you/her to make sure you do not/she does not have HIV, we will give you/her study pills. We will discuss any side effects they may cause and develop a plan for remembering to take your/her pill every day at around the same time. We will also use a lottery-like system to determine whether you/your child will receive counseling based on how much PrEP drug is in your/her blood.

Stored Samples

Some of the blood samples collected at the enrollment and follow-up visits will be stored for other testing that is part of this study. Samples may be tested for drugs used to prevent and treat HIV infection, including Truvada®. If you/your child have/has HIV or hepatitis infection, the stored blood may also be used to study the HIV and hepatitis virus, and the body's response to these infection. Samples may also be used to learn more about other infections transmitted through sex, and to evaluate and improve laboratory methods for evaluating infections. The stored samples will be labeled with only your/your child's study number and will be tested at special laboratory facilities that may be located in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. Results from this testing will not be returned to the study site or you/your child.

Leftover Samples

There may be some blood samples leftover after all of the study testing has been completed. We would like to use these samples for future research studies related to HIV infection, hepatitis, and other infections people can get when they have sex. If you agree for us to use the leftover samples, you will be asked to sign a separate form. If you do not agree to have your/your child's leftover samples stored, you/your child can still be in this study. If you agree to store your leftover samples but change your mind later, you can contact study staff. We will then destroy your/your child's leftover samples.

What will happen if you/your child permanently stop taking your/her study drugs (if applicable):

If you/your child permanently stop taking the study drugs during the study for any reason, we will ask you/her to continue to come for your/her regular study visits, but you/she will no longer have certain

procedures, like answering questions about taking the study pills or having your/her blood tested for Truvada®.

RISKS AND/OR DISCOMFORTS

Risks potentially related to the Truvada® medication

You/Your child may have symptoms or side effects while participating in the study. These symptoms or sides effects may be due to participation in the study or due to illnesses that have no relation to the study, like a cold or flu. You/Your child should tell the staff at the study clinic about any symptoms that you/she feel while you are/she is participating in the study. You/she will be given a telephone number so you/she can contact the clinic. You/your child should call them if you/she experience any symptoms.

The side effects that might happen in a few people taking Truvada® are well known because the medication has been used by many people. Some mild side effects are expected to occur in up to 1 in 10 persons who take Truvada®. Other side effects are more serious, but are expected to occur in less than 1 in 100 persons who take Truvada® and resolve when Truvada® is stopped. Occasional side effects include: mild problems of kidney function that are only detected by laboratory tests; lack of energy/fatigue; upset stomach, vomiting, soft or liquid stools; dizziness. Many of these side effects only last for the first month of taking the pills and then go away completely or get better with time.

Rare side effects include: rash; problems with how your/your child's liver works; serious kidney damage; allergic reaction. In some people, there was a slight difference in the thickness of their bones which doctors could see in special x-rays. But people who had these changes did not have broken bones more often than people who did not take Truvada®. Lactic acidosis has occurred in HIV infected persons taking Truvada®, in combination with other drugs. Lactic acidosis is a rare condition that can cause shortness of breath, nausea, and liver failure. This is a serious side effect of some medications used for HIV infection but is infrequently observed with Truvada. You/your child should call or come to the study clinic if you have/she has unexplained increased or decreased urination, weight loss, cramps, muscle pain, dizziness, excessive fatigue, nausea, vomiting, or shortness of breath. If you have/your child has these symptoms, or any other symptoms that concern you/her, the study staff will evaluate your/your child's symptoms and determine whether you/she should stop Truvada® pills. Depression, headache, inability to sleep, and unusual dreams have also been reported in HIV infected persons taking Truvada. ®

The use of potent antiretroviral drug combinations may rarely be associated with an abnormal placement of body fat and wasting. Some of the body changes include:

- Increase in fat around the waist and stomach area
- Increase in fat on the back of the neck
- Thinning of the face, legs and arms
- Breast enlargement

Other medications

Many medications can be taken at the same time as the medications used in this research study. However, some medications should not be taken while you are/your child is taking Truvada®. When you visit the study clinic, we will ask you/your child about other medications that you are/she is taking. The medications used in this study may have side effects that no one knows about yet. The researchers will let you/her know if they learn anything that might make you change your/her mind about continuing to participate in the study.

HIV testing

We will perform an HIV test at every visit, which is routinely done to make sure that you are/your child is HIV negative before starting or continuing PrEP. You/your child will be counseled before and after this

test is done. [Sites to insert reporting responsibilities in the state the site is located in. Also include whether if a participant tests positive, the results will become part of public health records, or any other record (medical file, etc.)] You/your child can come to the clinic and ask for an HIV test anytime you are/she is worried.

Risk of acquiring HIV infection and drug resistance

You/your child may become infected with HIV during this study. It is very important to talk to your/her counselor about all the different ways you/your child might be able to keep yourself/herself from getting HIV, like using condoms every time you have/she has sex and keeping your/her number of sexual partners low. If you/your child becomes infected with HIV while you are/she is taking PrEP, you/she could become infected with a strain of the HIV virus that might be harder to treat with Truvada® or other medications used for HIV treatment. We call this “resistance” which is very rare in people who take PrEP. Resistance to any medications used to treat HIV may make effective HIV treatment more difficult and may limit your/your child’s treatment options. If you/your child become infected with HIV, we will offer testing for HIV drug resistance to you/your child as part of your/her care. You/your child will be able to discuss treatment and the generation of resistance to medications with the study doctor. If you have/your child has any questions about the risks of symptoms or side effects, including anything we have said here please talk to your/your child’s study doctor.

Pregnancy

During this study, you/your child will receive counseling at each visit about the potential that you/she may become pregnant. You/your child will also receive counseling about your/her options for preventing pregnancy. You/your child can receive some forms of contraception from the study clinic or be referred to an appropriate clinic for contraception. You/your child may choose whether or not you/she want to receive contraception.

Although infants born to HIV-infected women taking Truvada® during pregnancy have not been found to have a greater chance of being born early, weighing less or having birth defects than babies from women who were not taking PrEP, we do not know for sure if these drugs are safe to the fetus in women who become pregnant. One study of women who were infected with HIV found that women who were taking one of the drugs in Truvada while they were pregnant did have babies that were born early or lower weight more often. For this reason, if you/your child become pregnant, you/she will need to stop taking PrEP while you/she continue to be followed in this study until your/her last visit. If you are/she is still pregnant after your/her last visit, we will ask you/your child or your/her doctor to provide updates on the progress of your/your child’s pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

Not all ways to prevent becoming pregnant can prevent HIV transmission, and some may actually increase the risk of getting HIV. We will talk with you/your child throughout the study about ways to protect yourself/herself from getting HIV. You/your child should also discuss with your/her health care provider and the study clinic staff ways to continue using contraception that works during your/her participation in the study.

Blood Draws

Taking blood samples may cause some pain, bruise your/your child’s arm, or make you/her feel lightheaded. In rare cases you/your child may faint. There is also a slight chance of infection when blood is drawn. You/your child may be nervous while you are/she is waiting for your/her HIV test result. If the tests show that you have/she has HIV, you/she may worry about your/her health and future. You/your child will receive counseling before and after the test to help address your/her concerns. We will make every effort to protect your/your child’s confidentiality during the study. However, it is possible that others may learn that you are/she is part of this study and they may think that you are/she is infected with

HIV or at high risk for infection with HIV. Because of this you/she could have trouble finding or keeping a job. You/your child could also have problems with your/her family, friends and community.

Sensitive Questions

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

Mobile Phones

Information that you/your child send us from your/her mobile phone programs will be kept confidential. We will not be able to access any private information on your/your child's mobile phone. We will ask you/her to reply with a code word before we send a text to make sure that you are/she is the person using the phone at that time. However it may be possible for your/her information to be viewed by others who have access to your/her phone. We will do everything possible to make sure that your/her information is protected. (Sites to modify as needed: We will not mention the research study when texting you/her, but only text reminders about keeping up your/her health.)

STI Testing

You/Your child will be tested for gonorrhea, chlamydia, trichomonas vaginalis and syphilis. [Note to sites: Insert here any reporting responsibilities for your state or local jurisdictions or reporting of these infections to public health authorities]. If you/your child have any of these infections, we will provide you/her with treatment.

Other risks

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

There may also be some social risks to participating in this study. You/your child may feel embarrassed or uncomfortable with some of the questions you/she will be asked, some of the procedures that will be done, or some of the test results that you/she will receive. You/your child may also experience stigma as a result of being involved in a study about HIV because people may assume that you are HIV-infected. If you have/your child has HIV or other infections, knowing this could make you/her worried. Trained study counselors will help you/her deal with any feelings or questions you have/she has.

BENEFITS

We will test you/your child for HIV and other sexually transmitted infections throughout this study. If you/your child take your/her Truvada® every day, it will help you/her to avoid HIV. The counseling you/she can get during this study may help you/your child to avoid HIV and other sexually transmitted infections. If you have/your child has or become infected with HIV, this counseling may help you/her to learn how to better care for yourself/herself and avoid passing HIV to your/her sexual partners. If you/she become HIV infected, or have another sexually transmitted infection, we will either treat you/your child here or refer you/her for care and treatment. At the screening visit we will also check if you have/she has hepatitis B infection. If you have/your child has never had hepatitis B infection, we will offer you/her hepatitis B vaccination. During the study you will have tests to check on the health of your/her kidneys. If any health problems are found, you/she will be referred for care. At every visit you/she will receive condoms free of charge.

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

NEW INFORMATION

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

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

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

- You/She could be harmed by continuing to take tablets.
- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you/your child.
- You/your child are not able to attend clinic visits or complete all of the study procedures.
- Other reasons, as decided by the study staff.
- If you are under X years, you may be withdrawn because your parent or guardian withdraws consent for you to participate.

You/your child will NOT be withdrawn from this study only because you tell/she tells us that you do not/she does not want to or did not take the PrEP pills.

If you/your child withdraw early from the study, we will ask you/your child to come in for a final visit with all the exams and tests listed above.

ALTERNATIVES TO PARTICIPATION

Sites to include/amend the following if applicable: There may be other studies going on here or in the community that you/your child may be eligible for. If you wish/she wishes, we will tell you/her about other studies that we know about. There also may be other places where you/your child can go for HIV counseling and testing. We will tell you/her about those places if you wish.

COSTS TO YOU

There will be no cost to you/your child for study related visits, study products, physical examinations, laboratory tests, or other procedures. *[Sites to amend if applicable:* Phone cards will be provided to help pay for SMS costs on your/her mobile phones.]

REIMBURSEMENT

You/your child will receive [\$xx] for your/her time, effort, and travel to and from the clinic at each scheduled visit. *[Sites to insert information about local reimbursement for the study.*

CONFIDENTIALITY

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

The study staff will also use your/your child's personal information, if needed, to verify that you are not/she is not taking part in any other research studies. This includes other studies conducted by [site name] and studies conducted by other researchers that study staff know about. Any publication of this study will not use your/your or your child's name or identify you/ you or her personally.

Your/your child's records may be reviewed by:

- the US NIH
- the US Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- [insert names of applicable IRBs or other regulatory or local agencies]
- study staff
- study monitors
- the company that makes the study drug (Gilead)

[Sites to include/amend the following if applicable:] [Local/state/national] regulations require study staff to report the names of people who test positive for [HIV and other infections] passed during sex to the [local health authority]. Outreach workers from the [health authority] may then contact you/your child about informing your/her partners, since they also should be tested. If you do not/she does not want to inform your/her partners yourself/herself, the outreach workers will contact them, according to the confidentiality guidelines of the [health authority].

A description of this study will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

While you are/your child is attending study visits, sitting in the waiting room or attending events with other participants (such as adherence clubs), staff members may take notes on what is said about using the pills or taking part in this study. We are doing this to help us learn more about young women's experiences with PrEP and how to make taking PrEP easier for young women who need it. We will not record your/your child's name or participant ID on these notes.

You/your child will be invited to participate in monthly adherence clubs which are events where participants will come together to talk about any problems or successes they have taking the PrEP pills. We will ask everyone at these events not to tell friends, family or others about who attends. Participants should be aware that in a group setting it is not possible to maintain confidentiality. They should consider carefully information that they wish to disclose in a group setting as it is not possible to guarantee confidentiality. You/your child can also use a nickname so others do not know your/her real name. But it is possible that someone may recognize you/your child and tell others.

If you are under X years we will also need to obtain the consent of your parent or legal guardian in order for you to participate. We will explain to your parent/legal guardian that we will not share the results of your HIV, pregnancy, or other tests with them, but if you become HIV infected, pregnant or have any serious medical conditions we will strongly encourage you to tell your parent/legal guardian yourself. We will also not share with them the results of any questions you answer including when or if you are having sex, your use of contraception, if you are using drugs or alcohol and/or if you are taking your PrEP pills.

To protect you from harm, we will encourage you to tell a trusted adult (this does not have to be your parents/legal guardian) about certain situations but we will not inform your parents without your permission. We will help and support you when you tell others about these hard situations:

- If you become pregnant or end a pregnancy.
- If you have a positive HIV or STI test result.

If you are a parent or guardian of a participant, we will keep the information listed below, private and will not share this information with you:

- Your child's attitudes towards sexual behavior and reasons for staying in the study.
- Your child's answers to questions about sexual behavior and whether they are having sex.
- Any birth control information we talk about and your child's access to contraceptives if they choose.
- The results of tests (including pregnancy and STIs) and treatment that your child has consented to without the help of an adult.

RESEARCH-RELATED INJURY

[Sites to specify institutional policy:] It is unlikely that you/your child will be injured as a result of study participation. If you are/she is injured, the *[institution]* will give you/her immediate necessary treatment for your/her injuries. You/She *[will/will not]* have to pay for this treatment. You/your child will be told where you/she can get additional treatment for your/her injuries. There is no program to pay money or give other forms of compensation for such injuries either through this institution or the US NIH. You do not/your child does not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you/you and your child ever have any questions about the study, or if you have/she has a research-related injury, you/you and your child should contact *[insert name of the investigator or other study staff]* at *[insert telephone number and/or physical address]*.

If you have/your child has questions about your/her rights as a research participant, you/your child should contact *[insert name or title of person on the IRB or other organization appropriate for the site]* at *[insert physical address and telephone number]*.

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

SIGNATURE PAGE FOR PARTICIPANTS

SCREENING AND ENROLLMENT CONSENT FOR PARTICIPANTS OF LEGAL AGE TO PROVIDE INDEPENDENT CONSENT

HPTN 082

**Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African
women: A Vanguard Study**

Final Version 1.0/ 8 December 2015

If you have read this consent form and you understand the information, and you voluntarily agree to join the study, please sign your name below.

I agree to take part in this study.

Participant Name (print)

Participant Signature and Date

Study Staff Conducting

Consent Discussion (print)

Study Staff Signature and Date

SIGNATURE PAGE FOR PARTICIPANTS

SCREENING AND ENROLLMENT ASSENT FOR PARTICIPANTS NOT OF LEGAL AGE TO PROVIDE INDEPENDENT CONSENT

HPTN 082

**Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African
women: A Vanguard Study**

Final Version 1.0/ 8 December 2015

If you have read this consent form and you understand the information, and you voluntarily agree to join the study, please sign your name below.

_____ I agree to take part in this study.

_____ Participant Name (print)

_____ Participant Signature and Date

_____ Study Staff Conducting
Consent Discussion (print)

_____ Study Staff Signature and Date

**SIGNATURE PAGE FOR PARENT/GUARDIAN OF PARTICIPANTS NOT OF LEGAL AGE
TO PROVIDE INDEPENDENT CONSENT**

HPTN 082

**Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African
women: A Vanguard Study**

Final Version 1.0/ 8 December 2015

If you have read this consent form and you understand the information, and you voluntarily agree to allow your child to join the study, please sign your name below.

_____ I agree for my child to take part in this study.

_____ Parent/Guardian Name (print)

_____ Parent/Guardian Signature (or mark) and Date

_____ Study Staff Conducting
Consent Discussion (print)

_____ Study Staff Signature and Date

_____ Witness (for illiterate parents/guardians)
(print)

_____ Witness Signature and Date

Appendix IIB: Sample Storage Informed Consent Form

HPTN 082

Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study

**Final Version 1.0/ 8 December 2015
DAIDS Document ID: 12068**

Sponsored by: Division of AIDS, US National Institute of Allergy and Infectious Diseases, US National Institute of Mental Health, US National Institutes of Health.

PRINCIPAL INVESTIGATOR: *[Insert Name]*

PHONE: *[Insert Number]*

POSSIBLE FUTURE TESTS

As we said in the consent form for the study, blood samples collected at the enrollment and follow-up visits will be stored for all participants for testing that is part of this study. Some of your/your child's blood drawn for this study may be leftover after all of the study tests are completed. We would like to use these leftover samples for future research studies to learn more about HIV prevention and HIV infection, hepatitis infection, and other infections people can get when they have sex. No additional samples will be collected for this research. These leftover samples will be stored with only your/your child's study number and will be stored and tested at special laboratory facilities that may be located in the US and other countries outside of [insert site country]. Only approved researchers will have access to them. People who work at the facility will also have access to your/her samples to keep track of them. These people won't have information that directly identifies you/your child. Your/your child's samples will not be sold or directly used to produce commercial products. All proposed future research studies using your/your child's leftover samples will be reviewed by the leadership of the HPTN network and representatives from the National Institutes of Health (NIH). There is no time limit on how long your/her samples will be stored. You/your child will be asked to sign at the end of this consent form to give permission for this. Even if you do not give permission to store your/her leftover blood after all of the study testing has been completed, you can still be in this study.

At any time, you may also withdraw your consent to have your leftover samples stored and used for future research. Please indicate by providing your initials in the spaces below if you agree to long-term storage of your blood samples.

SIGNATURE FOR PARTICIPANTS

I agree to have samples of my leftover blood stored and used for future testing related to HIV infection, hepatitis or other infections I can get when I have sex.

I do not agree to have samples of my leftover blood stored and used for future testing related to HIV infection, hepatitis or other infections I can get when I have sex.

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

SIGNATURE FOR PARENT/GUARDIAN OF PARTICIPANTS NOT OF LEGAL AGE TO PROVIDE INDEPENDENT CONSENT

At any time, you may also withdraw your consent to have your child's leftover samples stored for future research. Please indicate by providing your initials in the spaces below if you agree to allow your child's leftover blood samples for future research.

I agree to have samples of her leftover blood stored and used for future testing related to HIV infection, hepatitis or other infections she can get when she has sex.

I do not agree to have samples of her leftover blood stored and used for future testing related to HIV infection, hepatitis or other infections she can get when she has sex.

Parent/Guardian Name (print)

Parent/Guardian Signature (or mark) and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness (for illiterate parents/guardians)
(print)

Witness Signature and Date

Appendix IIC: Sample In-depth Interview Informed Consent Form

HPTN 082

Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study

**Final Version 1.0/ 8 December 2015
DAIDS Document ID: 12068**

Sponsored by: Division of AIDS, US National Institute of Allergy and Infectious Diseases, US National Institute of Mental Health (NIMH), US National Institutes of Health.

PRINCIPAL INVESTIGATOR: *[Insert Name]*

PHONE: *[Insert Number]*

INTRODUCTION

You are/your child is being asked to take part in a substudy of the HPTN 082 research study. Joining this substudy is voluntary. You/ or your child may refuse to join, or you/or your child may withdraw your/her consent to be in the study, for any reason. This research study is for young women who are participating in HPTN 082 who may be at risk for getting Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decide whether to join/allow your child to join the substudy, we would like to explain the purpose of the substudy, the risks and benefits to you/your child, and what is expected of you/your child.

PARTICIPATION IS VOLUNTARY

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

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

- Your/your child's participation is voluntary. You do not/your child does not have to take part in the substudy if you do not/she does not want to.
- You may decide not to/allow your child to take part in the substudy, or you/or your child may decide to leave the study at any time without losing your/her regular medical care.
- You are not/your child is not required to participate in these interviews in order to remain in the rest of the study (HPTN 082).
- If you decide not to/allow your child to take part in the study, you/she can still join another study at a later time if there is one available and you/she qualify.

PURPOSE OF THE STUDY

The purpose of the HPTN 082 study is find out whether young women in southern Africa at risk of HIV are willing to start and continue to take PrEP every day for up to one year. This sub-study will ask young

women what they like and do not like about taking PrEP. We will also ask questions to find out what makes some young women more or less interested in starting PrEP. Finally, if you are/she is taking PrEP we will ask about difficulties you/she had taking PrEP and things that made taking PrEP easier.

In order to understand better what makes it easier or harder for young women in this study to take their PrEP pills every day, we will be doing interviews with up to 25 young women at each site (75 total). You have/your child has been selected to take part in two interviews. The first will happen after the Week 13 visit and the second will be after the Week 26 visit.

These interviews will ask you/your child questions about:

- How and when you/she decided to take PrEP,
- whether you/she feel that you/she personally are at risk of HIV,
- if you/she decided not to take PrEP, some of the reasons why you/she made that decision,
- how you/she made daily pill-taking part of your/her routine if you/she decided to take PrEP,
- where you/she kept your/her PrEP pills if you/she decided to take PrEP,
- whether you/she talked to your/her family members, peers, and partner(s) about being in this study or taking PrEP pills,
- if you/your child decided to take PrEP, if you/she had any symptoms or side effects from the pills, and how this might have influenced your/her decision to take the pills,
- if you/she decided to take PrEP and you/she was randomized to hear the results of the lab tests which tests the amount of drug in your/her blood, how you/she felt about hearing these results, and
- other related topics.

PROCEDURES

The interview will be led by a member of the research team that you do not/she does not work with during the study. If any of the questions make you/your child upset, either you/she or the interviewer may stop the interview at any time. You/your child will also be provided with contact and referral information if any of the questions raise issues that you/she would like to talk about later.

[To be modified to reflect site practices: The first interview will take place in a location that the study staff have determined will provide you/your child with privacy and confidentiality such as the clinic, or another appropriate place. The study team will talk with you/your child about this so you know where to go for the interview. If you/your child agree, the second interview may take place in your/her home or another location within your community. The team will discuss this with you/your child to see if you agree.

Each interview should take about 1 hour. There will be no cost to you/or your child for participation. You/your child will receive [insert local amount] for your/her time and effort.

BENEFITS

You/your child may not receive any other direct benefit from being in this part of the study; however, you/she or others in your community may benefit from this study later.

RISKS

To minimize any discomfort and to protect your/her privacy the interview will be conducted in a private area that will allow you/her to speak comfortably without being overheard. Although we hope that you/she will be comfortable answering all of the questions openly and honestly, please keep in mind that you/she may refuse to answer any of the questions, or stop the interview completely, at any time. The greatest risk may involve your/her privacy and confidentiality. The steps that the study team have taken to

protect your/your privacy are described below.

PRIVACY

Every effort will be made to keep your/your child's personal information confidential. Your/her personal information (name, address, phone number) will be protected by the research clinic. Your/her name, or anything else that might identify you/her personally, will not be used in any publication of information about this study.

To help assure that we get the best understanding possible from your/your child's answers during the interview, the entire interview will be audio-recorded. After the interview is finished, the recording will be typed (called a transcript) by people who know how to do this. All identifying information will be removed from the transcript. Your/your child's name will not be included on the transcript. These recordings will be destroyed after all analysis is completed.

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

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

If the study staff learns of possible child abuse and/or neglect or a risk of harm to you/your child or others, we will tell the proper authorities as we are required to do by the law.

NEW INFORMATION

You/your child will be told any new information learned during this study that might affect your/her willingness to stay in the study. You/your child will also be told when the results of the study may be available, and how to learn about them.

WHY YOU/YOUR CHILD MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR/HER CONSENT

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

- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you/her.
- Other reasons, as decided by the study staff.

ALTERNATIVES TO PARTICIPATION

Sites to include/amend the following if applicable: There may be other studies going on here or in the community that you/your child may be eligible for. If you/your child wish, we will tell you/her about other studies that we know about.

COSTS TO YOU/YOUR CHILD

There will be no cost to you/your child for participating in these in-depth interviews.

REIMBURSEMENT

You/your child will receive [\$xx] for your/her time, effort, and travel to and from the clinic for these interviews. [Sites to insert information about local reimbursement for the study.]

CONTACT

For questions about this study, contact:

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

For questions about your/your child's rights as a research participant, contact:

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

**Signature page for In-depth Interview Informed Consent Form for Participants of Legal Age to
Provide Independent Informed Consent HPTN 082**

**Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African
women: A Vanguard Study**

Final Version 1.0/ 8 December 2015

If you have read this consent form and you understand the information, and you voluntarily agree to join the substudy, please sign your name below

_____ I agree to take part in this substudy.

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

**In-depth Interview Informed Assent Signature Page for Participants NOT of Legal Age to Provide
Independent Informed Consent**

HPTN 082

**Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African
women: A Vanguard Study**

Final Version 1.0/ 8 December 2015

If you have read this consent form and you understand the information, and you voluntarily agree to join the substudy, please sign your name below

_____ I agree to take part in this substudy.

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

**Sample In-depth Interview Informed Consent Signature Page for Parents/Guardians of Minors
below the Legal Age to Provide Informed Consent HPTN 082**

**Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African
women: A Vanguard Study**

Final Version 1.0/ 8 December 2015

If you have read this consent form and you understand the information, and you voluntarily agree to allow your child to join the substudy, please sign your name below

_____ I agree to let my child take part in this substudy.

Parent/Guardian Name

Parent/Guardian Signature and Date

Witness (for illiterate parents/guardians)
(print)

Witness Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Appendix III: Draft HIV Prevention Readiness Measure (HPRM) – Modified

1. I am ready to start taking medication (PrEP) to protect against HIV.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

2. Most of the people I live with know that I am taking PrEP.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

3. I believe taking PrEP can keep me healthy.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

4. Taking PrEP would give me bad side effects. (R)

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

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

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

6. I feel like I have a stable place to live.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

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

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

8. I have a strong, trusting relationship with my medical provider.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

9. I would know who and when to call for refills of my PrEP medication.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

10. Sometimes a homeless shelter is the only place I have to sleep. (R)

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

11. Most of my family and friends know I am taking PrEP.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

12. Taking PrEP medication would not really help me. (R)

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

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

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

14. I regularly go to the clinic and meet with my medical provider.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

15. PrEP medication would be poison to my body. (R)

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

16. I want to start taking PrEP medications to protect against HIV infection.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

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

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

18. Taking my PrEP medication as prescribed would keep me from getting sick.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

19. I feel supported by my family and friends when times are tough.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

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

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

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

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

22. I know that I will be able to take my PrEP medication correctly.

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

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

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

In the past month, how often have you... (Introduction for questions 24 through 31)

24. Felt lonely or sad. (R)

1=Never

2=Rarely

3=Sometimes

4=Almost Always

5=Always

25. Been told you seem sad or depressed. (R)

1=Never

2=Rarely

3=Sometimes

4=Almost Always

5=Always

26. Felt isolated or lonely, even when around other people. (R)

1=Never

2=Rarely

3=Sometimes

4=Almost Always

5=Always

27. Felt that things were going your way.

1=Never

2=Rarely

3=Sometimes

4=Almost Always

5=Always

28. Felt confident in your ability to handle your personal problems.

1=Never

2=Rarely

3=Sometimes

4=Almost Always

5=Always

29. Felt you could not cope with all the things you had to do. (R)

1=Never

2=Rarely

3=Sometimes

4=Almost Always

5=Always

30. I shouldn't tell the people I live with that I am taking PrEP. (R)

1=Strongly Disagree

2=Disagree

3=Neither Agree nor Disagree

4=Agree

5=Strongly Agree

31. How many people you live with have you told that you are taking PrEP?

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

(R) denotes reverse-scored items

Survey was modified based on reliability testing and factor analysis conducted from ATN 110 data, the alcohol and drug use factor was eliminated due to poor reliability.