Evaluation of stepped PrEP adherence support for young South African women using a SMART design

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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
CAB	Community Advisory Board
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CRF	Case Report Form
CT	*Chlamydia trachomatis*
DBS	Dried Blood Spots
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
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	*Neisseria gonorrhoeae*
GCP	Good Clinical Practices
HBV	Hepatitis B virus
HepBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
ICF	Informed consent form
iPrEx OLE	(iPrEx) Open Label Extension
IRB	Institutional Review Board
MSM	Men who have sex with men
MTN	Microbicides Trial Network
NIH	(United States) National Institutes of Health
PEP	Post Exposure Prophylaxis
PK	Pharmacokinetics
PMTCT	Prevention of Mother-to-Child Transmission
PrEP	Pre Exposure Prophylaxis
RHI	(Wits) Reproductive Health and HIV Institute
SAE	Serious Adverse Event
SMS	Short message service
SOC	Standard-of-care
SOP	Standard Operating Procedures
STI	Sexually transmitted infection
TFV-DP	Tenofovir disoproxil fumarate diphosphate
TFV	Tenofovir
TV	*Trichomonas vaginalis*
UK	United Kingdom
US	United States
VOICE	Vaginal and Oral Interventions to Control the Epidemic (Trial)

PrEP SMART

Evaluation of stepped PrEP adherence support for young South African women using a SMART design

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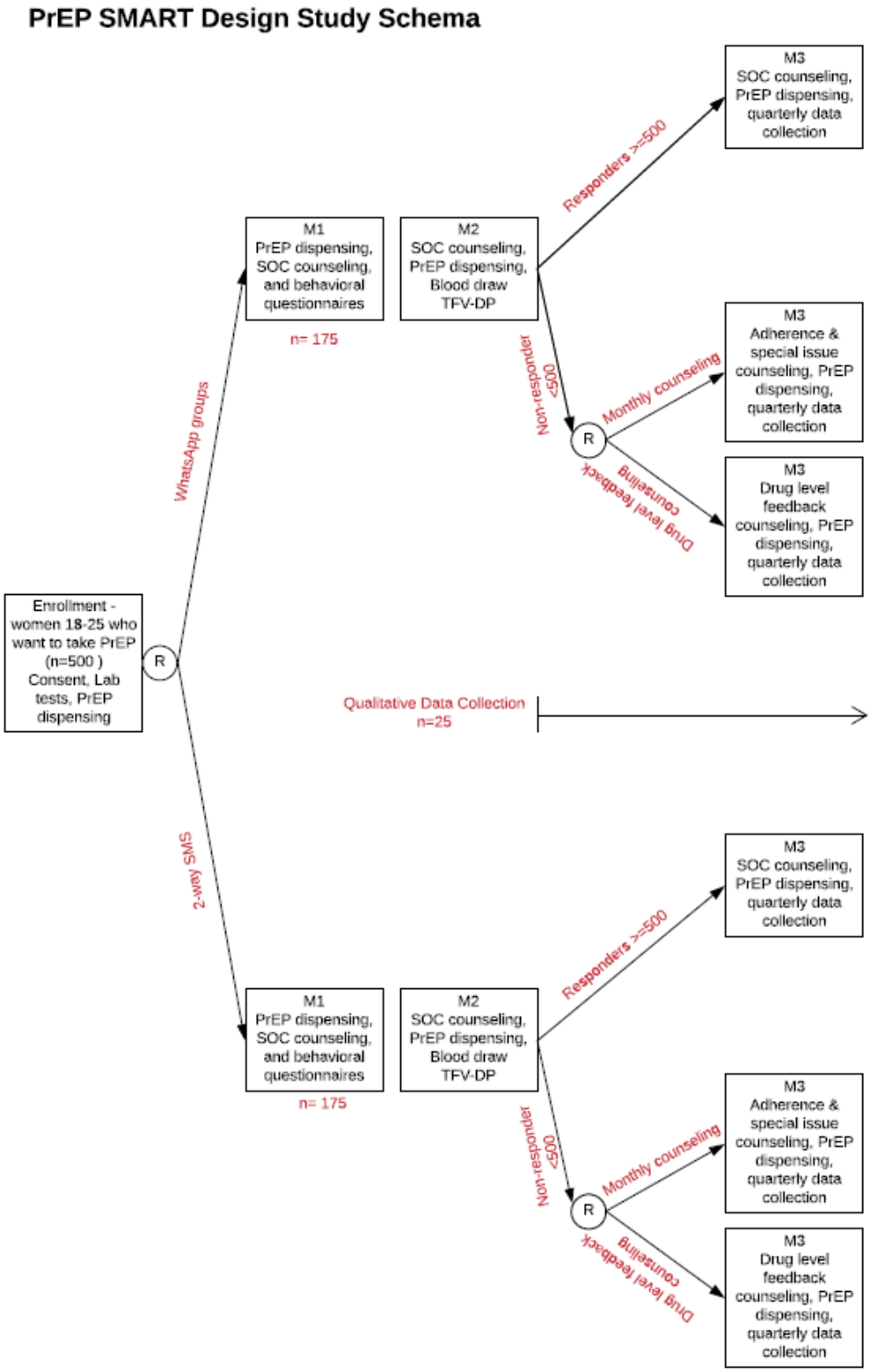
SCHEMA

Rationale:	Sequential multiple assignment randomized trials (SMARTs) are useful experimental designs for the development of high-quality adaptive interventions. The SMART design utilized in this study will allow us to 1) develop optimal adaptive intervention strategies to facilitate PrEP adherence support; 2) identify important tailoring variables that are associated with response or non-response to a given intervention; and 3) evaluate decision rules for scaling up PrEP adherence support for South African young women.
Purpose:	To test a stepped model of scalable adherence support strategies in South African young women who initiate PrEP, using a SMART design.
Design:	Eligible women who accept open-label daily oral PrEP will be enrolled and randomized to SOC adherence support (brief counseling) and either WhatsApp groups or weekly two-way SMS messages. These mHealth interventions are aimed at increasing PrEP adherence during follow-up by providing peer support for PrEP adherence (WhatsApp groups), clinical support to manage side effects and address adherence issues (SMS messages), and reminders about daily PrEP pill-taking (both WhatsApp groups and SMS messages). Follow-up visits will occur monthly for 3 months and, in both groups, tenofovir drug levels at month 2 will be used as an objective measure of adherence to determine whether they have achieved high adherence based on their initial randomization. Women with high adherence (i.e., TFV-DP ≥500 fmol/punch from DBS, 'responders') will continue with the adherence support to which they were initially randomized and will attend quarterly visits for a total of 9 months of follow-up. 'Non-responders' will be identified based on TFV-DP <500 fmol/punch or missed drug refills at their Month 1 or 2 study visits and will continue initial randomization (WhatsApp or two-way SMS) plus be randomized to either more intensive adherence support – continued monthly visits with adherence and problem-focused counseling at months 3-8 *or* quarterly visits between months 3-9 with feedback about adherence based on drug levels at months 3 and 6. The primary outcome for the combined intervention is the proportion with high adherence measured by TFV-DP levels at 9 months. Secondary outcome includes measuring TFV-DP at 2 months to assess short-term intervention effects on PrEP use (See overview of study design on page 9.) We will also conduct qualitative data collection with a purposive sample of approximately 25 responders and non-responders after their 2-, 6-, and exit study visits. In addition, we will conduct in-depth interviews with approximately 10 key informants and 15 clinic staff members.
Study Population:	HIV-uninfected women ages 18-25 in Johannesburg, South Africa.
Study Size:	Up to 500 women who accept PrEP will be consented and randomized (1:1) to SOC adherence support and either WhatsApp groups or weekly two-way SMS.
PrEP Regimen:	All participants will be provided once daily oral emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (FTC/TDF).
Study Duration:	Approximately 48 months, including submissions to Institutional Review Boards (IRBs) and the South African Health Products Regulatory Authority (SAHPRA, formerly the Medicines Control Council), recruitment, and 9 months of follow-up per participant.
Primary Objective:	To evaluate the proportion of young South African women who adhere well to PrEP with regular clinic visits and mHealth interventions alone, the proportion of women who adhere well to PrEP with intensified interventions (i.e. monthly visits and special issue counseling or quarterly visits with drug-level feedback about recent adherence), and the optimal

	sequence of intensifying adherence support among young women who have low adherence after the first two months of use.
Secondary Objectives:	• To assess the proportion who achieve high adherence early (month 2). • To assess the correlates of PrEP adherence, after adjusting for study arm, including adherence at prior study visits, sociodemographic factors, individual-level and partner-level characteristics, use of 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 characterize SMS response rates and the content and frequency of use of WhatsApp groups. • To qualitatively explore factors that influence women's decisions to use PrEP and adhere to PrEP and their satisfaction/preferences for with their assigned intervention(s). • To qualitatively explore perceptions of our intervention package and opinions on scalability of the interventions from clinic staff and key informants' perspectives.
Exploratory Objectives:	• To assess HIV incidence and to assess the association with detectable TFV-DP in PrEP users who acquire HIV infection during the study. • To describe antiretroviral (ARV) drug resistance among women who acquire HIV infection. • To assess acceptability and feasibility of a urine point-of-care test for drug-level feedback counseling.
Study Site:	Ward 21 CRS, Wits RHI, University of the Witwatersrand, in Johannesburg, South Africa.

OVERVIEW OF STUDY DESIGN

Figure 1. Study schema for a stepped PrEP adherence support intervention



1.0 INTRODUCTION

1.1. Background and Prior Research

Young African women between the ages of 16 and 25 are an important population for PrEP implementation, representing three of the four million young people living with HIV in sub-Saharan Africa. Young African women have had 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 a core biomedical intervention for young African women 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 and subgroups of women <30 years old and ≥30 years old.[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 adherence, as measured by detectable TFV in plasma.[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: differences in level of uncertainty about their risk for HIV infection; ambivalence about using antiretroviral (ARV) drugs for HIV prevention; concerns about potential side effects; stigma and disapproval from others who might associate ARVs as being for treatment rather than for prevention; partner's reactions and potential rejection; 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 delivery of a known efficacious and approved product; 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 may not predict PrEP uptake and adherence among at-risk participants who are offered open-label product. Adherence to oral PrEP has been 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.[16] 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.[17, 18] Encouragingly, the Proud Study among MSM offered PrEP in STI clinics in the United Kingdom (UK) with non-research providers and quarterly visits for PrEP refills and brief counseling, and showed a highly significant 86% reduction in HIV incidence in the immediate PrEP arm, compared to the delayed PrEP arm. 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.[19] Notably, adherence to oral PrEP was high among MSM who self-identified as being at high risk of acquiring HIV, when PrEP was known to be efficacious and delivered in clinical settings by non-research staff with quarterly visits and brief adherence counseling.

The Partners Demonstration Project was an open-label, demonstration project among research-naïve East African heterosexual HIV serodiscordant couples that evaluated 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 high-risk couples,[20] 20% of whom were <25 years old. Importantly, PrEP uptake was very high (95% at enrollment), adherence was high (86% with detectable TFV), ART initiation was high among the HIV-infected partners (80% by 12 months with 90% viral suppression), and HIV transmission was reduced by 96% compared to a counterfactual HIV incidence.[21]

In sum, 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.

1.2. Rationale

1.2.1. PrEP adherence support for young African women

Given persistently high HIV incidence rates (5-8%) among young women in sub-Saharan Africa, PrEP is an important prevention method that must be evaluated for its utility in young African women. Randomized, placebo-controlled PrEP efficacy trials have demonstrated that adherence to PrEP is crucial for protection against HIV infection. Adherence levels have been lower among young persons, including young African women; PrEP adherence in theVOICE trial was negatively associated with age <25 years.[2] 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.

There is a gap in how to deliver PrEP to young African women with a focus on maximizing adherence. The studies of PrEP among young South African women indicate that young women are motivated to use PrEP but there is substantial drop-off in the first few months and women may need additional adherence support when they have quarterly visits. First, in HPTN 067/ADAPT which randomized women to daily, time-driven intermittent or event-driven dosing of oral PrEP, half of the Cape Town participants were ≤25 years and adherence was highest in the daily dosing arm during the first few months of follow-up (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).[22] Second, an open-label study (PlusPills) assessed PrEP acceptability, safety, and use among adolescents ages 15-19 in South Africa, enrolled 148 adolescents (99 women, 49 men). PrEP was well-tolerated, with no safety concerns. Adherence was reasonable (57% with detectable tenofovir in blood at 12 weeks) but decreased significantly when visit spacing increased from monthly to quarterly.[23]

Available data from open-label PrEP demonstration projects among youth indicate that they may have greater adherence challenges with daily pill-taking than older persons, even in the context of known efficacy of PrEP. A study of 18-22 year old MSM in the US demonstrated that TFV-DP levels indicating ≥4 pills/week in the prior 3 weeks declined from 56% at week 4 to 34% at week 48, with a noticeable drop-off occurring

at 24 weeks.[24] Recent results from the adolescent companion study showed an even more dramatic drop-off.[25] Relevant to 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 but tenofovir levels dropped to <50% between months 3 and 6. [22]Similar drop-offs in PrEP adherence were observed when visits switched from monthly to quarterly in the PlusPills study with young South African women.[23]

An ongoing open label study of oral PrEP in southern African women, HPTN 082, indicates a high prevalence of psychological and social factors which might increase risk of HIV acquisition but also present challenges with adherence and effective use of PrEP. HPTN 082 randomized young women, who were between 16-24, at risk of HIV, and interested in PrEP, to receive drug-level feedback at 1 or 2 months. At enrollment into HPTN 082, 41% of participants had depression based on a CES-D-10 score ≥11, intimate partner violence was reported by 50% in the past year, and transactional sex by 22% in the past 3 months. STI prevalence was remarkably high with 30% chlamydia prevalence, 8% gonorrhea and 7% trichomonas, and yet only 16% reported a moderate or high chance of acquiring HIV in the next year. [26] This gap between behavioral and biologic markers of risk of HIV and perceived risk may be a factor in influencing PrEP uptake and adherence. HPTN 082 results will be available in early 2019, and will provide important findings on the effectiveness of drug-level feedback on PrEP adherence at 6 and 12-months of follow-up. In addition, HPTN 082 has found that peer influence was important in influencing PrEP uptake, with 62% of participants reporting a friend encouraged them to take PrEP. All women in HPTN 082 were provided weekly two-way SMS messages in the first 3 months, and offered participation in adherence clubs thus this study will also provide data on the influence of social support interventions on PrEP adherence. Preliminary data has indicated that SMS response rates are approximately 70% throughout follow-up. Adherence clubs were also well-attended by young women; 50- 60% attended at least one adherence club between their quarterly visits.

In summary, objective markers of adherence with drug levels as well as qualitative data from the randomized, placebo-controlled trials and open label studies of PrEP indicate that adherence interventions for adolescents and young adults may require more frequent contact, peer support, drug level feedback, or triage (i.e., for side effects, disclosure issues or adherence barriers).[27] In addition, adherence support strategies need to recognize developmental issues,[28] including social and sexual relationships, future planning skills, as well as broader contextual issues such as caregiver support, depression, [29] and gender-based violence.[30] Preliminary data from HPTN 082 indicate that SMS, drug level feedback, and adherence clubs were well-received by southern African young women initiating PrEP. However, HPTN 082 will not be able to determine the optimal sequence or combination of adherence support that is most effective for African young women, which this study is designed to assess.

The goal of this study is to evaluate whether HIV-uninfected South African women ages 18-25 years who are at high risk for HIV infection will decide to use PrEP and demonstrate sufficient adherence to achieve HIV prevention benefits from this promising biomedical prevention intervention. It is important to evaluate which adherence support strategies are effective, and the proportion who respond to an initial simple, scalable adherence support approach. The aims of this study are to offer PrEP and scalable adherence support interventions to sexually-active young women living in a high HIV prevalence and incidence setting who perceive themselves to be at risk of HIV infection and are motivated to use PrEP to reduce their risk, to identify the proportion and characteristics of women who need additional adherence support, and to assess whether more frequent visits or drug level feedback is more effective in achieving higher adherence. 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 adherence; counseling and risk assessments to determine women's perceived risks and benefits of PrEP; and a stepped approach to adherence counseling to support the women who are motivated to use PrEP but encounter issues in daily pill-taking.

Rationale for a scaled approach to PrEP adherence for young women using a SMART design

The biomedical HIV prevention field is at a critical point where rates of new HIV infections remain very

high among young women in sub-Saharan Africa in spite of progress in HIV testing and treatment coverage. The hope is that longer-acting, less adherence-dependent HIV prevention formulations will be shown to be effective, but realistically this involves five years or more to complete efficacy studies and longer for program implementation of long-acting PrEP formulations if shown to be efficacious. Thus, to have an impact on HIV incidence among young African women in the short-term, the critical question is whether oral PrEP can provide a usable, effective strategy that is under women's control, and yet requires high, but not perfect adherence. Young women may need more frequent contact or other intensive adherence support, as objective drug levels indicate declining adherence in prior studies as visits went from monthly to quarterly. The challenge is to identify what PrEP adherence support strategies are both scalable and effective at PrEP initiation, and what more intensive strategies work for the subset who need more intensive adherence support.

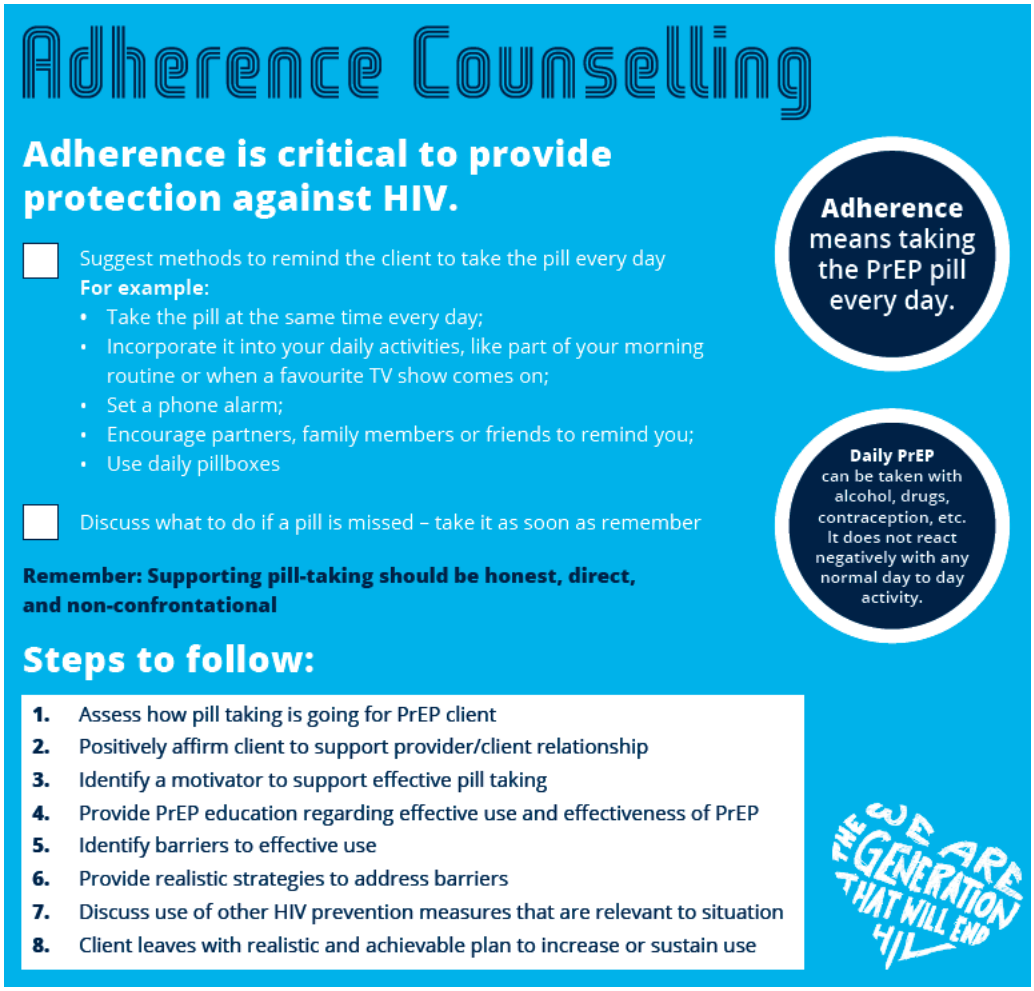
Currently, many PrEP demonstration projects among African YW are providing the similar adherence interventions to all YW who initiate PrEP without differentiated adherence support strategies (e.g., HPTN 082). However, for large scale PrEP implementation, a stepped approach to adherence support is needed, beginning with simple, easily scalable adherence support provided initially, such as brief counseling and two-way text messages or WhatsApp groups. *We hypothesize that a stepped PrEP adherence support model is feasible, resource-saving overall, and is analogous to models of differentiated care for HIV, in which frequent visits with tailored patient counseling, adherence monitoring, and counseling are directed to the minority of HIV-positive persons who have not achieved viral suppression.*

We will use a sequential multiple assignment randomized trial (SMART) design[31-43] to assess the response rate to simple, stepped PrEP adherence support strategies. The schema of the SMART design is shown in the figures on page 9-10. The first randomization is to evaluate adherence after 2 months of a basic adherence support, including brief counseling and *either* participation WhatsApp groups *or* weekly two-way text messages (described below). Mobile health interventions are being scaled up in the South African context for a number of health issues. An objective measure of adherence, such as a drug level measurement (analogous to the first viral load assessment in the first 3-6 months after ART initiation), would provide an objective measure to differentiate young women who are doing well with minimal support from those who need more intensive support, either through monthly clinic visits or feedback about adherence based on drug levels with counseling.

Standard of care in both arms of initial randomization: Brief adherence counseling and one-way SMS reminder messaging

It is clear that the effectiveness of daily oral TDF/FTC is tightly correlated with adherence. The study will provide adherence support with SOC counseling at baseline, Months 1-3 for all participants, and all quarterly follow-up visits for participants with high levels of adherence. Counseling will be client-centered and follow the South African Department of Health guidelines for counseling on PrEP[44] and will include an emphasis on the known relationship between adherence and TDF/FTC efficacy. Using a client-centered approach to frame the discussion about adherence, adherence counseling will include education around the importance of daily pill taking and supportive strategies that link pill taking to the participant's daily routine (i.e., daily calendar, planning for travel, daily habits). Counseling will also focus on the importance of returning for study visits and pill refills on or as close to the scheduled date as practical. All participants will also receive out one-way SMS messages reminding them about upcoming clinic visits.

Figure 2. South African SOC PrEP Counseling Guidelines



Randomization: WhatsApp groups vs Two-way SMS

<u>WhatsApp groups</u>

Peer support has been shown to improve adherence in outpatients starting ART,[37] hard to reach patients,[45] and adolescents.[46] Group-based interventions for youth offer an effective way to implement intervention content while providing social support from peers, given the importance of peer opinion during adolescence. In this age group, peer norms play an important role in shaping behaviors.[47-49] Peer groups have been found to offer social and emotional support to encourage the management of health behavior, such as diabetes self-management, and help participants cope with negative emotions.[50] With the uptake of social media by many youth worldwide, peer group social support interventions have begun to successfully translate to social media.[51, 52] ART adherence groups have been effective used in South Africa, including for adolescents and young adults.[53-55] 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.[56, 57] In HPTN 082, the PrEP clubs have provided a highly acceptable forum for staff and YW to interact outside of the clinic, and a foundation for promoting relationships between staff and YW as well as between YW. In another study conducted in Johannesburg and Tanzania, young women were randomized to SOC counseling and SMS reminders vs. SOC plus empowerment clubs. These were adherence clubs with a four session empowerment curriculum. No differences in PrEP persistence were observed between those that did or did not attend clubs, but as in 082 only 50% of participants attended at least one club. Barriers to club attendance included time, distance to the venue, being busy or forgetting. In-person clubs may offer logistical barriers to participation that could be overcome through virtual whats app groups. [58]

WhatsApp-based adherence support clubs, which are based on the in person PrEP adherence clubs in HPTN 082, have had high acceptability and attendance. In the implementation of these projects, WhatsApp is used commonly by young women to discuss side effects and to hear other young women's experiences with PrEP. WhatsApp groups would be more scalable than in person adherence clubs, as used in HPTN 082, by being more flexible (not needing persons to travel to an adherence club) but still achieving the peer-driven approach of in-person clubs. The WhatsApp groups will include between 25-50 participants. Women randomized to WhatsApp groups will be counseled on and receive written instructions on WhatsApp group use, group rules/norms, and group name. Each group will be led by a study staff group facilitator and a PrEP Ambassador (a young woman experienced in taking PrEP) who will be responsible for moderating these clubs to answer questions about PrEP, facilitate discussions, introduce topics of interest, monitor member conduct and enforce group rules. The group facilitator will also invite individuals to the group and will remove individuals from the group when they exit the study, if they request to be removed, and if they exhibit conduct that violates the group rules. Groups will also be given the option to meet in person if members would like.

Two-way SMS to triage those with concerns

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.[59] 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.[60] 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.[61] 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.[62] In HPTN 082, weekly two-way SMS in the first 12 weeks of PrEP use was implemented to provide triage to young women who have concerns or issues with PrEP. This two-way SMS is based on the Kenyan WelTel intervention;[61] in HPTN 082 young women receive a discrete message "Are you well, girlfriend?" and are asked to respond yes or no- the latter indicating that they need a staff member to respond if they are having side effects, adherence challenges or other issues. HPTN 082 participants received a call-back from staff within 24 hours if they respond through SMS that they are experiencing challenges with PrEP use. Participants who did not respond to the SMS were also followed up. The two-way SMS system has been relatively simple to implement in HPTN 082. Notably, 70% of young women responded to 2 way SMS messages, which is higher than the 50% response rate in the WelTel study of 2 way SMS for ART adherence support in Kenya. [61]

In addition to these two-way SMS messages, we will also periodically send one-way SMS messages including facts about PrEP and HIV prevention to keep participants engaged in the intervention and improve PrEP knowledge and self-efficacy. One-way SMS messages have been shown to be an acceptable way to provide HIV-related information to young African women and have been linked with improved knowledge about HIV prevention behaviors, adherence to health promotion behaviors, and healthcare engagement.[63, 64]

Rationale for definition of non-responders at month 2:

PrEP will be dispensed according to participant visit schedule. At month 2, blood will be drawn for a dried blood spot (DBS) to measure intracellular tenofovir diphosphate levels (TFV-DP), which provide a measure of cumulative adherence behavior over the prior 4-6 weeks.[16, 39, 40, 65, 66] Based on a comparison of the iPrEx open label extension and STRAND study with directly observed dosing of TDF-FTC, a threshold of 700 fmol/punch threshold represented consistent dosing (≥ 4 times a week) and was associated with 100% efficacy.[67] A subsequent directly-observed therapy study was conducted among US women and men demonstrated that DBS values were dose-proportional, and women that had 21% higher

TFV-DP levels than men, but values were within 13% of the previous model.[68] Dr. Anderson has worked closely with the University of Cape Town (UCT) pharmacology laboratory to validate the TFV-DP DBS assay with excellent correlation, and the UCT lab will perform DBS TFV-DP assays for this study.

While Dr. Anderson's work has demonstrated the utility of DBS as a marker of PrEP pill-taking and has suggested a threshold of 700 fmol/punch to represent dosing ≥ 4 times per week, our work with serodiscordant couples in sub-Saharan Africa has shown that this threshold may misclassify approximately 40% of women as non-adherent to PrEP when they are actually taking at least 4 doses per week (sensitivity of DBS with a threshold of 700 fmol/punch compared to MEMS data indicating ≥4 doses per week = 60%; 95% CI: 42-78%) (personal communication, M Pyra). This threshold may also misclassify approximately 8% of women as adherent when they were taking fewer than 4 doses per week (specificity compared to MEMS data = 92%; 95% CI: 81-100%). Alternatively, a threshold of 500 fmol/punch yielded a sensitivity estimate of 87% (95% CI: 75-99%) and a specificity of 84% (95% CI: 70-98%) in this cohort. Given these empirical sensitivity and specificity estimates from our data among a similar cohort of sub-Saharan African women, and the importance of allocating resources for our enhanced adherence support interventions primary to women who are truly non-adherent, we have chosen 500 fmol/punch as the threshold for determining "non-responders" in this cohort based on drug-level results from the 2-month study visit.

The 2-month DBS TFV-DP level will be used as an objective marker of adherence, and as an indicator of women's 'response' to their initial randomization (SOC adherence counseling with either WhatsApp groups or two-way SMS). Women with TFV-DP levels <500 fmol/punch or missed refills (at the 1- or 2-month study visit) will be randomized to more intensive adherence support at their month 3 study visit. All women will regardless of their TFV-DP levels will continue with their initial intervention (WhatsApp groups or two-way SMS messages).

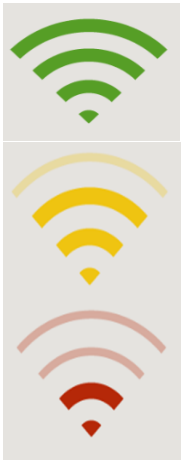
Second randomization for non-responders' at Month 3: Quarterly drug level feedback vs. monthly clinic visits with special issue counseling

Drug level feedback

The basis for the use of drug level feedback is that women in VOICE qualitative interviews reported a desire for feedback about their adherence with directed counseling.[15] HPTN 082 randomized Zimbabwean and South African young women to standard adherence support (counseling, two-way SMS, and adherence clubs) with or without drug level feedback based on TFV-DP levels in dried blood spots. There was no difference in adherence levels at six months by arm and, the cost and logistics of the DBS TFV-DP levels do not warrant use for PrEP adherence counseling. Notably, almost 40% of women in the drug level feedback arm across all study sites either did not receive counseling because DBS had to be batch-shipped and performed, and the results were not back at the next montly visit, or did not receive the appropriate counseling message due to transcript errors in coding the laboratory results.[70] Although retrospective drug level feedback in addition to standard adherence support did not increase adherence at six months in HPTN 082 compared to standard adherence support, modifications to the DBS counseling approach to reduce laboratory shipment and testing delays and/or same day counseling using point of care tenofovir assays should be evaluated as potential improved strategies to support PrEP adherence. Point of care assays will be simpler to implement, easier to provide adherence messaging at the same encounter, and much less costly to implement than DBS assays which only two laboratories can perform. DBS-based adherence counseling may also be limited if participants have difficulty remembering their pill-taking behavior and adherence barriers from several months ago. In contrast, a recent US-based PrEP demonstration project found that drug-level feedback counseling using plasma tenofovir levels, which indicate a shorter period of PrEP use over the past week, significantly improved PrEP adherence among young men who have sex with men.[67] The shorter recall period about adherence behavior with the plasma tenofovir assay may explain these different findings, and a point of care assay would similarly provide an indicator of recent PrEP dosing and reduce participant burden to remember pill-taking over a longer period

of time. However, more research is needed on the acceptability and feasibility of using a point of care assay for drug level feedback counseling for PrEP participants.

We will plan to use DBS levels to counsel participants at the months 3 and 6 visits. Although DLFB using DBS levels did not significantly impact PrEP adherence among AGYW in HPTN 082, the study team has learned critical lessons on how to manage the process to ensure sample collection, testing and reporting timelines are reduced and transcript errors in coding laboratory results and delivering the correct counseling message are minimised. Qualitative data from this study has also shown that DLFB via DBS was feasible and acceptable to young women. Importantly ,we will be able to improve our DLFB counseling procedures using DBS from these key lessons learned in HPTN 082 and have the potential to answer questions about the impact of DBS DLFB counseling for AGYW when done with fewer transcription errors and in this stepped-up care approach. The DBS TFV-DP provides an objective measure of cumulative adherence in the prior 4-6 weeks, which is not susceptible to the 'white coat effect' of taking medication immediately prior to clinic. The threshold of 700 fmol/punch, which represented consistent dosing (≥ 4 times a week) and was associated with 100% efficacy in iPrEx,[687] is being used for adherence counseling in HPTN 082. However, we will use a threshold of 500 fmol/punch at the 2-month study visit to more sensitively classify consistent dosing in this cohort cohort. The thresholds and counseling about adherence based on drug level feedback at months 3 and 6 are depicted below. These thresholds and counseling messages were developed in consultation with Drs. Anderson and Hosek.



>500 fmol/punch
Key message: You are doing great! Keep up the good work and remember that taking one PrEP pill every day is needed for strong protection against HIV.

Between detectable to 499 fmol/punch
Key message: It looks like you are trying to take the PrEP medication, but are having some difficulties. Remember that taking one pill every day is needed for strong protection against HIV. How can we help you do even better?

No TFV-DP detected (confirm BLQ level)
Key message: It looks like you haven't been able to take the PrEP medication. Is PrEP something that you are still interested in? If yes, how can we help you?

We will also introduce a new point of care urine assay for drug level feedback counseling at the month 9 visit to assess acceptability and feasibility of this assay compared with using DBS for drug level feedback (DLFB). Such an assay was not available at the start of PrEP SMART enrollment, but has since become available. This point of care urine (POC) assay was recently developed to measure TFV levels in urine[7069]. A POC assay could support real-time adherence monitoring to provide drug level feedback about recent PrEP dosing in the week prior to the clinic appointment, however more work is needed to determine the acceptability and feasibility of a urine POC assay for drug-level feedback counseling, given the shorter adherence assessment window. The POC lateral flow assay has a threshold of 1500ng/mL consistent with dosing in the last 4-7 days based on a directly observed therapy study, is being developed in collaboration with Alere Diagnostics, and will cost approximately $3.[724] Approximately 2-3 minutes after 3-4 drops of urine are placed on the urine test strip, a "control" line should appear. An additional "tenofovir test line" will appear only if a participant has TFV levels <1500 ng/mL indicative of no recent PrEP dosing. This threshold will be used to provide drug-level feedback counseling at the month 9 visit as depicted below. We plan to assess acceptability and feasibility of this new POC assay by using it for additional drug level feedback counseling among all participants during their Month 9 visit. All participants receiving the urine POC assay will be subsequently asked about their perceptions of acceptability, feasibility, and satisfaction with the assay. The subset of participants that previously received DLFB counseling using DBS will also be asked to reflect on which DLFB counseling option they preferred (DBS versus urine). DLFB

counseling using the urine assay will also provide an opportunity to counsel all participants on opportunities to continue receiving PrEP through other mechanisms in South Africa after they are exited from the study. Counselors will engage participants in a discussion of HIV risk perception and link interested young women to further PrEP services. The counseling messages were developed in consultation with Drs. Gandhi and Hosek:

Control line only (one line appears on test)
Key message: It looks like you took a PrEP pill recently--you are doing great! Remember that taking one PrEP pill every day is needed for strong protection against HIV. Are you still interested in taking PrEP after your participation in this study is complete today?

Control and tenofovir test line (two lines appear on test)
Key message: It looks like you haven't been able to take the PrEP medication in the past few days. Is PrEP something that you are still interested in? If yes, how can we help you continue to access and take PrEP after your participation in this study is complete today?

Monthly clinic visits with problem-focused adherence counseling
The drug levels from open label PrEP studies among young MSM in the US (ATN 110 and 113) and the PlusPills study among young women in Cape Town indicate a significant drop in adherence when visit intervals decrease from monthly to quarterly. It is possible that youth who have difficulty adhering to PrEP after the first three months of follow-up will continue to need more frequent contact and specialized adherence counseling when establishing adherence habits, especially for pill-taking for HIV prevention in which they are not being reminded by signs of illness. In addition, youth may be impacted by 'present bias' or discounting due to hypothetical risks that they do not want to think about (i.e., HIV infection). Frequent visits throughout follow-up could keep them more engaged in PrEP and allow for more intense counseling about side effects, disclosure, relationship issues, and other factors that might impact their adherence. Special adherence counseling will be based on cognitive-behavioral and problem-solving strategies and include an assessment of adherence barriers and facilitators as well as plans to address identified barriers through behavioral skills building. In contrast, participants who adhere well to PrEP after the first three months of monthly study visits may have formed effective habits for PrEP pill-taking and can be switched to quarterly visits with SOC counseling plus their assigned mHealth intervention in order to allocate intensive counseling resources to participants who need them most.

2.0 STUDY OBJECTIVES

2.1. Primary Objective(s)

The primary objective of this study is:

- To evaluate the proportion of young South African women who adhere well to PrEP with regular clinic visits and mHealth interventions alone, the proportion of women who adhere well to PrEP with intensified adherence support interventions (i.e. problem-focused counseling or drug-level feedback).

2.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the proportion of women who achieve high adherence early (month 2).
- To evaluate the optimal sequence of intensifying adherence support among young women who have low adherence after the first two months of use.

- To identify correlates of PrEP adherence, 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 characterize SMS response rates and the content and frequency of use of WhatsApp groups
- To qualitatively explore factors that influence women's decisions to use PrEP and adhere to PrEP and their satisfaction with their assigned intervention(s).
- To qualitatively explore perceptions of our intervention package and opinions on scalability of the interventions from clinic staff and key informants' perspectives.

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To assess HIV incidence, and to assess the association with detectable TFV-DP in PrEP users who acquire HIV infection during the study.
- To describe antiretroviral drug resistance among women who acquire HIV infection.
- To assess acceptability and feasibility of a urine point-of-care test for drug-level feedback counseling.

3.0 STUDY DESIGN

3.1. Design

This is a randomized single-site prospective study to assess a stepped model of scalable adherence support strategies in South African young women who initiate PrEP.

Women will be consented to have 9 months of follow-up. PrEP will be offered as part of a comprehensive package of sexual and reproductive health care that includes – HIV testing, counseling, condoms, contraception, and testing for and treatment of STIs. Up to 500 women will be consented and randomized. Women will receive their assigned interventions until month 9 (the primary endpoint) and will be exited from the SMS and WhatsApp messages at the 9-month visit.

At enrollment women will be randomly assigned in a 1:1 ratio to receive standard adherence support counseling with monthly clinic visits and one-way SMS reminder messages and *either* participation in WhatsApp groups *or* weekly two-way SMS communication.

At month 3, women who had TFV-DP <500 fmol/punch (based on a blood sample collected at month 2) or who miss PrEP refills at the 1- or 2-month visits will undergo a secondary randomization to continue monthly follow-up visits with problem-focused counseling until M8 vs quarterly visits with drug level feedback at months 3 and 6. Women will also continue to receive the adherence support from their orginal randomization (i.e., SOC adherence counseling, one-way SMS reminder messages, and WhatsApp groups or two-way SMS). Women who have TFV-DP ≥500 fmol/punch at 3 months (based on a blood sample collected at month 2) will continue to receive the adherence support in their original randomization (SOC adherence counseling, one-way SMS reminder messages, and either WhatsApp groups or two-way SMS) with quarterly visits. Table 1 depicts the four adaptive interventions and decision rules for determining non-adherence and re-randomizing women at their month 3 visit:

Table 1. Adaptive intervention decision rules

Adaptive intervention	Decision rule
Non-response definition: TFV-DP levels <500 fmol/punch or missed refills	

First, offer monthly SOC counseling and WhatsApp group intervention; then add drug level feedback with quarterly visits for non-responders and switch responders to quarterly SOC visits and continued WhatsApp groups	First-stage intervention option = {SOC + WhatsApp} IF evaluation = {non-response} THEN second-stage intervention option = {DLFB + first-stage intervention option + quarterly study visits} ELSE continue on first-stage intervention option with quarterly study visits
First, offer monthly SOC counseling and two-way SMS intervention; then add drug level feedback with quarterly visits for non-responders and switch responders to quarterly SOC visits and continued two-way SMS	First-stage intervention option = {SOC + SMS} IF evaluation = {non-response} THEN second-stage intervention option = {DLFB + first-stage intervention option + quarterly study visits} ELSE continue on first-stage intervention option with quarterly study visits
First, offer monthly SOC counseling and WhatsApp group intervention; then add monthly follow-up visits with special issue adherence counseling for non-responders and switch responders to quarterly SOC visits and continued WhatsApp groups	First-stage intervention option = {SOC + WhatsApp} IF evaluation = {non-response} THEN second-stage intervention option = {Monthly visits and specialized counseling + first-stage intervention option} ELSE continue on first-stage intervention option with quarterly visits
First, offer monthly SOC counseling and two-way SMS intervention; then add monthly follow-up visits with special issue adherence counseling for non-responders and switch responders to quarterly SOC visits and continued two-way SMS	First-stage intervention option = {SOC + SMS} IF evaluation = {non-response} THEN second-stage intervention option = {Monthly visits and specialized counseling + first-stage intervention option} ELSE continue on first-stage intervention option with quarterly visits

All women will receive periodic one-way SMS messages reminding them about upcoming clinic appointments during the follow-up period.

A subset of up to 25 women will also be recruited to participate in serial qualitative interviews, to explore factors that influence women's decisions to use PrEP and adhere to PrEP and their satisfaction with their assigned intervention(s) after their Month 2, Month 6, and study exit visits. A subset of 10 key informants (e.g., PrEP program managers, health department officials) and 15 clinic staff members will also be recruited to participate in in-depth interviews to explore their perceptions of the PrEP SMART interventions and facilitators and barriers to future intervention scale-up.

At month 9, women will be offered the option of drug level feedback counseling via a new urine POC test, as available, to assess acceptability and feasibility of the urine test.

Finally, we will review SMS and WhatsApp message content to determine participant engagement with the interventions and identify key themes around PrEP use, HIV risk perceptions, and intervention satisfaction.

3.2. Study Population

Sexually active young women ages 18-25 wanting PrEP at the Ward 21 clinic, Wits RHI, in Johannesburg, South Africa.

3.3. Eligibility

3.3.1. Inclusion Criteria

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

- Female at birth

- Age 18-25 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
- Able and willing to provide adequate locator information
- Regular access to a mobile phone with SMS and WhatsApp capacity
- Agrees not to participate in other research studies involving drugs or medical devices for the duration of study participation

3.3.2. Exclusion Criteria

Young women who meet any of the following criteria will be excluded from enrolling in 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
- A reactive or positive HIV test at Enrollment
- Any reported PrEP use within the last 6 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
- Positive pregnancy test

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.

4.0 STUDY PROCEDURES AND INTERVENTIONS

4.1. Recruitment and Screening Process

All recruitment materials will be approved by IRBs/ECs at the University of the Witwatersrand and the University of Washington. A variety of recruitment approaches will be used. Recruitment may be conducted through community events and mobilization, partnerships with voluntary counseling and testing centers, home-based and mobile HIV testing programs, health clinics, and pharmacies that provide emergency contraception and post-exposure prophylaxis. Recruitment may also include a patient-facing PrEP decision support tool to aid young women in considering their risk of HIV and motivation for using PrEP.

4.2. Study Procedures

An overview of the study visit and procedures schedule is presented in Appendices IA-B. Presented in the study schema figure shown on pages 9-10 and the figure (Figure 1B) and text below is additional information on visit-specific study procedures.

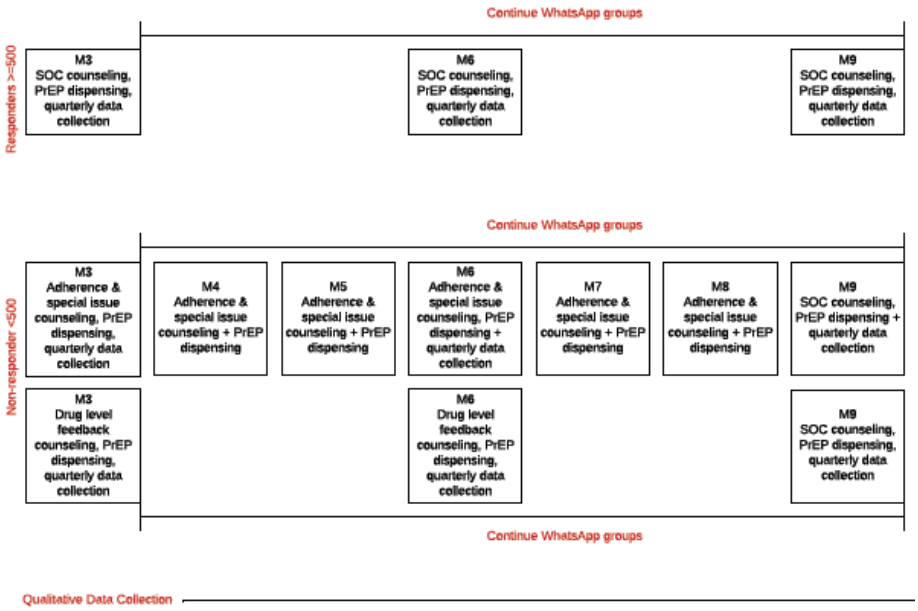


Figure 3. Schematic summary of visit and intervention procedures.

4.2.1. Enrollment Visit

Women who agree to study participation will be consented for 9 months of follow-up. Women who are confirmed HIV- and not pregnant will be randomized to participate in one of two basic strategies for adherence support:

- Standard of care adherence counseling sessions and WhatsApp group participation
- Standard of care adherence counseling sessions and weekly two-way SMS communications

Randomization will be conducted with a ratio of 1:1 between the two study arms. Envelopes will be used to assign primary randomization.

Locator information will be collected and mobile phone numbers will be validated and texting and WhatsApp capacity assessed. Demographic and behavioral data will be collected, including information about HIV and pregnancy risk perception, depressive symptoms, trauma, stigma, HIV prevention, self-efficacy, self-esteem, sexual relationship power, transactional sex, intimate partner violence, alcohol and drug use, sexual behavior (number of partners, partner's HIV status, vaginal and anal sex with partners), and PrEP interest and readiness.

Clinical evaluations and procedures will include a contraception assessment, counseling and provision if desired, HIV pre and post-test counseling, risk reduction counseling and condom provision. Medical history including assessment for acute HIV and STI symptoms and concomitant medications will be conducted and a symptom-directed physical exam will be performed if indicated. Women who have symptoms potentially consistent with acute HIV infection (fever, rash, pharyngitis) will have enrollment deferred for at least 2 weeks at which time repeat serologic testing will be performed (and if positive will result in study exclusion). STI treatment will be administered per local standard of care. Blood, urine, and a self-administered vaginal swab will be collected.

HIV testing will be conducted according to national algorithm. Testing will be conducted for pregnancy, Hepatitis B serology (HepBsAg), serum creatinine for creatinine clearance, and diagnostic STI testing for trichomonas, gonorrhea, chlamydia and syphilis. Plasma and DBS will be stored.

One bottle of PrEP will be dispensed and women will be counseled per South African national guidelines, including 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, eligibility criteria have been confirmed including that the participant's has been confirmed HIV negative and she is not pregnant, and the participant has been randomized.

4.2.1.1. Standard of Care counseling sessions

For this study, SOC adherence counseling will follow South African guidelines. Using the PrEP Follow-Up Counseling Checklist developed by the South African Department of Health, 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. The SOC adherence counseling sessions will include: PrEP information review (i.e., why adherence is important, relationship between adherence and PrEP efficacy); examination of adherence barriers and facilitators - including possible disclosure to partners and parents, and problem-solving around adherence (i.e. reviewing calendar for daily habits, planning for travel or schedule disruptions). Counselors will keep a progress note for each session. Counseling sessions may be audio-recorded to ensure fidelity to counseling messages. Audio-recorded sessions will be reviewed by study team members in the U.S.

4.2.1.2. **Intervention: Randomization to WhatsApp groups**

WhatsApp groups will include 25-50 participants. At the enrollment randomization visit, women randomized to WhatsApp groups will meet the staff facilitator and be told the name of their WhatsApp group and instructions on appropriate WhatsApp group use, including group rules. Participants will receive written instructions on these rules as well as instructions on how to contact the staff facilitator outside of the group. Each group will also include a PrEP Ambassador who will be a young woman with previous PrEP experience. The staff facilitator and PrEP Ambassador will be responsible for moderating these clubs to answer questions about PrEP, facilitate discussions, introduce topics of interest, monitor member conduct and enforce group rules. Group members will also have the option to meet in person.

4.2.1.3. Intervention: Randomization to weekly two-way SMS

Participants randomized to receive weekly SMS text messaging will receive a two-way SMS, in which they will receive a confidential message of "Are you fine, girlfriend?" and are instructed to text the site staff if they are ok (yes) or need a call-back (no). If a participant responds "no" or fails to respond, a staff member will call back within 24 hours to assess and address the issues and determine if they need to be seen (i.e., for side effects). A log will be kept of responses (and non-responses) from participants, as well as the outcome of triage and referrals. In addition to these two-way SMS messages, we will also periodically send one-way SMS messages including facts about PrEP and HIV prevention to keep participants engaged in the intervention and improve PrEP knowledge and self-efficacy.

4.2.2.Month 1 visit

Locator information will be updated.

Clinical evaluations and procedures will include a contraception assessment, counseling and provision if desired, HIV pre and post-test counseling, risk reduction counseling and condom provision. Blood will be collected. HIV testing will be conducted according to national algorithm. Plasma and DBS will be stored. Participants with positive HBsAg results will be referred for care and treatment of active infection.

Urine will be collected and urine pregnancy testing conducted. Social harms and SAEs will be assessed and participants will receive additional counseling and referrals related to their SAEs as necessary.

A prescription for two bottles of PrEP will be written, one bottle of PrEP will be dispensed if no contra-indcations, and women will be counseled per South African national guidelines.

4.2.3. Month 2 visit

Locator information will be updated. Blood will be collected for DBS. PrEP adherence will be assessed using DBS. One bottle of PrEP will be dispensed and women will be counseled per South African national guidelines**.**

4.2.4. Month 3 randomization visit

Women with high adherence (i.e., TVF-DP ≥500 fmol/punch based on Month 2 drug levels) who have not missed PrEP refills at Month 1 or 2 will be considered 'responders'. Responders will move to quarterly visits and continue to be offered the adherence support they were randomized to at enrollment. Pharmacy refills will be verified using electronic pharmacy records.

'Non-responders' (i.e., TFV-DP <500 fmol/punch or missed PrEP refill) will be randomized to a more intensive adherence support – continued monthly counseling visits or quarterly visits with counseling based on drug levels at months 3 and 6. Randomization will be conducted with a ratio of 1:1 between the two study arms. We will use envelopes in order to assign "non-responding" subjects to the second intervention. Envelopes will be prepared by study staff in Seattle and site staff in Johannesburg will open the envelopes in the specified order only when they are ready to randomize a "non-responding" participant.

All women will continue with the intervention they were assigned in their initial randomization (WhatsApp groups or two-way SMS) regardless of if they are classified as responders or non-responders. Additional month 3 visit procedures are included in section 4.2.5.

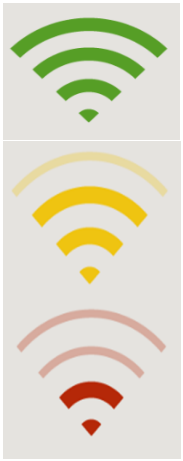
In the case of public health emergencies, study procedures that require in person visits may be delayed, including blood draws to determine secondary randomization. Therefore, secondary randomization may be conducted using blood drawn from visits occurring between months 1 and 3.

4.2.4.1. Intervention: Monthly counseling visits

Women who are randomized to continue monthly visits will have visits at months 4, 5, 7, and 8 that are focused on counseling. During these visits, women will receive SOC counseling that is tailored to identify problems impacting adherence, generate alternative solutions, make decisions about the alternatives, and collaboratively decide on a plan regarding how to implement the solutions. Additionally, they will have special issue counseling that explores their experiences with intimate partner violence, mental health issues such as depression and anxiety, and drug and alcohol use. Counselors will keep a progress note for each session. Counseling sessions may be audio-recorded to ensure fidelity to counseling messages and these audio-recordings will be reviewed by study team members in the U.S.. Women in this arm will have all procedures listed in 4.2.5 at their 3, 6, and 9month visits.

4.2.4.2. Intervention: Counseling based on drug levels at 3 and 6 months

Women who are randomized to counseling based on drug levels will move to quarterly visits and receive adherence counseling based on DBS levels collected 2 and 6 months after PrEP initiation. Adherence counseling will be provided in person or remotely, depending on pandemic conditions. The following thresholds and counseling messages will be used for drug level feedback counseling at these visits:



>500 fmol/punch
Key message: You are doing great! Keep up the good work and remember that taking one PrEP pill every day is needed for strong protection against HIV.

Between detectable to 499 fmol/punch
Key message: It looks like you are trying to take the PrEP medication, but are having some difficulties. Remember that taking one pill every day is needed for strong protection against HIV. How can we help you do even better?

No TFV-DP detected (confirm BLQ level)
Key message: It looks like you haven't been able to take the PrEP medication. Is PrEP something that you are still interested in? If yes, how can we help you?

4.2.5. Quarterly Follow-up Visits

Quarterly visits will occur at 3, 6, and 9 months for all participants in all arms.

At all quarterly follow-up visits, locator information will be updated with specific attention paid to phone number changes. Behavioral data will be collected including information about HIV and pregnancy risk perception, sexual behavior (number of partners, partner's HIV status, vaginal and anal sex with partners), depression, stigma, HIV prevention self-efficacy, sexual relationship power, transactional sex, intimate partner violence, self-esteem, trauma, and alcohol and drug use.

Clinical evaluations and procedures will include a contraception assessment, counseling, and provision if desired, HIV pre and post-test counseling, risk reduction counseling, and condom provision. Medical history including assessment for acute HIV, STI symptoms, and concomitant medications will be conducted. If indicated, a symptom-directed physical exam will be conducted. STI treatment will be administered per local standard of care based on test results, physical exam, or participant-reported symptoms. Social harms and SAEs will be assessed and participants will receive additional counseling and referrals related to their SAEs as necessary. Blood and urine will be collected. At the month 6 and study exit visit, a self-collected vaginal swab will be collected.

Sufficient PrEP will be dispensed to last until the following quarterly scheduled study visit. Participants randomized to monthly visits will be dispensed PrEP at those visits.

HIV testing will be conducted according to the national algorithm. Pregnancy testing will be conducted on urine. Plasma and DBS will be stored.

At month 6, serum creatinine testing will be conducted for creatinine clearance. At months 6 and study exit visit, STI testing will be conducted for trichomonas, chlamydia, gonorrhea and syphilis.

At month 9, we will offer participants the option of receiving drug level feedback counseling via a new urine POC assay to assess acceptability and feasibility of this approach. We will use drug level counseling messages previously described in section 1.2.1. Following the drug level feedback counseling, we will ask participants to answer a series of questions on their feelings about the urine POC test and to compare the acceptability of drug level feedback counseling based on the urine POC test versus DBS testing. This counselling will focus on participants continued interest in taking PrEP, and facilitiate linkage to PrEP services for ongoing PrEP access following study exit.

4.2.6. 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.

4.2.7. Remote Visits

In response to the COVID19 pandemic, study visits may be conducted remotely. Prior to remote visits, staff will confirm with participants whether or not they wish to proceed with remote visits. Participants may be supplied with HIV self-test kits and urine pregnancy test kits and instructions for use at an in-person visit or via delivery. Study staff will confirm readiness for remote visits by phone to ensure participant safety and confidentiality. Remote visit procedures will be detailed in a standard operating procedure. PrEP may be delivered to participants at their homes following successful assessment by a clinician over the phone and following review of self-test results. Data will be collected during the in-depth interviews and short questionnaires on the feasibility and acceptability of remote visit procedures. Where it is not possible to complete all visit procedures remotely, this will be noted as a protocol deviation. Missed procedures may be completed at subsequent in person visits.

4.3. Qualitative data collection

The use of qualitative methods that give young women the opportunity to discuss their PrEP adherence barriers and facilitators in their own words and their experiences with the different interventions will result in a more culturally-sensitive approach to the study of PrEP adherence strategies among young women in Africa. Interviews will be conducted with a purposive sample of approximately 25 women and will include:

1. Young women who accept and adhere to PrEP (when possible these women will be selected based on drug levels at month 2).
2. Young women who have low drug levels at 2 months.

We will conduct interviews with samples of participants from each of the four possible interventions (two-way SMS messages, WhatsApp support groups, drug-level feedback, and monthly visits). These in-depth qualitative interviews will occur at three visits. The first will be after the month 2 visit. The second will be after their month 6 visit. The third will be after the month 9 visit or study exit. The first interview will explore the decision to take PrEP, barriers and facilitators to PrEP adherence, and experiences with either the SMS messages or the WhatsApp support groups within the first 2 months of PrEP use. This interview will also assess how women incorporated daily pill-taking into their daily routines, where they stored product, whether they disclosed their PrEP use with family members, peers, and their partner(s), whether they experienced side effects and/or other barriers to pill-taking and how that influenced their adherence in the first 2 months, and whether their risk perception and motivation to use PrEP changed over the first 2 months of use. Finally, the interview will assess their opinions about receiving and responding to SMS messages, satisfaction with support received through the WhatsApp groups, technical issues with SMS and WhatsApp messages, influence of the SMS and WhatsApp groups on their PrEP use, and concerns about message privacy and disclosure.

The second interview will further explore barriers and facilitators to PrEP adherence, and will include a discussion of participant's reaction to second randomization and allocation to counseling about their TFV results or monthly visits with special adherence counseling, as applicable.

In the final interview, research staff will ask women to provide a narrative history and timeline of their sexual relationships, living conditions, and other important factors in their lives over the prior 9 months.

Interview guides will be developed using reviews of local literature and youth community advisory board (YCAB) 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.[732] 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 and feelings about the study interventions 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 and approximately one social scientist. 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.[743] 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 adherence and intervention arm, 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 three time points with up to 25 young women or until saturation/redundancy are reached. We will also conduct debriefs with the qualitative interviewers and the counseling staff to explore their views on participant's experiences with the in-depth interviews and the interventions.

We will also interview approximately 10 key informants (e.g., PrEP program managers, health department staff) and 15 staff members to assess their perceptions of our intervention package and opinions on scalability of the interventions. We will also ask additional questions on their perceptions of providing more intensive psychosocial and mental health counseling services for AGYW in PrEP delivery settings to inform future counseling intervention work with this population. These questions are motivated by early findings from this study, and other recent PrEP projects in this setting, of a high need for mental health services and targeted psychosocial counseling around depressive symptoms, stress and anxiety, and gender-based violence and trauma among adolescent girls and young women seeking PrEP. Key informants will include individuals working on PrEP delivery, funding, policy, and/or implementation for AGYW in South Africa. Staff will include any doctors, nurses, recruitment officers, WhatsApp group facilitators, counselors, study coordinators, and other individuals with direct contact with AGYW at the clinic and engagement in PrEP delivery services. Key informant interview will assess: attitudes toward PrEP and mental health counseling for adolescent girls and young women and opinions of the inclusion of mental health care in PrEP delivery; opinions on needs for staff competencies and training and clinic supports for mental health and HIV service delivery; and potential contextual facilitators and barriers to integrating a mental health counseling intervention with PrEP delivery for South African adolescent girls and young women. Staff interviews will assess: experiences with PrEP delivery in the clinic; perceptions of PrEP SMART interventions; feelings of rapport with adolescent girls and young women; barriers to PrEP and counseling service delivery; satisfaction with clinic flow and suggestions for improvements;

attitudes toward PrEP and psychosocial and mental health counseling for adolescent girls and young women and opinions of the inclusion of further psychosocial support services in PrEP delivery; and potential facilitators and barriers to integrating a more intensive mental health counseling intervention with PrEP delivery for South African adolescent girls and young women. Interview guides will be semi-structured and based on the local literature and findings from PrEP SMART thus far. Trained researchers/ethnographers will conduct all interviews with oversight from the protocol team. All interviews will be audio-recorded and transcribed and translated into English by trained site staff.

In addition to data collection using in-depth interviews, we will also download SMS and WhatsApp messages and conduct a thematic content analysis of text messages to explore key themes around PrEP adherence, perceptions of the interventions, and participants' level of engagement with the SMS and WhatsApp services. At the end of each week, the WhatsApp discussion group moderator will export the content of the group chats from WhatsApp. The WhatsApp exports will initially contain identifiable patient information (phone numbers) and therefore will be protected with great care to ensure data security and avoid a breach of confidentiality. Site study staff will deidentify chats by permanently removing all phone numbers and names and replacing them with sequential study ID numbers. De-identified data will then be stored as a password protected file on a secure sever. We will follow a similar procedure to deidentify SMS data. Study staff will download the SMS data from the Telerivet platform on a weekly basis, permanently replace phone numbers and names with study ID numbers, and save deidentified data as a password protected file on a secure server. We will use descriptive statistics to summarize SMS and WhatsApp response rates and free-text SMS and WhatsApp responses will be will be analyzed using qualitative software methods.

4.4. PrEP

Participants will be provided with PrEP in the form of oral emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (FTC/TDF) for once daily dosing. Prescriptions will be written as follows: 1 bottle at enrollment, 2 bottles at month 1, 3 at months 3 and6. Bottles will be dispensed as follows: 1 bottle at each visit until month 3 and then 3 bottles at months 3 and 6. Participants will be directed to take PrEP once daily with or without food throughout follow up. If a participant forgets to take PrEP at the correct time, it may be taken later in the day; however, no more than one tablet should be taken on any calendar day.

4.4.1. PrEP 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. TDF/FTC was approved by the South African African Health Products Regulatory Authority (SAPHRA, formerly the Medicines Control Council) as PrEP in 2015.

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 pharmacy in the original container.

4.5. Contraceptive Use and Pregnancy

Contraception use will be assessed at every study visit. Contraception counseling and provision will be offered at all study visits. For women who become pregnant, PrEP offers a strategy to reduce HIV risk in the peri-conception period, and data from PrEP clinical trials and demonstration projects have demonstrated that peri-conception use is safe in terms of pregnancy incidence, pregnancy outcomes, and infant outcomes.[754]

Current WHO guidance indicate that there is no safety-related rationale for disallowing or discontinuing PrEP during pregnancy and breastfeeding for HIV-negative women who are receiving PrEP and remain

at risk of HIV acquisition.[765] The guidelines conclude that in such situations, the benefits of preventing HIV acquisition in the mother and the accompanying reduced risk of mother-to-child HIV transmission outweigh any potential risks of PrEP, including any risks of fetal and infant exposure to the drugs in PrEP regimens. Women who become pregnant while taking PrEP will be counselled about the benefits and risks of continuing during pregnancy, and allowed to continue PrEP if they choose.

4.6. Post-exposure prophylaxis

In the event of sexual assault or possible HIV exposure and if the participant reports inconsistent PrEP use, post-exposure prophylaxis (PEP) will be offered in accordance with local guidelines for one month. PrEP will be discontinued during the one month of PEP, and restarted following repeat HIV testing to exclude possible HIV seroconversion.

4.7. HIV Seroconversion

HIV testing will be performed at the following study visits – Enrollment, Month 1, and all quarterly visits. Participants who have at least one positive HIV rapid test will be instructed to discontinue PrEP immediately. Participants who have a positive HIV self-test at a remote visit will be requested to come to the research clinic for study staff to conduct additional HIV testing. All possible seroconverters will have locator information updated and will receive counseling. Blood will be collected and pregnancy testing will be conducted. HIV EIA, CD4, viral load, and genotypic resistance testing will be conducted in order to confirm seroconversion. In addition, a DBS and plasma sample will be archived for tenofovir testing. All other visit procedures corresponding to the study visit will also be conducted.

Participants with confirmed HIV infection will have one additional study visit, ideally within 1 month of the possible serconversion visit at which time the participant will receive laboratory results. Confirmed seroconverters will permanently discontinue PrEP and the participant will be linked to a local HIV care clinic for appropriate follow-up and clinical management. All exit study visit procedures will be conducted and the participant will be permanently exited from the study.

4.8. Participant Retention

Participants will be in the study for 9 months of follow-up and retention procedures may include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Collection of detailed locator information at the Enrollment 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.
- Rapid and multi-faceted 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.

4.9. Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. The site investigator 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. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, or site IRBs terminate the study prior to its planned end date.

Every reasonable effort will be made to complete final evaluations 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. Participant non-adherence to the intervention(s) or PrEP is not a reason for participant withdrawal from the study and we will continue to follow participants even if they decline the interventions (e.g., reply "STOP" to the two-way SMS messages) prior to the completion of follow-up.

5.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

5.1. Safety Monitoring

Close cooperation between the Protocol co-Chairs 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 investigators are responsible for continuous close monitoring and management of SAEs.

5.2. Adverse Event Definition and Reporting

For the purposes of this study, only serious adverse events (SAEs), creatinine clearance <60 ml/min, tolerability or side effects to PrEP that lead to discontinuation, and social harms associated with study participation will be recorded.

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.

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.

5.3. Relationship to PrEP

Relatedness is an assessment made by a study clinician of whether or not the event is related to PrEP. 'Not related' will be noted for SAEs among participants who discontinue PrEP.

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.

5.4. Creatinine Clearance

Creatinine clearance will be calculated using the Cockcroft-Gault Equation. If the calculated creatinine clearance is <60mL/min, PrEP will be halted temporarily and creatinine testing repeated within two weeks. If renal function returns to normal (CrCL ≥60 mL/min), PrEP may be re-started.

5.5. 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 participant will be contacted 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 Enrollment) or stabilizes. PrEP will be discontinued if the CrCl decreases below 60 ml/min and serum creatinine will be monitored. 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.

5.6. 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. A social harm that is reported by the participant and judged by the study staff to be serious or unexpected will be reported to the site's IRBs at least annually, or according to local requirements.

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. While maintaining participant confidentiality, the site may engage the Youth Community Advisory Board (YCAB) in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

6.0 STATISTICAL CONSIDERATIONS

6.1. Review of Study Design

SMART design to evaluate response to scalable adherence strategies. At enrollment, women will be randomized to either the SOC adherence support plus WhatsApp groups, to provide social support, or SOC adherence support plus weekly two-way SMS messages, to triage and provide additional counseling to manage side effects, adherence issues, or any other concerns. All participants will attend monthly visits for the first 3 months of follow-up and will receive periodic one-way reminder SMS messages about upcoming clinic appointments. In both groups, intracellular tenofovir drug levels based on DBS collected at 2 months will be used as an objective measure of adherence. At the Month 3 visit, women who are classified as "responders" (those with high adherence, based on a TFV-DP threshold of 500 fmol/punch measured at the Month 2 visit) will continue with the SOC counseling and their initial randomization of either two-way SMS or WhatsApp groups but they will be switched to a quarterly visit schedule. Non-responders (those with low adherence based on the Month 2 visit drug levels) will be randomized to more intensive adherence support – monthly visits for SOC adherence and special issue counseling or quarterly visits with drug level feedback at 3 and 6 months in addition to their initial randomization arm intervention (two-way SMS or WhatsApp and one-way reminder SMS messages). Follow-up visits will occur for all participants monthly until Month 3 and then quarterly for 9 months for responders and non-responders randomized to drug level feedback. Non-responders who are randomized to monthly visits will continue to have monthly visits until M9; the month 4, 5, 7, and 8 visits will be special issue counseling visits. We will discontinue all interventions by the month 9 study visit (participants will be exited from two-way SMS and WhatsApp, special issue counseling and drug-level feedback will not occur at the month 9 visit). The primary outcome for the combined intervention is the proportion with high adherence measured by

intracellular TFV-DP levels at 9 months. Drug levels will be measured retrospectively using DBS samples. We will utilize DBS TFV-DP levels to assess cumulative dosing in the prior month. A threshold of 500 fmol/punch for counseling participants. For the outcome, we will use a category of 700 fmol/punch to categorize participants as highly adherent as this was associated with high efficacy in open label use of PrEP among MSM. The threshold of TFV-DP levels and HIV incidence in women PrEP users has not been identified. [16]

The secondary adherence measurements will be TFV-DP concentrations at Month 2.

6.2. Endpoints

6.2.1. Primary Endpoint

The primary outcome is dried blood spot drug concentrations above 700 fmol/punch at 9 months.

6.2.2. Secondary Endpoints

- TFV-DP concentrations above 700 fmol/punch at 2 months.
- TFV-DP concentrations at 2 and 9 months as a continuous measurement
- Correlates of PrEP adherence at 2 and 9 months, adjusted for study arm.
    - Covariate characteristics assessed at baseline and follow-up will include: Sociodemographic characteristics; partnership characteristics; partner's HIV status; sexual behaviors; HIV risk perception; HIV stigma; PrEP interest; self-efficacy; alcohol and drug use; gender-based violence (GBV); disclosure to peers, family members, teachers, and partner(s) about PrEP use and participation in the study, and level of engagement with the different intervention approaches (e.g., number of SMS messages sent, number of WhatsApp messages sent, satisfaction with intervention received).
- Proportion of young women who discontinue PrEP, timing of discontinuation, and factors associated with PrEP discontinuation.
- Frequency of responding to SMS and WhatsApp messages over follow-up, stratified by "responder" or "non-responder" status after Month 3; content of WhatsApp discussions over follow-up, stratified by "responder" or "non-responder" status after Month
- Qualitative factors that influence women's decisions to use and adhere to PrEP, acceptability of PrEP in the first 2 months after PrEP acceptance, and satisfaction/preferences for the randomized intervention(s) received.
- Qualitative perceptions of our intervention package and opinions on scalability of the interventions from clinic staff and key informants' perspectives.

6.2.3. Exploratory endpoints

- Incident HIV infections, and adherence prior to HIV seroconversion based on drug levels
- Genotypic resistance among incident HIV infections
- Acceptability and feasibility of a urine point-of-care test for drug-level feedback counseling, among the subset of women who accept drug level feedback counseling via a new urine POC assay at their month 9 exit visit.

6.3. Accrual, Follow-up, and Sample Size

For the SMART trial design, the goal is to enroll and randomize up to 500 women in order to achieve an analysis sample size of approximately 350 women who return for their one-month study visit and will want to continue PrEP for a further 9 months: 175 per arm randomized into the first intervention at enrollment, continuing past their 1-month study visit and evaluable at 9 months. Up to 500 women who initiate PrEP will be enrolled over a period of approximately 18 months. 350 evaluable women

would have 96% power for the initial randomization to detect an increase from 40% response at 2 months to SOC + two-way SMS to 60% with the SOC + WhatsApp groups. Among the estimated 70-105 non-responders in each initial group, we have 79-96% power in each group of non-responders to detect a 30% difference in adherence at 9 months between women randomized to monthly counseling or drug level feedback. Pooling across the initial randomization, with 149-166 women we would have ~80% power to detect ~ 15-20% difference (Table 2).

Table 2: Power to assess differences in adherence by intervention strategies in each of the first and second stages using a one-sided $\alpha = 0.025$.

First Randomization			Second randomization (Pooled across first randomization)			
% Adherent				% Adherent		
WhatsApp + SOC N = 175	SMS + SOC N = 175	Power	Non-responders Total N	Monthly visits	Drug Level Counselling	Power
65%	40%	**99%**	166	40%	25%	84%
				50%	30%	89%
60%	40%	**96%**	175	40%	25%	86%
				50%	30%	91%
55%	40%	**84%**	184	40%	25%	88%
				50%	30%	91%

6.4. Data Analysis

6.4.1. Primary Analyses

We will conduct primary analyses to assess the effect of the randomized interventions on drug concentrations at 9-months post-randomization by 1) comparing the first-stage intervention options on TFV-DP levels at the 9-month visit; 2) comparing the second-stage intervention options on TFV-DP levels at the 9-month visit among participants classified as "non-responders" to the initial intervention; and 3) comparing the four adaptive intervention strategies described in Table 1.

For the analyses of first-stage intervention options, logistic regression will be used to assess effect of the each primary randomized intervention on 9-month adherence by comparing TFV-DP levels in Groups 1-3 versus Groups 4-6 shown in Figure 1B on page 10. For the analyses of second-stage intervention options among non-responders, logistic regression will also be used to assess the effect of the intensified adherence intervention (second randomization) within each arm of the first randomization, and in the absence of interaction, pooled across the first randomization (Groups 2 and 5 versus Groups 3 and 6). For analyses comparing the adaptive intervention approaches, each of the 4 overall strategies (2 initial x 2 intensification interventions in non-responders) will be ranked by their overall adherence response (Table 3), with inverse-probability weighting and standard errors taking into account that women who respond to their first-assigned treatment are consistent with *two* of strategies embedded within our SMART design and over-represented in our analysis datasets. Because of the high expected post-randomization drop-out before M1, we will adjust for confounders of PrEP continuation and adherence and M1 drop-out in the analysis.

Table 3. Combination of adherence intervention strategies in SMART design. [*Note that under each of the four strategies embedded in our trial design, young women who are adhering ("responding") will continue to receive their originally-assigned method of support (i.e., WhatsApp groups or weekly two-way SMS).]*

Standard of care brief counseling and one-way SMS reminder messages with WhatsApp peer support, followed by quarterly drug level counseling for non-responders
Standard of care brief counseling and one-way SMS reminder messages with WhatsApp peer support, followed by monthly visits with problem-focused counseling for non-responders
Standard of care brief counseling and one-way SMS reminder messages with two-way SMS support, followed by quarterly drug level counseling for non-responders
Standard of care brief counseling and one-way SMS reminder messages with two-way SMS support, followed by monthly visits with problem-focused counseling for non-responders

6.4.2. Secondary Analyses

The primary analyses will be repeated to assess the intervention effects on dried blood spot drug concentrations above 700 fmol/punch at 2 months. 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). We will also assess the intervention effects on continuously measured TFV-DP concentrations (measured in dried blood spots) Months 2 and 9.

The correlates of response (PrEP adherence based on drug levels) at 2 and 9 months will be assessed using logistic regression modelling, evaluating demographic, behavioral, perceived risk, stigma, self-efficacy, relationship power, transactional sex, IPV, and alcohol use and PrEP adherence by intervention strategy. We will also assess whether level of engagement with the primary intervention (WhatsApp and SMS) is a mediator in the pathway between intervention assignment and PrEP drug levels at Months 2 and 9.

Survival analysis will be used assess the effect of the adherence strategies as well as individual characteristics (demographics, etc.) on time to PrEP discontinuation for those who choose to stop PrEP before 9 months.

Sensitivity analyses will be performed to assess whether loss-to-follow up is covariate-dependent, and if so, all analyses will be rerun using weighting to account for potentially informative drop-out. Secondary analyses will also explore the possibility of a WhatsApp peer group effect, as young women interacting with one another through the intervention may exhibit correlated outcomes.

7.0 HUMAN SUBJECTS CONSIDERATIONS

8.1. Ethical Review

The protocol, ICF, participant education and recruitment materials, and other requested documents — and any subsequent modifications — 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.

8.2. Informed Consent

Written informed consent will be obtained from each study participant. The ICFs describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The ICF will be translated into local languages and the accuracy accuracy of the translation will be verified by performing an independent back-translation. The site will assess literacy

in one of the study languages as described in study specific SOPs. Participants will be provided with a copy of their ICFs if they are willing to receive them.

8.3. Study oversight

This study will be subject to oversight by an independent data monitoring committee that will periodically review data from the study, including study execution, adherence, HIV incidence, HIV drug resistence and serious adverse events. The independent data monitoring committee will provide recommendations to the study team as part of approximately six-monthly reviews. Reports from all reviews will be provided for submission to overseeing IRB/ECs.

8.4. 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

Staff 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 the study site will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (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.

Mobile Phones, SMS, and WhatsApp

For participants who are randomized to participate in two-way SMS texting and WhatsApp groups to support PrEP adherence, it is possible that timing or volume of messages will be inconvenient to participants or may exceed cell phone plan limits and obligate participants' to pay for them. The site will develop a system to provide compensation for mobile phone charges and data limits 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. Lost or stolen phones are a practical reality. To mitigate these risks, 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.

Participants may be at risk of confidentiality breaches if a third party gains access to a participant's phone and views the WhatsApp communications. Participants may also receive unwanted comments from other group members. We will establish group norms prior to WhatsApp group enrollment and will inform all participants of these norms. A group facilitator will monitor the WhatsApp groups regularly for violations

of group norms or rules and will exit participants from the WhatsApp group who commit such violations. Participant identies may also become known if they have a photo linked to their WhatsApp account. We will ensure that all participants are aware of these risks of participating in the WhatsApp group during the informed consent process. Finally, participants will be able to send personal messages directly to the group administrator to discuss any concerns or issues privately and they will be informed during the consent process that they can reply "STOP" to any SMS messages or remove themselves from the WhatsApp group if they wish to discontinue messages.

Study Drug Side Effects

All participants who experience side effects or other clinical events during the study will receive follow-up by study staff. If treatment is required beyond the capacity of the study staff, study clinicians will refer the participant to appropriate services or organizations that can provide appropriate care.

HIV drug resistance in HIV seroconverters

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 Enrollment, Month 1 and quarterly for all participants. Persons with acute viral syndromes that may reflect acute HIV infection will have study enrollment delayed for two weeks at which time they will have additional HIV testing. If acute HIV infection is suspected after Enrollment for any participant accepting PrEP, the participant will undergo evaluation. 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 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. If a participant becomes infected during the study, real-time resistance testing will be conducted for clinical management.

8.5. 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 9 months of open label oral PrEP, HIV counseling and testing, as well as free STI screening. 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 and will be referred for care.

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. Reimbursement amounts will be specified in the study informed consent forms (ICFs).

8.6. Study records

All study-related records including administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the study, including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents are stored in a secure manner at the study site.

8.7. Confidentiality

The study site will establish a standard operating procedure for confidentiality protection. 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. WhatsApp chats will be exported and de-identified to remove all participant phone numbers and identifying information. De-identfied chats will be stored on a secure server and participant messages will be labeled with a unique study identification number.

Participants' study information will not be released without their written permission, except as necessary for oversight by:

- The Protocol Chair or designees
- Study funders
- Site IRB/ECs
- University of Washington
- Any additional study sponsors

9.0 REFERENCES

1. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, Malahleha M, Owino F, Manongi R, Onyango J, Temu L, Monedi MC, Mak'Oketch P, Makanda M, Reblin I, Makatu SE, Saylor L, Kiernan H, Kirkendale S, Wong C, Grant R, Kashuba A, Nanda K, Mandala J, Fransen K, Deese J, Crucitti T, Mastro TD, Taylor D. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012;367(5):411-22.
2. Marrazzo J, Ramjee G, Nair G, Palanee T, Mkhize B, Nakabiito C, Taljaard M, Piper J, Gomez Feliciano K, Chirenje M, VOICE Study Team. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/embricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003). 20th Conference on Retroviruses and Opportunistic Infections (CROI); March 3-6; Atlanta, GA 2013. Abstract 26LB.
3. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapia M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernandez T, Veloso VG, Buchbinder SP, Chariyalertsak S, Schechter M, Bekker LG, Mayer KH, Kallas EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010;363(27):2587-99. PMCID: 3079639.
4. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, Tappero JW, Bukusi EA, Cohen CR, Katabira E, Ronald A, Tumwesigye E, Were E, Fife KH, Kiarie J, Farquhar C, John-Stewart G, Kakia A, Odoyo J, Mucunguzi A, Nakku-Joloba E, Twesigye R, Ngure K, Apaka C, Tamooh H, Gabona F, Mujugira A, Panteleeff D, Thomas KK, Kidoguchi L, Krows M, Revall J, Morrison S, Haugen H, Emmanuel-Ogier M, Ondrejcek L, Coombs RW, Frenkel L, Hendrix C, Bumpus NN, Bangsberg D, Haberer JE, Stevens WS, Lingappa JR, Celum C, Partners PrEP Study Team. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012;367(5):399-410. PMCID: 3770474.
5. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, Chiamwongpaet S, Kitisin P, Natrujirote P, Kittimunkong S, Chuachoowong R, Gvetadze RJ, McNicholl JM, Paxton LA, Curlin ME, Hendrix CW, Vanichseni S. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013;381(9883):2083-90.
6. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, Henderson FL, Pathak SR, Soud FA, Chillag KL, Mutanhaurwa R, Chirwa LI, Kasonde M, Abebe D, Buliva E, Gvetadze RJ, Johnson S, Sukalac T, Thomas VT, Hart C, Johnson JA, Malotte CK, Hendrix CW, Brooks JT. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012;367(5):423-34.
7. Hendrix CW. Exploring concentration response in HIV pre-exposure prophylaxis to optimize clinical care and trial design. Cell. 2013;155(3):515-8.
8. Murnane PM, Celum C, Mugo N, Campbell JD, Donnell D, Bukusi E, Mujugira A, Tappero J, Kahle EM, Thomas KK, Baeten JM. Efficacy of preexposure prophylaxis for HIV-1 prevention among high-risk heterosexuals: subgroup analyses from a randomized trial. AIDS. 2013;27(13):2155-60. PMCID: 3882910.
9. Corneli AL, Deese J, Wang M, Taylor D, Ahmed K, Agot K, Lombaard J, Manongi R, Kapiga S, Kashuba A, Van Damme L. FEM-PrEP: Adherence Patterns and Factors Associated With Adherence to a Daily Oral Study Product for Pre-exposure Prophylaxis. J Acquir Immune Defic Syndr. 2014;66(3):324-31. PMCID: 4059551.
10. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodi N, Nair G, Palanee T, Nakabiito C, van der Straten A, Noguchi L, Hendrix CW, Dai JY, Ganesh S, Mkhize B, Taljaard M, Parikh UM, Piper J, Masse B, Grossman C, Rooney J, Schwartz JL, Watts H, Marzinke MA, Hillier SL, McGowan IM, Chirenje ZM, Team VS. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015;372(6):509-18. PMCID: 4341965.
11. Ware NC, Wyatt MA, Haberer JE, Baeten JM, Kintu A, Psaros C, Safren S, Tumwesigye E, Celum CL, Bangsberg DR. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. J Acquir Immune Defic Syndr. 2012;59(5):463-8. PMCID: 3826169.
12. Amico KR, Mansoor LE, Corneli A, Torjesen K, van der Straten A. Adherence support approaches in biomedical HIV prevention trials: experiences, insights and future directions from four multisite prevention trials. AIDS Behav. 2013;17(6):2143-55. PMCID: 3672509.
13. van der Straten A, Stadler J, Montgomery E, Hartmann M, Magazi B, Mathebula F, Schwartz K, Laborde N, Soto-Torres L. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. PLoS ONE. 2014;9(2):e89118. PMCID: 3931679.
14. Corneli AL, McKenna K, Headley J, Ahmed K, Odhiambo J, Skhosana J, Wang M, Agot K. A descriptive analysis of perceptions of HIV risk and worry about acquiring HIV among FEM-PrEP participants who seroconverted in Bondo, Kenya, and Pretoria, South Africa. J Int AIDS Soc. 2014;17(3 Suppl 2):19152.
15. Van der Straten A, Musara P, Etima J, Woeber K, Montgomery E, Hartmann M, Levy L, Benny T, Cheng H, Piper J, Grossman CI, Mensch B, M-dS T. Disclosure of Pharmacokinetic (PK) Drug Results Promotes Open Discourse on Non-adherence among Women in VOICE. Research for Prevention (R4P); ; Oct 28 - 31,; Cape Town, South Africa 2014.

16. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, Hosek S, Mosquera C, Casapia M, Montoya O, Buchbinder S, Veloso VG, Mayer K, Chariyalertsak S, Bekker LG, Kallas EG, Schechter M, Guanira J, Bushman L, Burns DN, Rooney JF, Glidden DV. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. 2014;14(9):820-9.
17. Cohen S, Vittinghoff E, Anderson P, Doblecki-Lewis S, Bacon O, Chege W, Elion R, Buchbinder S, Kolber M, Liu A. Implementation of PrEP in STD and community health clinics in the US: high uptake and drug concentrations among MSM in the Demo Project. 9th International Conference on HIV Treatment and Prevention; Miami, FL 2014. Abstract #377.
18. Liu A, S. C, E. V, P. A, S. D-L, O. B, Chege W, Elion R, Buchbinder S, Kolber M, Group DPS, editors. Adherence, sexual behavior and HIV/STI incidence among men who have sex with men (MSM) and transgender women (TGW) in the US PrEP demonstration (Demo) project. 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention; 2015 19 - 22 July; Vancouver, BC, Canada.
19. Molina J-M, Capitant C, Charreau I, Meyer L, Spire B, Pialoux G, Chidiac C, Delfraissy J-F, Tremblay C. On Demand PrEP With Oral TDF-FTC in MSM: Results of the ANRS Ipergay Trial. Conference on Retroviruses and Opportunistic Infections. Seattle, WA2015.
20. Kahle EM, Hughes JP, Lingappa JR, John-Stewart G, Celum C, Nakku-Joloba E, Njuguna S, Mugo N, Bukusi E, Manongi R, Baeten JM, Partners in Prevention HTS, the Partners Pr EPST. An empiric risk scoring tool for identifying high-risk heterosexual HIV-1-serodiscordant couples for targeted HIV-1 prevention. J Acquir Immune Defic Syndr. 2013;62(3):339-47. PMCID: 3620695.
21. Baeten J, Heffron R, Kidoguchi L, Celum C, Mugo N, Bukusi E, Katabira E, Asiimwe S, Haberer J, Donnell D. Near Elimination of HIV Transmission in a Demonstration Project of PrEP and ART. Conference on Retroviruses and Opportunistic Infections. Seattle, WA2015.
22. Bekker L-G, Hughes J, Amico R, Roux S, Hendrix C, Anderson PL, Dye BJ, Elharrar V, Stirratt MJ, Grant R. HPTN 067/ADAPT Cape Town: A comparison of daily and nondaily PrEP dosing in African women. Conference on Retroviruses and Opportunistic Infections (CROI); February 24, ; Seattle, WA 2015.
23. Gill K, Dietrich J, Gray G, Pigwell T, Kayamba F, Bennie T, Myer L, Johnson L, Spiegel H, Slack C, Elharrar V, Strode A, Rooney J, Bekker L-G. Pluspills: an open label, safety and feasibility study of oral pre-exposure prophylaxis (PrEP) in 15-19 year old adolescents in two sites in South Africa IAS 2017: 9th IAS Conference on HIV Science; July 23-26; Paris, France 2017. Abstract TUAC0207LB.
24. Hosek S, Rudy B, Landovitz R, Kapogiannis B, Siberry G, Rutledge B, Liu N, Brothers J, Mulligan K, Zimet G, Lally M, Mayer K, Anderson P, Kiser J, Rooney J, Wilson CM. An HIV pre-exposure prophylaxis (PrEP) demonstration project and safety study for young MSM. J Acquir Immune Defic Syndr. 2017;74(1):21-9. PMCID: 5140725.
25. Hosek S, Landovitz R, Rudy B, Kapogiannis B, Siberry G, Rutledge B, Liu N, Brothers J, Rooney J, Wilson C, ATN. An HIV pre-exposure prophylaxis demonstration project and safety study for adolescent MSM ages 15-17 in the US. International AIDS Conference; July Durban, South Africa 2016.
26. Celum C, Delany-Moretlwe S, Hosek S, Dye BJ, Bekker L-G, Mgodi N, Mabuza W, Mvuyane GZ, Mukaka S, Donnell D, Pathak S, Noble H, Lennon D, Fogel JM, Anderson P. Risk behavior, perception, and reasons for PrEP among young african women in HPTN 082. CROI; 4-7 March 2018; Boston, Massachusetts 2018.
27. WHO. WHO Implementation tool for pre-exposure prophylaxis (PrEP) of HIV infection. Module 12: Adolescents and young adults. Geneva: World Health Organisation.; 2018.
28. Pettifor A, Bekker LG, Hosek S, DiClemente R, Rosenberg M, Bull SS, Allison S, Delany-Moretlwe S, Kapogiannis BG, Cowan F. Preventing HIV among young people: research priorities for the future. J Acquir Immune Defic Syndr. 2013;63 Suppl 2:S155-60. PMCID: 3746811.
29. Reisner SL, Mimiaga MJ, Skeer M, Perkovich B, Johnson CV, Safren SA. A review of HIV antiretroviral adherence and intervention studies among HIV-infected youth. Top HIV Med. 2009;17(1):14-25. PMCID: 3752381.
30. Sikkema KJ, Neufeld SA, Hansen NB, Mohlahlane R, Van Rensburg MJ, Watt MH, Fox AM, Crewe M. Integrating HIV Prevention into Services for Abused Women in South Africa. AIDS and Behavior. 2010;14(2):431-9.
31. Butler AC, Chapman JE, Forman EM, Beck AT. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. Clin Psychol Rev. 2006;26(1):17-31.
32. Bolton P, Bass J, Betancourt T, Speelman L, Onyango G, Clougherty KF, Neugebauer R, Murray L, Verdeli H. Interventions for depression symptoms among adolescent survivors of war and displacement in northern Uganda: a randomized controlled trial. JAMA. 2007;298(5):519-27.
33. Rahman A, Malik A, Sikander S, Roberts C, Creed F. Cognitive behaviour therapy-based intervention by community health workers for mothers with depression and their infants in rural Pakistan: a cluster-randomised controlled trial. Lancet. 2008;372(9642):902-9. PMCID: 2603063.
34. Cohen JA, Mannarino AP, Murray LK. Trauma-focused CBT for youth who experience ongoing traumas. Child Abuse Negl. 2011;35(8):637-46. PMCID: 3171639.

35. Safren SA, Otto MW, Worth JL, Salomon E, Johnson W, Mayer K, Boswell S. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. Behavior Res Ther. 2001;39(10):1151-62.
36. Safren SA, O'Cleirigh C, Tan JY, Raminani SR, Reilly LC, Otto MW, Mayer KH. A randomized controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. Health Psychol. 2009;28(1):1-10. PMCID: 2643364.
37. Simoni JM, Huh D, Frick PA, Pearson CR, Andrasik MP, Dunbar PJ, Hooton TM. Peer support and pager messaging to promote antiretroviral modifying therapy in Seattle: a randomized controlled trial. J Acquir Immune Defic Syndr. 2009;52(4):465-73. PMCID: 2795576.
38. Rosenstein D, Seedat S. Child and adolescent cognitive behaviour therapy in South Africa: An editorial review. J Child Adolesc Ment Health. 2011;23(2):69-73.
39. Castillo-Mancilla J, Seifert S, Campbell K, Coleman S, McAllister K, Zheng JH, Gardner EM, Liu A, Glidden DV, Grant R, Hosek S, Wilson CM, Bushman LR, MaWhinney S, Anderson PL. Emtricitabine-triphosphate in dried blood spots as a marker of recent dosing. Antimicrob Agents Chemother. 2016;60(11):6692-7. PMCID: 5075074.
40. Zheng JH, Rower C, McAllister K, Castillo-Mancilla J, Klein B, Meditz A, Guida LA, Kiser JJ, Bushman LR, Anderson PL. Application of an intracellular assay for determination of tenofovir-diphosphate and emtricitabine-triphosphate from erythrocytes using dried blood spots. J Pharm Biomed Anal. 2016;122:16-20. PMCID: PMC4764437.
41. Epstein RM, Street RL, Jr. The values and value of patient-centered care. Ann Fam Med. 2011;9(2):100-3. PMCID: Pmc3056855.
42. Lei H, Nahum-Shani I, Lynch K, Oslin D, Murphy SA. A "SMART" design for building individualized treatment sequences. Annu Rev Clin Psychol. 2012;8:21-48. PMCID: 3887122.
43. Murphy SA. An experimental design for the development of adaptive treatment strategies. Stat Med. 2005;24(10):1455-81.
44. National Department of Health. PrEP implementation pack: South Africa 2016-2017. 2018 [updated 2018; cited 2018 March 6]; Available from: https://www.prepwatch.org/wp-content/uploads/2017/07/SA_ImplementationPack.pdf.
45. Deering K, Shannon K, Sinclair H, Parsad D, Gilbert E, Tyndall M. Piloting a peer-driven intervention model to increase access and adherence to antiretroviral therapy and HIV care among street-entrenched HIV-positive women in Vancouver. AIDS Patient Care STDS. 2009;23(8):603-9.
46. Spiegel HM, Futterman DC. Adolescents and HIV: prevention and clinical care. Curr HIV/AIDS Rep. 2009;6(2):100-7.
47. Denison JA, Banda H, Dennis AC, Packer C, Nyambe N, Stalter RM, Mwansa JK, Katayamoyo P, McCarraher DR. "The sky is the limit": adhering to antiretroviral therapy and HIV self-management from the perspectives of adolescents living with HIV and their adult caregivers. J Int AIDS Soc. 2015;18(1):19358. PMCID: Pmc4296051.
48. Mutumba M, Bauermeister JA, Musiime V, Byaruhanga J, Francis K, Snow RC, Tsai AC. Psychosocial challenges and strategies for coping with HIV among adolescents in Uganda: a qualitative study. AIDS Patient Care STDS. 2015;29(2):86-94.
49. Kim SH, McDonald S, Kim S, Foster C, Fidler S. Importance of Self-Motivation and Social Support in Medication Adherence in HIV-Infected Adolescents in the United Kingdom and Ireland: A Multicentre HYPNet Study. AIDS Patient Care STDS. 2015.
50. Fisher EB, Boothroyd RI, Coufal MM, Baumann LC, Mbanya JC, Rotheram-Borus MJ, Sanguanprasit B, Tanasugarn C. Peer support for self-management of diabetes improved outcomes in international settings. Health Aff (Millwood). 2012;31(1):130-9.
51. Young SD, Holloway I, Jaganath D, Rice E, Westmoreland D, Coates T. Project HOPE: online social network changes in an HIV prevention randomized controlled trial for African American and Latino men who have sex with men. Am J Public Health. 2014;104(9):1707-12. PMCID: 4151951.
52. Horvath KJ, Oakes JM, Rosser BR, Danilenko G, Vezina H, Amico KR, Williams ML, Simoni J. Feasibility, acceptability and preliminary efficacy of an online peer-to-peer social support ART adherence intervention. AIDS Behav. 2013;17(6):2031-44. PMCID: 3674213.
53. Grimsrud A, Lesosky M, Kalombo C, Bekker LG, Myer L. Implementation and Operational Research: Community-Based Adherence Clubs for the Management of Stable Antiretroviral Therapy Patients in Cape Town, South Africa: A Cohort Study. J Acquir Immune Defic Syndr. 2016;71(1):e16-23.
54. Grimsrud A, Sharp J, Kalombo C, Bekker LG, Myer L. Implementation of community-based adherence clubs for stable antiretroviral therapy patients in Cape Town, South Africa. J Int AIDS Soc. 2015;18:19984. PMCID: 4444752.
55. Luque-Fernandez MA, Van Cutsem G, Goemaere E, Hilderbrand K, Schomaker M, Mantangana N, Mathee S, Dubula V, Ford N, Hernan MA, Boulle A. Effectiveness of patient adherence groups as a model of care for stable patients on antiretroviral therapy in Khayelitsha, Cape Town, South Africa. PLoS One. 2013;8(2):e56088. PMCID: 3571960.

56. Rasschaert F, Decroo T, Remartinez D, Telfer B, Lessitala F, Biot M, Candrinho B, Van Damme W. Adapting a community-based ART delivery model to the patients' needs: a mixed methods research in Tete, Mozambique. BMC Public Health. 2014;14:364. PMCID: Pmc3990026.
57. Solomon S, al e. Community based ART adherence clubs: A community model of care for ART delivery. 7th South African AIDS Conference; June Durban, South Africa 2015.
58. Delany-Moretlwe S, Chersich M, Harvey S, Stangl A, Baron D, Columbini D, Scorgie F, Naicker N, Kapiga S. Empowerment clubs did not increase PrEP continuation among adolescent girls and young women in South Africa and Tanzania - Results from the EMPOWER randomised trial. AIDS 2018; 23-27 July 2018; Amsterdam 2018.
59. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487-97.
60. Kaufman ZA, Braunschweig EN, Feeney J, Dringus S, Weiss H, Delany-Moretlwe S, Ross DA. Sexual risk behavior, alcohol use, and social media use among secondary school students in informal settlements in Cape Town and Port Elizabeth, South Africa. AIDS Behav. 2014;18(9):1661-74.
61. Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, Jack W, Habyarimana J, Sadatsafavi M, Najafzadeh M, Marra CA, Estambale B, Ngugi E, Ball TB, Thabane L, Gelmon LJ, Kimani J, Ackers M, Plummer FA. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. 2010;376(9755):1838-45.
62. Finitsis DJ, Pellowski JA, Johnson BT. Text message intervention designs to promote adherence to antiretroviral therapy (ART): a meta-analysis of randomized controlled trials. PLoS One. 2014;9(2):e88166. PMCID: 3914915.
63. Ronen K, Unger JA, Drake AL, Perrier T, Akinyi P, Osborn L, Matemo D, O'Malley G, Kinuthia J, John-Stewart G. SMS messaging to improve ART adherence: perspectives of pregnant HIV-infected women in Kenya on HIV-related message content. AIDS Care. 2018;30(4):500-5. PMCID: PMC5839109.
64. Unger JA, Ronen K, Perrier T, DeRenzi B, Slyker J, Drake AL, Mogaka D, Kinuthia J, John-Stewart G. Short message service communication improves exclusive breastfeeding and early postpartum contraception in a low- to middle-income country setting: a randomised trial. Bjog. 2018;125(12):1620-9. PMCID: PMC6179930.
65. Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR, Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. AIDS Res Hum Retroviruses. 2013;29(2):384-90. PMCID: 3552442.
66. Anderson P, Liu A, Castillo-Mancilla J, Seifert S, McHugh C, Wagner T, Buchbinder S, Bushman L, Kiser J, MaWhinney S. Tenofovir diphosphate (TFV-DP) in Dried Blood Spots (DBS) Following Directly Observed Therapy: DOT-DBS Study CROI 2017: Conference on Retroviruses and Opportunistic Infections; February 13-16; Seattle, Washington, USA 2017. Abstract 419.
67. Landovitz RJ, Beymer M, Kofron R, Amico KR, Psaros C, Bushman L, et al. Plasma Tenofovir Levels to Support Adherence to TDF/FTC Preexposure Prophylaxis for HIV Prevention in MSM in Los Angeles, California. J Acquir Immune Defic Syndr. 2017;76(5):501-11. Epub 2017/09/14. doi: 10.1097/qai.0000000000001538. PubMed PMID: 28902074; PubMed Central PMCID: PMCPMC5681370.
68. Anderson PL, Glidden DV, Liu A, Buchbinder S, Lama JR, Guanira JV, McMahan V, Bushman LR, Casapia M, Montoya-Herrera O, Veloso VG, Mayer KH, Chariyalertsak S, Schechter M, Bekker LG, Kallas EG, Grant RM, iPrEx Study T. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. Sci Transl Med. 2012;4(151):151ra25. PMCID: PMC3721979.
69. Anderson P, Liu A, Castillo-Mancilla J, Seifert S, McHugh C, Wagner T, Buchbinder S, Bushman L, Kiser J, McWhinney S. TFV-DP in dried blood spots (DBS) following directly observed therapy: DOT-DBS Study. CROI 2017: Conference on Retroviruses and Opportunistic Infections; February 13-16; Seattle, Washington, USA 2017. Abstract 419.
70. Gandhi M, Bacchetti P, Okochi H, Spinelli M, Baeten J, Rodrigues W, Wang G, Vincent M, Kubiak R, Tawon Y, Klinvuayaem V, Sukrakanchana P, Siriprakaisil O, Cressey T, Drain P. Validation of a urine TFV immunoassay for real-time PrEP and ART adherence testing. CROI 2019: Conference on Retroviruses and Opportunistic Infections; March 4-7; Seattle, Washington, USA 2019. Abstract #464.
71. Celum C, Mgodi N, Bekker L, Hosek S, Donnell D, Anderson P, Dye B, Pathak S, Agyei Y, Fogel J, Marzinke M, Makgamathe K, Kassim S, Mukaka S, Noble H, Adeyeye A, Delany-Moretlwe S, Team HS. PrEP adherence and effect of drug level feedback among young African women in HPTN 082. 10th IAS Conference on HIV Science July 21-24; Mexico City, Mexico 2019.
72. Gandhi M, Bacchetti P, Spinelli MA, Okochi H, Baeten JM, Siriprakaisil O, Klinbuayaem V, Rodrigues WC, Wang G, Vincent M, Cressey TR, Drain PK. Brief Report: Validation of a Urine Tenofovir Immunoassay for Adherence Monitoring to PrEP and ART and Establishing the Cutoff for a Point-of-Care Test. J Acquir Immune Defic Syndr. 2019;81(1):72-7. PMCID: PMC6456396.
73. Bowleg L. The problem with the phrase women and minorities: intersectionality-an important theoretical framework for public health. Am J Public Health. 2012;102(7):1267-73. PMCID: 3477987.
74. Office of Behavioral and Social Sciences Research. Qualitative Methods in Health Research: Opportunities and Considerations in Application and Review National Institute of Health. 2001;02-5046.

75. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, Wangisi J, Were E, Heffron R, Matthews LT, Morrison S, Ngure K, Baeten JM, Partners Pr EPST. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. JAMA. 2014;312(4):362-71. PMCID: 4362516.
76. WHO. Preventing HIV during pregnancy and breastfeeding in the context of PrEP. Technical brief. . Geneva2017.

Appendix IA: Schedule of Study Visits and Procedures

	Enrollment	Month 1	Month 2	Month 3	Months 4, 5, 7, 8	Months 6 & 9/Exit
Administrative and Behavioral Evaluations/Procedures						
Informed Consent	X					
Collect/Update Locator information	X	X		X		X
Validate phone number and texting capacity	X	X		X		X
Collect demographic information	X					
Apply inclusion/exclusion criteria	X					
Behavioral data collection	X	X		X		X
Standard HIV risk reduction counseling and condom provision	X	X	X	X	X	X
Assess PrEP interest	X					
Study drug adherence assessment		X	X	X	X	X
Study drug supply	X	X	X	X	X	X
Randomization	X			[X]		
Adherence counseling and support	X	X	X	X	X	X
Clinical Evaluations/Procedures						
Acute HIV assessment	X	X		X		X
Medical history (including concomitant meds and STI symptoms)	X	X		X		X
Contraceptive assessment and associated counseling as appropriate	X	X		X		X
Symptom-directed physical exam	[X]	[X]		[X]		[X]
STI syndromic assessment and management	X	X		X		X
Blood collection	X	X	X	X		X
Participant vaginal swab collection for STI testing[1]	X					X
Urine collection	X	X		X		X
Laboratory Evaluations/Procedures						
HIV testing	X	X		X		X
Hepatitis B serology (HBVsAg)	X					
Serum creatinine (for creatinine clearance)	X					M6
Urine pregnancy testing	X	X		X		X
STI testing (TV, GC/CT, syphilis)	X					X
Drug level concentration[3]			X	[X]		[M6]
Plasma storage	X	X		X		X
DBS storage	X	X		X		X

[] As indicated
[1] Participant collected vaginal swab samples will be used for TV, CT/GC testing; urine will be used if self-collected vaginal samples not acceptable.

[2]Drug level concentration will be conducted for all participants at M2 and for those randomized to receive drug level feedback at M3 and M6.

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

	Possible seroconversion (≥positive HIV rapid test)	Confirmatory Visit
Administrative Evaluations/Procedures		
Update locator information	X	X
Linkage to HIV care and associated counseling		X
Clinical Evaluations/Procedures		
Symptoms directed physical exam	X	
Stop PrEP	X	
Blood collection	X	
Urine collection	X	
Laboratory Evaluations/Procedures		
HIV EIA	X	
Pregnancy testing	X	
CD4 cell count testing	X	
Viral load testing	X	
Plasma storage for tenofovir levels	X	
DBS storage for TFV-DP levels	X	
Genotypic resistance testing	X	