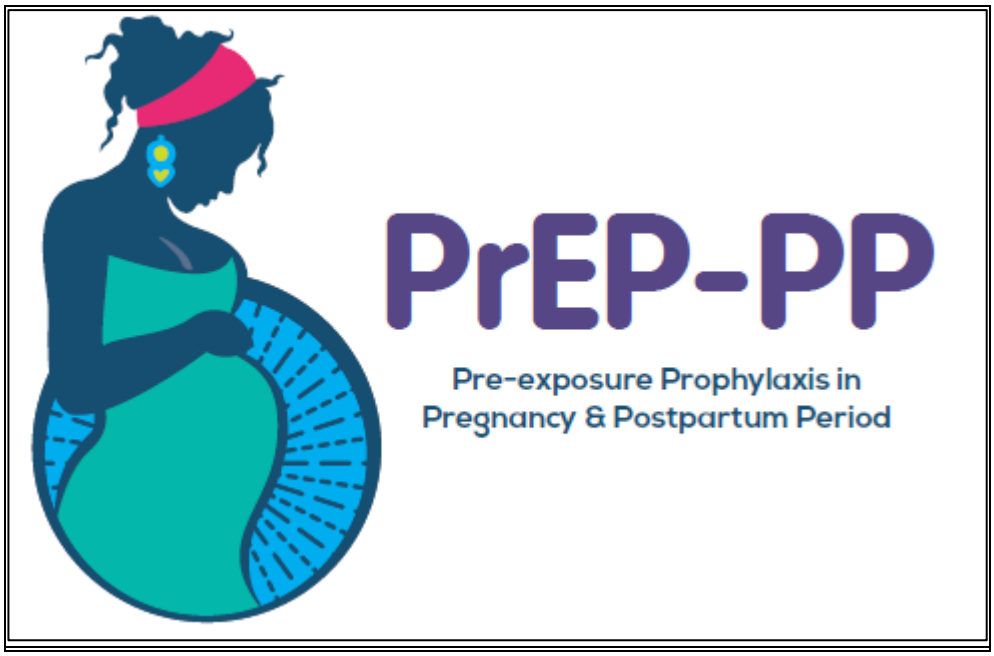
Evaluation of Pre-exposure Prophylaxis Cascade in Pregnant and Breastfeeding Women in Cape Town, South Africa (Formative Study)



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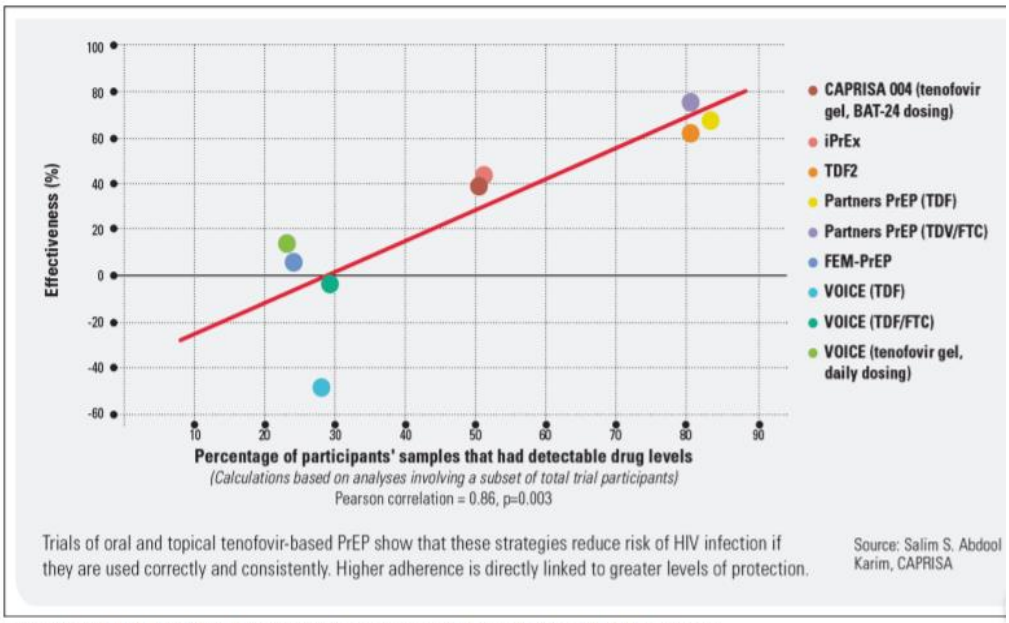
1. Background and rationale:

Pregnant and breastfeeding women in South Africa are at very high risk of HIV acquisition and vertical HIV transmission during pregnancy, labour and breastfeeding [1-4]. One-third to half of perinatal HIV transmission occurs in women who are seroconvert during the pregnancy and post-partum period [5-6]. Effective use of pre-exposure prophylaxis (PrEP) could contribute to eliminating maternal HIV acquisition, and hence mother to child transmission (MTCT) of HIV. However, PrEP efficacy requires high levels of adherence, and adherence requires high levels of acceptability, yet there are few data on acceptability and adherence in pregnant and breastfeeding women in high HIV prevalence communities.

Risk of HIV acquisition in pregnant and breastfeeding women: Despite increased access to HIV testing and counseling, condom promotions and antiretroviral therapy for male partners, maternal HIV incidence continues to be very high during and after pregnancy. In South Africa it is estimated that maternal HIV incidence was as high as 10.7 per 100-person years (PY) which is highest in urban health facilities at 12.4 per 100 PY [3]. High HIV incidence in pregnancy contributes to the majority of infant HIV infection [1, 4]. Mothers who seroconvert after their first antenatal visit account for approximately 34% of vertical transmission [3]. In a recent meta-analysis, vertical HIV transmission risk was significantly higher in women with incident versus chronic HIV infection in the postpartum period (odds ratio of MTCT in pregnancy [OR]=2.9, 95% confidence interval [CI]=2.2, 3.9) or in pregnancy and postpartum periods combined (OR=2.3, 95% CI=1.2, 4.4) [4]. Biological mechanisms of increased susceptibility of HIV acquisition during pregnancy and breastfeeding may be due to hormonal changes that alter genital mucosal surfaces or distribution of target cells at these surfaces [3]. However, behavioral factors also play a role including increased condomless sex during pregnancy, (multiple) sex partners of unknown serostatus and substance use during pregnancy and breastfeeding periods [3].

Interventions to prevent maternal HIV acquisition: We urgently need effective interventions to reduce HIV incidence in pregnant and breastfeeding women. PrEP is one of the only female-controlled methods that is effective for preventing HIV acquisition and safe in pregnancy. Recent meta-analyses demonstrated that use of tenofovir is not associated with increased adverse events during pregnancy or breastfeeding [6-11]. In new guidelines on PrEP, the World Health Organization (WHO) stated that "PrEP can also be considered as an additional prevention choice for HIV-negative pregnant women who are at substantial risk of HIV infection, as part of a comprehensive prevention of mother to child transmission (PMTCT) package" [12]. Currently, however, there is limited data on PrEP acceptability, initiation, and adherence in pregnant and breastfeeding women in high HIV incidence communities [2, 13-15].

PrEP for HIV involves the use of daily antiretroviral (ARV) medications to prevent HIV acquisition, similar to prophylaxis for malaria. Tenofovir (TDF) and tenofovir/emtricitabine (TDF/FTC) in a single tablet fixed-dose combination (FDC) are the ARV agents primarily used in oral PrEP studies to date, though studies of other formulations are under way. In December 2015, the TDF/FTC combination pill was approved for use as PrEP by the Medicine Control Council in South Africa, in combination with safer sexual practices [27]. Daily PrEP may be used intermittently during periods of perceived HIV acquisition risk, rather than continually and lifelong, as is the case with ARV treatment. HIV testing, and estimation of creatinine clearance are recommended as baseline health measures. PrEP should not be given to those with abnormal renal function, nor should it be commenced in individuals with acute viral symptoms.



Source: AVAC Report 2013: Research & Reality: http://www.avac.org/sites/default/files/infographics/PrEP_by_Numbers_jan2016.jpeg

FIGURE 1: Effectiveness and adherence in trials of oral and topical tenofovir-based prevention.

To date there have been 10 randomized controlled trials of TDF-based PrEP reporting HIV outcomes. The studies have involved over 17,000 people and have demonstrated an overall reduction in HIV acquisition risk of 51% (women RR 0.57 [95% CI 0.34–0.94] and men RR 0.38 [95% CI 0.2–0.6]) [27-32]. Three studies in which there was high adherence to TDF (> 70% of drug detection) showed PrEP was most efficacious [27-30]. PrEP access is increasing in South Africa primarily in men who have sex with men (MSM) and sex workers. However, as of February 2018, only approximately 5000 people were on PrEP in South Africa, and there are two clinical trials ongoing in pregnant women in South Africa, including IMPAACT 2009, "Pharmacokinetics, Feasibility, Acceptability, and Safety of Oral Pre-Exposure Prophylaxis for Primary HIV Prevention during Pregnancy and Postpartum in Adolescents and Young Women and their Infants" which is an ongoing trial in Zimbabwe, Uganda, South Africa and Malawi (http://impaactnetwork.org/studies/IMPAACT2009.asp).

PrEP safety in pregnant and breastfeeding women: Studies of PrEP use in pregnancy and breastfeeding are more limited than those in nonpregnant adult populations. However, an increasing number of studies are addressing this question, and available evidence underscores its safety in this pregnancy and breastfeeding women and their infants (1–6). Importantly, a recent systematic review demonstrated that PrEP was not associated with increased pregnancy-related adverse events. No studies have found adverse effects among infants exposed to tenofovir disoproxil fumarate (TDF) as part of treatment for HIV-infected women during pregnancy [6-8] or breastfeeding [9-12]. Specifically, Mofenson et al's systematic review identified seven studies of TDF in HIV-uninfected women. They report, "No statistically significant differences were observed between TDF and comparison non-TDF regimens in pregnancy incidence, stillbirth/pregnancy loss, preterm delivery less than 37 weeks, low birth weight <2500/<1500 g, small for gestational age, birth defects, or infant (>14 days) or maternal mortality." Their study concluded that "given available safety data, there does not appear to be a safety-related rationale for prohibiting PrEP use during pregnancy/lactation or for discontinuing PrEP use in HIV-uninfected women receiving PrEP who become pregnant and are at continuing risk of HIV acquisition." Based on the existing WHO guidelines and research, potential risks of PrEP adverse events outweigh the benefits of using PrEP when sexually active during pregnancy and breastfeeding periods.

PrEP safety in young women: There is very limited data on PrEP use specifically in pregnant adolescents less than 18 years of age (7–9). Very recently, one Phase II clinical trial has been completed in youth ages

15-17, looking at safety and feasibility in young men who have sex with men (10). This study demonstrated safety of TDF-FTC in 78 participants with only one adverse event possibly related to the study drug. There were no adverse effects on kidney function, liver function or bone density. A second study that includes adolescent girls has completed, but final results are not yet available (11). Finally, additional safety data is available from studies focused on the use of the TDF and FTC as antiretroviral therapy in HIV+ youth (7,12). One study looking at long term TDF use in 12- to 17-year-olds over a median of 96 weeks (longer than the proposed timeline of this study) showed no discontinuations due to the study drug and there was no significant decrease in bone mineral density, and kidney function was consistent with normal changes seen in adolescents. Thus, available data suggest that PrEP and its component drugs are safe in adolescent populations, though more studies are needed in both adolescents as a whole, and pregnant adolescents in particular.

PrEP safety in infants: Available data on infant outcomes after exposure to TDF-FTC suggest that there are no significant differences in health outcomes, including birth weight, preterm delivery, birth defects, or infant mortality, as summarized in a pair of recent systematic reviews (6,13). Long-term effects on infants have not been investigated in the context of PrEP, though this is becoming an area of active research, with studies such as IMPAACT 2009 focusing on both maternal and infant health outcomes after use of PrEP in the pregnancy and breastfeeding periods (14). However, one short-term study looked at drug levels in mothers and their breastfeeding infants in the context of PrEP treatment (5). They found that FTC was below 0.5% of the target therapeutic level given to infants to prevent postnatal HIV infection. TDF levels were even lower, <0.01% of target therapeutic levels and undetectable in 94% of infants.

Additional data on safety of TDF-FTC on HIV-uninfected infants is drawn from studies of HIV-infected mothers taking ART during pregnancy and breastfeeding while tracking health of infants who remain HIV-uninfected. One such study showed a mild decrease in infant serum phosphate levels between 6 and 12 months, but no decrease in serum creatinine levels with prolonged exposure (15).

No studies assessing long-term outcomes of infants exposed to PrEP are available. What data are available come from studies of health outcomes of HIV-uninfected infants in the context of ART use by HIV-infected mothers. One such study examined infant health after *in utero* TDF exposure with a median infant age of 25 months. This study found no differences in infant mortality, serum creatinine or phosphate levels, or immune cell function based on TDF exposure (16). In contrast, multiple studies demonstrate significant morbidity and mortality among infants exposed to HIV versus those who are not. One recent study looking at HIV-exposed, uninfected infants whose mothers were not on ART prior to labor and delivery, and who were subsequently formula-fed, found that up to 23% of infants had serious adverse events up to 6 months after delivery (17). Other studies have confirmed an increase in morbidity and mortality among HIV-exposed infants as compared to those not exposed, and are summarized in a recent meta-analysis that estimates HIV-exposure leads to a 70% increase in all-cause mortality, corresponding to a risk-ratio of 1.70 (18). However, this increased risk is attributed to HIV exposure, not TDF exposure (18).

Though the data on short- and long-term infant outcomes after exposure to PrEP are limited, comparing available data of TDF exposure versus exposure to HIV during pregnancy and breastfeeding clearly indicate that preventing maternal HIV infection confers significant benefit to the infant as well as the mother. The benefit of PrEP treatment of pregnant and breastfeeding women must thus consider both the dramatically decreased risk of infant HIV infection (0.5% for chronic vs. 30% for acute maternal HIV infections (19)) as well as the increase in all-cause mortality among HIV-exposed infants (a 70% increase versus those who are not HIV exposed). These two metrics clearly demonstrate that the benefits of PrEP outweigh the minor risks by at least 5:1.

Side effects of PrEP: Side effects associated with FTC/TDF include diarrhea, nausea, fatigue, headache and rash, which are seen in about 10% of participants during the initiation of therapy [33]. While these early symptoms are generally well-tolerated and dissipate over a few weeks, such side effects may be less tolerable for pregnant or postpartum women. For HIV-infected pregnant and postpartum women, such risks – including the adverse bone and renal effects of TDF – are offset by the significant health benefits of taking the drug as part of ART. However, the risk of adverse drug effects in relation to the potential HIV prevention benefits for HIV-uninfected women at increased risk for infections requires further evaluation. Tenofovir is a highly-charged anion that does not readily permeate across epithelial barriers. The water soluble pro-drug administered by mouth, TDF, is well absorbed in the gut and is rapidly converted to the active form, tenofovir. While tenofovir is present in amniotic fluid and cord blood, a study of 50 HIV uninfected lactating women receiving 10 days of directly observed oral dosing with TDF/FTC PrEP found low infant drug levels and breastmilk penetration [11]. This suggests the risk of postnatal exposure to PrEP in breastfed infants is low**.**

Renal damage: TDF use has been associated with a small and asymptomatic decrease in glomerular filtration rate in HIV-infected individuals. Reports from completed PrEP clinical trials reveal no clinically significant elevations in serum creatinine but transient decrease in estimated glomerular filtration rates and a return to baseline levels within four weeks of PrEP discontinuation [34]. PrEP is not recommended for people with decreased renal function at baseline (GFR < 60ml/min).

Bone demineralization: Consistent with data on reduced bone mineral density (BMD) among HIV-infected adults on ARVs, PrEP use has been associated with an approximate 1% reduction in BMD among trial participants [35]. The effect on BMD was shown to be reversible in young African women adherent to PrEP in the VOICE trial with a follow-up dual-energy x-ray absorptiometry (DXA) scan 48 weeks after stopping study drug [35].

Adverse pregnancy outcome: A secondary analysis from the Partners PrEP study found no differences between women with incident pregnancies while taking PrEP in rates of preterm birth, congenital anomalies, or infant growth in the first year of life and women taking placebo; however, all women stopped the study medication at time of pregnancy detection, which occurred a median of 35 days (IQR: 29–45) after conception [36]. The rates of adverse birth outcomes did not differ according to study arm (78). The Partners Demonstration Project, an open-label delivery study in Kenya and Uganda, HIV-uninfected women in serodiscordant relationships were given the option of continuing PrEP even after pregnancy was diagnosed. Of the 34 who became pregnant, 30 elected to continue PrEP antenatally. When compared to 96 women who became pregnant in the Partners PrEP clinical trial, there were no differences in pregnancy loss, preterm delivery, or congenital anomalies, though sample sizes were small [36].

HIV and pregnancy in young women: Young South African women aged 15–24 years contribute nearly 30% of all new HIV infections in the region. In South Africa, this percentage translates to 113,000 new infections in young women per year, more than four-times the number contributed by their male peers (Figure 2). Further, adolescent girls have high pregnancy rates in South Africa. Approximately 3.7% of 16-year-old girls and 7% of 17-year-old girls were pregnant in 2013 (Figure 3).

Our study proposes to enroll pregnant adolescents 16-19 who have a parent or guardian who provides consent to their participation in the study. The specific age range – enrollment of adolescent and young women 16-19 years – covers a critical period of risk of HIV acquisition. This age range falls squarely within the period of adolescence defined by the World Health Organization as 10-19 years of age. Because of the high HIV incidence and existing policy supporting PrEP among adolescent girls, it would be unethical

to not provide adolescent girls and young women with PrEP that might prevent them from acquiring HIV [18].

Our team is comprised of highly experienced adolescent HIV prevention researchers, including Dr. Linda-Gail Bekker and Dr. Landon Myer, who have a long history of research that seeks to address the key health issues facing South African adolescent girls while at the same time protecting this vulnerable population. The research sites have considerable experience in conducting clinical research in adolescent populations.

Figure 2. HIV incidence (%) by age and sex in South Africa

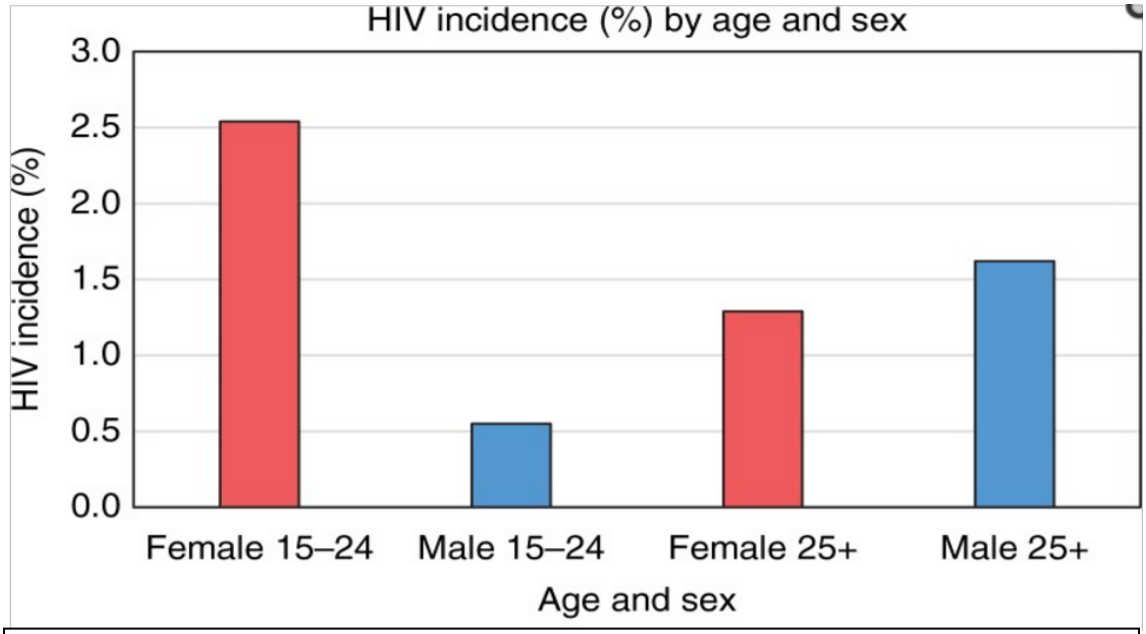
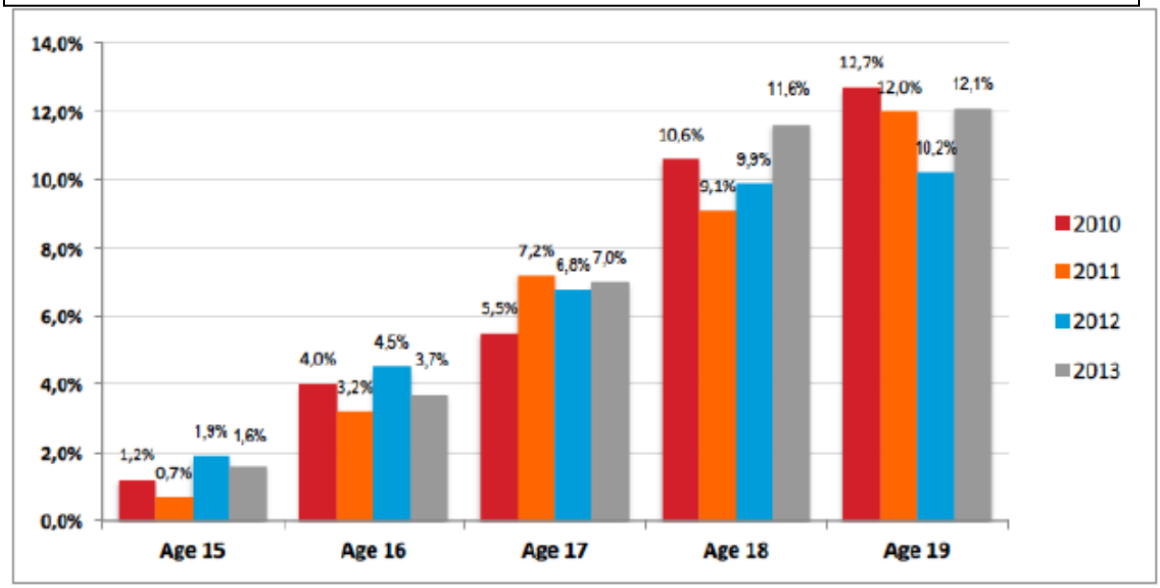


Figure 3. Adolescent pregnancy in South Africa, 2010-2013



Our study, PrEP-PP (PrEP in Pregnant and Postpartum women) will determine the distribution of women across the PrEP cascade (i.e. PrEP initiation, retention, and adherence) in a cohort of HIV- pregnant and breastfeeding adolescent girls and women in two public health facilities in South Africa to inform policymakers about the efficacy of PrEP integration into antenatal (ANC) and postnatal care in high HIV incidence communities.

2. Study objectives:

The objectives of the study are to:

1. Determine the distribution of women across the PrEP cascade:
    (1) Evaluate the proportion of pregnant and breastfeeding women who initiate PrEP out of all women offered PrEP
    (2) Evaluate the proportion of pregnant and breastfeeding women who are retained in the PrEP cohort
    (3) Evaluate the proportion of pregnant and breastfeeding women who initiate PrEP who adhere to PrEP using objective dried blood spot measures and subjective measures of self-reported pill count and adherence
    (4) Evaluate the proportion of pregnant and breastfeeding women on PrEP (and not on PrEP) who acquire HIV, who transmit HIV to their infant, and who report adverse events
2. Evaluate patient and provider-level factors associated with the PrEP cascade using quantitative and qualitative approaches (including in-depth interviews)

3. Study design

To address these objectives, we will conduct an observational cohort study in 220 pregnant women who will be recruited at the first antenatal care (ANC) visit from the Gugulethu Midwife Obstetric Units in Cape Town. We will follow the enrolled women through 12-months post-delivery.

Setting. The study will take place in two urban townships in Cape Town (Gugulethu MOU) with high HIV incidence that span the different socioeconomic, cultural, and ethnic groups in South Africa. We selected this community because of the high HIV prevalence there in pregnant and breastfeeding women, and because of the high number of mothers visiting every month for ANC and labour/delivery. Further, our team has several years' experience implementing research studies in those MOUs which will facilitate the integration of the study there. In 2017, Gugulethu saw over 3300 new ANC consultations per month, and 72% (n=2300) are HIV-negative. Considering our experience and patient flow, we are confident that at least 60 women/month per facility can be enrolled. Further, Drs. Myer, Bekker and colleagues have conducted research in the Gugulethu community for more than a decade and have substantial experience partnering with local health services. Building on this platform, we will use existing infrastructure in each clinic, including capacitating existing clinical providers, pharmacists and counselors, to provide PrEP care to pregnant and breastfeeding mothers. We will hire study staff to assist in the coordination, data management, and overall quality assurance of the counseling, drug provision and participation follow-up.

4. Study population

Study counselors will enroll consecutive eligible, consenting pregnant adolescent girls (≥16 years) and women in ANC (N=220 pregnant women) and follow them up for 12-months postpartum or until censorship for a mean of 18-months' follow-up.

Inclusion Criteria:

1. ≥16 years old
2. confirmed HIV-negative (using 2 rapid HIV test kits, confirmed with a 4th generation antigen HIV test),
3. lives within 20 kilometers of a clinic

4. confirmed to be pregnant
5. without psychiatric or medical contraindications to PrEP

Exclusion criteria:

Individuals not meeting the above criteria or meeting any of the following criteria will be excluded:

- Concurrent enrolment in another HIV-1 vaccine or prevention trial
- Medical hospitalization in the past year for any reason
- Receipt of TB treatment within the past 30 days
- History of renal disease
- Exhibiting psychotic symptoms (including hallucinations, suicidal or homicidal ideations, or violent behaviour)
- Currently or history of taking an anti-psychotic medication (such as for treatment of bipolar disorder, schizophrenia, or postpartum psychosis following a previous pregnancy)
- Positive Hepatitis B surface antigen (HBsAg) test on screening
- History of bone fracture not related to trauma
- Any other medical, psychiatric or social condition which in the opinion of the investigators would affect the ability to consent and/or participate in the study.

Study censorship will include:

1. Seroconversion
2. Moves away
3. Transfers out of care
4. Lost to follow up (e.g. does not return for study or clinical visit for >8 weeks and study staff are unable to track the participant, or she does not want to continue in the study).

Eligible, consenting women will receive R100 in grocery vouchers per visit for their time and effort in the study as well as additional money to cover the cost of transport to each study visit. All participants will also receive minor refreshments (e.g. sandwich and cool drink) on the day of their visit.

Procedures for the informed consent process are outlined below. Throughout, trained study staff will ensure that women are aware of their right to refuse and/or withdraw from the study at any time. In addition, study staff will emphasize that all study activities are entirely separate from routine ANC and postnatal care services received and that refusal or withdrawal from the study will have no impact on their ability to access any services provided at any public-sector health facility.

Inclusion of adolescent girls (16+ years old): Our study proposes to enroll pregnant adolescents 16 and 17 years old who will provide unassisted consent. The specific age range covers a critical period of risk of HIV acquisition. Further, *pregnant* adolescent girls are practicing condomless sex and are at elevated risk of HIV acquisition and mother to child transmission. Because of the high HIV incidence and existing policy supporting PrEP among adolescent girls, it would be unethical to not provide adolescent girls and young women with PrEP that might prevent them from acquiring HIV [18].

- All 16 and 17-year-old girls will provide unassisted consent if she chooses to participate.
- We will verify age on participant medical record and/or other official documents (eg, ID book)
- We will not have an upper age limit exclusion criterion for the study

Our definition of unassisted consent meets the following HREC conditions including:

- The study is no more than minimal risk; and

- The nature of the research is acceptable to the Committee, parents or legal guardians or the community at large.
    - Our study was approved by the HREC and adolescent girl and young women PrEP is actively being rolled out in South Africa. In particular, we note that HREC has approved projects to use PrEP in adolescent girls ages 16-17 without parental consent in this area (see HREC REF: 567/2016).
- Justification for why adolescents are needed in the study:
    - Adolescent girls have high HIV incidence and pregnancy rates in South Africa. Girls 16-17 years old are at a critical period of risk of HIV acquisition. Because of the high HIV incidence and existing policy supporting PrEP among adolescent girls, it would be unethical to not provide adolescent girls and young women with PrEP that might prevent them from acquiring HIV
- Justification for why adolescents should consent unassisted.
    - Our formative research has demonstrated that adolescent girls do not attend antenatal care with their parent/guardian and may find it difficult to get parental consent. Further, our study will include sensitive surveys on sexual behaviours which the adolescent may not want to share with their parents or guardians.

Based on our work in this setting, we anticipate that young women ages 16-17 comprised <5% of all HIV-negative pregnant women at the Gugulethu MOU, and in turn we anticipate that this population will comprise <5% of our study cohort.

5. Study procedures

The study will be integrated into the MOUs. Women will be recruited directly from antenatal care. We will train existing counsellors, nurses and midwives in PrEP treatment (including risks and benefits) and the study. A trained recruiter will recruit directly from women at their first ANC visit, and if interested, women will go to the study trailer (Green Clinic) in Gugulethu for the consent and study enrolment procedures. Consented, enrolled women will be invited to return monthly for visits that correspond with their next ANC visit. All study staff will be trained, salaried staff working for UCT.

The purpose of the study visits will be to evaluate the study objectives. Below are the detailed steps for patient recruitment, enrolment, consent and study participation (Figure 5).

For enrolment/baseline visit

Step 1: Health care providers in Gugulethu MOU provide group counseling to women at their first ANC visit, beginning with a session orientation, so that the patients know what to expect from the ANC service. This includes information about HIV testing and counselling, ART treatment for PMTCT, and the importance of HIV prevention for those women who test HIV-negative. The counselor will also be trained to provide simple information about PrEP, including what PrEP is, its benefits and risks, and the importance of daily adherence. The counselor will discuss the side effects that may occur in the first 1-2 weeks (similar to new ART patients) and will answer any questions about PrEP in the group setting.

Step 2: Following the South African National guidelines, patients privately receive pre-test counseling for HIV, including conducting a risk assessment and assessing her level of concern about having HIV. A discussion follows about the client's most recent risk exposure or behavior before and during pregnancy. The patient again is counseled about how best to reduce the risk of acquiring HIV

during pregnancy (and increased risk of MTCT), including previous risk reduction attempts, successful experiences in using condoms, knowledge of partner's serostatus, obstacles to risk reduction, and triggers and situations that increase the likelihood of high-risk behavior.

Step 3: Disclosure of HIV negative result and post-test counseling. The counselor shows the client the actual results on the test kit, and then explores the client's reactions to the test results**.** Additional counseling will be provided with information about PrEP if the woman is diagnosed HIV-negative.

Step 4: The counselor explains that the mother may be eligible to participate in a study of HIV prevention in pregnancy and breastfeeding periods, including PrEP for women who decide they want to take it. The counselor will review the benefits and risks of using PrEP and participating in the study and will conduct a screening questionnaire.

Step 5: If the client agrees to participate in the study (*she does not have to agree to take PrEP*), she will be referred to the study recruiter on site who will bring the mother to the Green Clinic in Gugulethu (study site) where the study counselor will evaluate study eligibility (see study inclusion, exclusion criteria), read the consent form and ensure that she understands the study design and consent form before signing, asking questions to ensure comprehension.

> **Infant consent form:** The participant will review and sign the infant consent form when she returns for her first post-partum visit with her infant.

Step 6: STI testing: Participants will self collect a vaginal swab that will be tested for baseline STIs (chlamydia, gonorrhea and trichomonas vaginalis) using Cepheid® point of care testing (will run during interview and PrEP counseling—steps 7-9). Participants will be treated if diagnosed with a STI according to National Guidelines. They will receive a partner notification letter to bring their partner in for treatment as well.

Step 7: All participants will be provided with a tablet to complete her audio computer assisted survey instrument (ACASI) baseline survey, which may take approximately 20- 30 minutes to complete.

Step 8: All participants will watch a video about PrEP (adapted from existing video from Dr. Bekker's ongoing PrEP studies in Cape Town), followed by a Q&A session with the study counselor.

Step 9: The participant will receive individual counseling about HIV prevention in pregnancy including PrEP. Risk reduction counseling will be provided for all women and will include:

- Consistent and correct use of condoms
- Knowing your status and partner's status
- If partner is HIV infected, should be on ART and achieve viral suppression
- Use of drugs and alcohol increases risk of HIV

Step 10: For all participants, the study nurse will draw blood to test for baseline creatinine tests and Hepatitis B.

- If woman is HebBsAG + she will be excluded from the study
- Women with low creatinine can participate in the study but can only receive PrEP if their eGFR >60mL/min
- The turnaround for renal function tests will be 24-48 hours. We will call participants who have started PrEP to return if their creatinine results are abnormal. They will be

requested to stop taking PrEP until their creatinine results return to normal and will be able to re-test the following month.

Step 11: Participants will receive counselling on the risks and benefits of PrEP. Following the counseling they will be asked: "Do you want to start taking PrEP today to prevent HIV? You will need to take it daily for it to be effective." Her response will be recorded.

If yes:

1. The nurse will provide the participant with a 1-month supply of TDF-FTC and invite her to return in 1 month for her next study visit.
2. Nurses will provide contact information to the participant and ask her to call to report any side effects or adverse events while on PrEP, and nurse will track and report serious adverse events to study PIs, Pediatrician, and Obstetrician to decide on how to treat women and infants who have adverse events.

If she says she does not want to start PrEP, woman will be in the deferred PrEP arm:

1. The nurse will schedule her to return in 1 month for the follow-up visit

Step 12: Participants will receive study staff contact information, instructions to call with any questions, and will be scheduled for their next visit in 1 month for the next study visit

Step 13: Participants will receive study staff contact information, instructions to call with any questions, and will be scheduled for their next visit in 1-week to return when test results have returned from the laboratory

Step 14: The study counselor will provide the mother with an appointment card and invitation for her partner to return to receive couples' HIV testing and counseling (if in a relationship). The session will end by encouraging the client to implement her/his risk-reduction plan (including PrEP if applicable and consistent condom use, couples testing) to prevent HIV acquisition.

Step 15: The participant will receive up to R250 per visit including reimbursement for the participant's time, transportation and including their refreshments during the study. Further, we will combine the study visits with existing ANC or post-partum/well-baby visits to minimize the travel to the facilities outside of normal clinical checkups.

2.For follow up return visits:

Follow up visits will be monthly until birth (to coincide with ANC visits) then every two months after birth (to coincide with post-partum, well-baby visits).

Step 1: In ANC: Healthcare providers provide counseling on HIV prevention and treatment at each ANC visit including HIV testing, as part of standard of care. In post-natal care and well-baby visits women may not receive regular HIV testing and messages and will receive this within step 2 (with study counselor). Following their ANC visit, enrolled women will be invited to attend the study site in each MOU to do the follow-up visit including the ACASI survey and prescription and adherence counseling (if on PrEP).

Step 2: ACASI survey at each visit in a private study room

Step 3: In the study room, the study counselors will provide PrEP-specific counseling including adherence counseling for those on PrEP (and management of side effects), or counseling about the risks and benefits of PrEP for women not yet on PrEP. Women not on PrEP will be asked if they are interested in starting PrEP at this visit.

Step 4: STI testing: At 3rd trimester visit and first postpartum visit, participants self-collect a vaginal swab for STI testing (chlamydia, gonorrhea and trichomonas vaginalis using Cepheid® point of care testing). Participants will be treated if diagnosed with a STI according to National Guidelines. They will receive a partner notification letter to bring their partner in for treatment as well.

Step 5 (for women on PrEP): At each visit the study counselor will ask, and record responses, all participants on PrEP about any side effects associated with TDF/FTC, including diarrhea, nausea, fatigue, headache and rash (which are seen in about 10% of participants during the initiation of therapy). We will encourage participants to contact the study nurse if they experience side effects between visits.

For participants on PrEP, the study nurse performs a blood draw for creatinine clearance and a finger prick for DBS testing for adherence measures and (if applicable for this visit). See Table 1 for study calendar.

Step 6: PrEP provision (for 1 or 2 months) and appointment reminder

Follow-up & retention: Tracing information will be taken at the enrolment visit and updated at each study visit. Retention activities will focus on scheduled measurement visits. Following our established approach in this setting, we will provide reminder calls to participants before their measurement visits, and initiate tracing, including home visits, for women who do not attend the measurement visit within one week of the scheduled visit.

PrEP provision: monthly for the first 3 months, and then 2-months intervals after that. Participants on PrEP will have regular monitoring with laboratory tests, including creatinine levels to check for changes in renal function and dried blood spots (DBS) for adherence measures. Those with HBsAg+ will be excluded from the study. We will test for HIV seroconversion at every study visit.

PrEP retention methods to improve adherence: Each study visit will include counselling from peer counsellors who will discuss the importance of retention and adherence to PrEP for effectiveness. We will adapt messages from ongoing PrEP studies conducted by co-I Prof. Bekker and team. We will also provide participants with a brochure to take home that discusses retention, adherence and side effects of PrEP. Each visit will include group and individual counselling. Group counselling will be led by a mother who has successfully taken PrEP for 3+ months to guide a discussion about the importance of retention, reminders on how to take the medication daily and how to address side-effects (e.g. nausea, headaches, etc).

In-depth interviews: We will select 30 women at random among women on PrEP and 30 women will be randomly selected among those not on PrEP to participate in a 1-hour in depth interview at first post-partum visit and at study end. The interviewer will follow a semi-structured discussion to review decisions to take (or not take) PrEP, side effects, issues related to adherence, disclosure of PrEP to others, and relationship status with open-ended questions.

<u>Laboratory tests in women on PrEP:</u>

- **Renal function (in all women):** Blood draws for creatinine levels will be taken at baseline, 3-month follow-up and at the end of the study, as per SA HIV Clinician Guidelines [26].
    - At enrollment: women with eGFR<60ml/min will be excluded from the study

- At 3-month follow up: Women will not be able to continue taking PrEP with an eGFR <60m/min but will be able to continue to participate in the study. If their creatinine results change at the following visit they will be eligible to start PrEP.

- **Hepatitis B infection (all women at baseline):** The blood draw will also be used to test for active Hepatitis B infection using Hepatitis B surface antigen (HBsAg). Women who test HBsAg+ will be excluded from the study and referred for care according to national protocol
- **DBS:** Dried blood spots will be prepared from finger pricks every two months in women on PrEP to evaluate adherence.
    - DBS cards will be prepared and stored following standard protocols and stored at -80°C for analysis at the end of the study with the clinical pharmacoanalytic laboratory of Dr. Lubbe Wiesner at UCT. Using techniques developed by Dr. Peter Anderson at University of Colorado [16] adherence will be defined as red blood cells containing TDF-DP ≥40ng/dl which is indicative of daily dosing [16]. As supplementary measures of PrEP adherence, we will use self-reported items that we will adapt from previous studies (including visual analogue scales as well as 3-day, 30-day and last visit recall questionnaires) (22-25), and pharmacy refill records to compare objective versus subjective measures and report on the effectiveness of each measure in correlation to the true measures of TDF-DP. We will determine final dosing and measures following reporting from ongoing PK studies of pregnant women on PrEP (e.g. Impaact 2009).

Laboratory tests in all women in the cohort:

- **STI testing (baseline, 3rd trimester and first postpartum visit):** Self-collected vaginal swab kits will be provided to all participants along with an explanation for their use. Swabs will be analyzed using on-site testing equipment (GeneXpert; Cepheid ®) for rapid testing of chlamydia, gonorrhea and trichomonas vaginalis. If they test positive, they will be treated by the nurse/midwife in ANC or postpartum care and a referral for her partner to receive STI treatment in the clinic.
- **HIV testing**. As part of the standard of care, all pregnant and breastfeeding women will be tested for HIV using serial rapid HIV tests at each antenatal and postnatal care visit. In addition, PrEP-PP study staff will have a stock of rapid HIV test kits to ensure that women get tested at each study visit.
    - **Seroconversion.** If a woman, infant or partner seroconverts at any point during the study, they will be referred to the clinician on duty to initiate ART, following counseling about PMTCT, breastfeeding, disclosure, and ART adherence, per the SA National Protocols [17]. Seroconverted women will be censored from the remainder of the study and referred to the clinic to initiate ART.
    - If a woman seroconverts while on PrEP, there may be a risk of ART resistance, though research has demonstrated that the risk of ART resistance is very low [12, 13]. In the case of seroconversion, Drs Bekker and Myer will follow seroconverters with the study team to evaluate if the patient achieves viral suppression within 6 months of ART start, and if not, she will be referred for specialist attention for testing for ART resistance and clinical follow-up.

Adverse events:

- **Maternal adverse events:** We will collect data on maternal adverse events by asking mothers about intercurrent medical events, which will be reviewed by an obstetrician, including any hospitalizations or illnesses. We will also track and report changes in creatinine or other toxicities in women on PrEP.
- **Infant adverse events:** We will collect data on infant adverse events by asking mothers about infant health or intercurrent medical events, which will be reviewed by a pediatrician.
    - Adverse birth outcomes will include infants that were small for gestational age, pre-term births, miscarriage and stillbirths.

Table 1: **PrEP-PP** cohort measures by participant study month

	Pregnancy						Post-partum											
Participant study month	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Study enrollment and consent of consecutive sample of HIV-negative pregnant women (N=220)	X																	
PrEP group, individual (or couples counseling where applicable) and information, education, counseling materials on PrEP in pregnancy and breastfeeding in local languages (at each visit)	X	X	X	X	X	X	X		X		X		X		X			X
Routine ANC and postnatal care, well-baby visit follow-up (as available in standard of care), including rapid HIV testing, pregnancy, and birth outcomes	X	X	X	X	X	X	X		X		X		X		X			X
ACASI survey to collect: behavioral acceptability, knowledge, and substance use data	X	X	X	X	X	X	X		X		X		X		X			X
Screening at enrolment for Hepatitis B surface antigen. If HBsAg+ = excluded from study	X																	
Laboratory testing for STIs (chlamydia and gonorrhoea) & treatment if positive	X				X		X											
For women on PrEP:																		
Laboratory tests of creatinine (if eGFR<60ml/min cannot continue on PrEP, refer to return in 1 month for re-test)	X			X			X								X			X
PrEP pharmacy refills and adherence supportive counseling monthly (for first 3 months on PrEP) then every 2 months for following months	X	X	X		X		X		X		X		X		X			X
DBS taken for TDF-DP adherence measures (bi-monthly in participants on PrEP)	X	X	X		X		X		X		X		X		X			X
In-depth interviews for 20 participants							X											X
Collect study data on: (1) PrEP counseling, (2) PrEP medication when requested, (3) regular appointments, (4) IEC materials, (5) adherence counselling and support by facility, through patient ACASI survey at every study visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Training, quality assurance and supervision:

1. *Existing DOH staff:* We will conduct an on-site half day training for existing counselors, nurses and midwives and Managers in the two study sites on the study protocol to ensure that they understand and support the integration of the study in their facility.
    a. **Inclusion of interviews for healthcare providers in health facility to understand their knowledge of and attitudes around PrEP:** We seek to interview existing health care providers including nurses, counselors, midwives and managers to understand their knowledge about PrEP, HIV prevention in pregnancy and any attitudes about PrEP that may affect future integration of

PrEP and PrEP uptake in the facility. We will interview approximately 20 health care providers and have one focus group in those providers in isiXhosa or Africaans. We will record, translate and transcribe their responses and analyze the results thematically in order to develop interventions around provider training and support.

2. *Study staff:* We will hire 2 counselors, 2 nurses, 2 coordinators who will receive a 3-day training program and they will be required to complete the entire training course. After completion of the training, the study PI will observe the counselor and nurse completing each step of the intervention with a mock patient. Upon satisfactory completion of observed sessions, the counselors and nurses will be certified to conduct the study intervention and will receive a completion certificate.
3. *Quality assurance* will occur on three levels. Day-to-day monitoring, supervision, and support of counselors will be carried out by the Study Coordinators (from UCT—1 per facility). The Study Coordinator will provide on the job training to ensure that counselors and nurses respect the study protocol. Adherence to the counseling protocol will be established by the Study Coordinator who will sit in on a random subsample of 20% of counseling sessions to ensure that counselors are adhering to study protocols.

Sources of data

There are four sources of data/materials for this trial: (1) survey measures (ACASI); (2) in-depth interview measures in 20 randomly selected women (n=10 who were on PrEP compared with 10 not on PrEP); (3) laboratory measures; and (4) information abstracted from routine care records, including related to PrEP. The collection of data materials will be conducted by a study measurement team comprised of one study coordinator, one study interviewer, and one fieldworker. All procedures for data collection (regardless of source) will be outlined in a study manual of procedures, with individual activities guided by standard operating procedures (e.g., DBS, specimen transport, or questionnaire administration).

Survey measures (ACASI)
At study measurement visits, questionnaires will be administered to mothers participating in the study using ACASI on a tablet with a site coordinator available for troubleshooting. ACASI will help reduce the amount of respondent bias when responding to sensitive questions around sex and substance use. Following standard procedures, the questionnaires will be translated into isiXhosa and Afrikaans and back translated to ensure appropriate phrasing. Questionnaires will include:

- Basic demographic information and obstetric history (enrollment only)
- Partner's HIV status
- Sexual behaviors in the past month and week including # of sex partners, type of sex, and frequency of sex and condom use
- Substance use information using the AUDIT-C and DAUDIT scales
- Risk perception scales
- Partner, community and social support for PrEP
- For PrEP users, questions related to PrEP adherence according to self-report (the 3-day and 1-month recall and a visual analog scale) and pharmacy-based pill counts will be conducted at each study measurement visit.
- Additional schedules will be used to collect data on symptoms in mothers that are potential side-effects of PrEP use (at all study visits)
- We will also use short questionnaires to collect data on all women's experiences in the study, and the acceptability of the PrEP initiation, including what kind of services were offered at each visit (e.g. counseling, peer mentorship, and IEC materials, medication)
- Self-reported symptoms related to STIs

- This will focus on the positive and negative aspects of their experiences of PrEP initiation in pregnancy and breastfeeding and any factors associated with PrEP initiation, retention, and adherence.

Interview measures

In addition, a subgroup of 20 randomly selected women participating in the study will be enrolled into a qualitative sub-study to complete one in-depth interview at the end of their study participation. We will randomly select 20 women to examine in more detail the acceptability of PrEP, barriers, and facilitators to PrEP adherence over time. We will randomly select 20 women who were on PrEP and 15 women not on PrEP. This type of 'process evaluation' information can play a critical role in interpreting the quantitative findings and understanding of how to generalize the intervention to other populations. We plan to conduct interviews after approximately 3 months of PrEP use, so at the first postpartum visit, and then at the end of the study. This sub-study will have a separate informed consent process, although these interviews will be timed to take place immediately after study visits scheduled for the trial. There will be no separate participant reimbursement for participating in those interviews.

In-depth interviews will be conducted in a private room by an experienced isiXhosa or Afrikaans-speaking research assistant and interviews will be digitally recorded for later transcription and translation. The interviewer will use a simple question guide to help ensure that key topics are investigated. Interview recordings will collect participant study ID numbers but will not record participant names in any form. Key constructs to be investigated during these interviews include:

- Experiences of study participation, including experiences with study staff, counselors, and clinicians
- Experiences of PrEP initiation and any side effects
- Individual, partner, and family experiences that could be facilitators or barriers to PrEP

6. Analytic Considerations

Our study is a formative study to evaluate acceptability, feasibility of PrEP integration into existing ante and postpartum care in South Africa. Our cohort of 220 women is a pilot that will provide estimates of the PrEP cascade and factors associated with attrition but is not sufficiently powered to evaluate differences in women in each step of the cascade. As a pilot, our study will inform future analyses on this topic.

Statistical analysis considerations

The primary analysis will focus on measuring the distribution of women across the PrEP cascade including: initiation, retention and adherence. **PrEP initiation** will be based on a woman's uptake of PrEP and allow for stoppage and re-initiation; **PrEP retention** will be defined as not missing >1 visit among those on PrEP (with separate analyses of PrEP stoppage). For **PrEP adherence** for women on PrEP we will measure both **perfect adherence** (i.e. level of objective adherence throughout pregnancy and breastfeeding periods) as well as "**prevention-effective" adherence** (i.e. adherence before and during times of sexual activity) in participants through objective and subjective measures to evaluate agreement between the two measures, and the level of under- or over-reporting. Primary adherence analyses will use objective measures (TDF-DP from DBS) taken on all those who enrolled and initiated PrEP; subsidiary analyses will consider (i) other adherence measures and (ii) multiple imputation for missing adherence data.

- **Use of PrEP will be measured** through alternate definitions of the main outcomes (e.g. adherence by self-report versus adherence by pharmacy refill), compared using measures of agreement and will be analyzed as independent models to contrast estimated associations.

- **Measurement of prevention-effective execution:** Execution refers to PrEP adherence during a time when at-risk sex happens. It is calculated by: number of doses reported, or recorded/number of expected doses based on HIV risk and PrEP initiation/discontinuation
- **Prevention-effective continuation:** Prevention-effective continuation describes the duration of PrEP use during periods of HIV risk and references the absolute time of use during pregnancy and breastfeeding periods. We will adapt the methodology from previous PrEP studies in SA including FEM-PrEP to create a semi-ordinal composite adherence score from blood specimens from DBS every 2-months.

Table 2: Study measures for PrEP-PP

Primary Outcomes	**Measurement**	**Source**	**Frequency**
PrEP initiation	# of women who initiate PrEP over time / total # of women in active cohort = proportion of women who initiate PrEP	Electronic provider log (REDCap)	Daily entry, weekly analysis
PrEP retention	# of women on PrEP who return for study visits (do not miss more than 1 visit) / total # of women in active cohort who are prescribed PrEP= proportion of women on PrEP who are retained in PrEP study	Electronic provider log (REDCap)	Daily, analysis weekly
PrEP adherence-subjective	# of women taking PrEP, who self-report taking their medication daily (& pill count to confirm this) during periods of sexual risk over time / total woman-time on PrEP in active cohort = PrEP adherence rate (subjective)	Electronic provider log (REDCap)	Daily, analysis weekly
PrEP adherence-objective	# of women taking PrEP who have >80% levels at >40ng/mL TDF-DP (indicating dosing in past 24 hours) at 3rd trimester, delivery, and 6 weeks postpartum (and during sexual risk periods during that time) / total woman-time on PrEP in active cohort = PrEP adherence rate (objective)	Lab analysis of TDF-DP measures	Quarterly
Secondary Outcomes			
Predictors of attrition at key steps in the PrEP cascade	Individual, pill/study and disease specific predictors of attrition	ACASI	ACASI: Every study visit
HIV outcomes	HIV testing data: HIV-uninfected, HIV-positive for mother and child (if mother seroconverts)	Electronic provider log (REDCap)	Every visit
Health outcomes and adverse events	Any side-effects, creatinine, any negative maternal or neonatal outcomes (for mother and infant)	Electronic provider log (REDCap)	During routine lab tests and visits

Each outcome will be described via cumulative incidences at fixed intervals (e.g., cumulative PrEP initiation by delivery) and incidence densities over time. The general statistical approaches to these outcomes are analogous; data will be described graphically, including product-limit graphs, with preliminary analyses based on standard approaches for rates and proportions. The modelling approach will vary depending on the nature of the outcome. **PrEP initiation** will be modelled using a probit model (preferred to estimate risk factors for common outcomes) with individual-level covariates as fixed effects; when time-dependent or visit-specific covariates are included in the analysis of cumulative initiation we will shift to a mixed-effects setting with random effects around individual participants. **PrEP retention** will be examined using similar approaches; in addition, we will use time-to-event methods to estimate factors associated with time to loss (non-retention) among women having initiated PrEP. **PrEP adherence** will be modelled using mixed effects probit models as above and generalized estimating equations to examine the marginal effect of individual-level covariates on adherence during the study [85]. Throughout, robust estimates of standard errors will be used.

The same modelling approaches will be used to explore secondary implementation questions such as the effect of individual, pill/study, and disease factors on PrEP initiation, retention and adherence outcomes (see Figure 1 for conceptual model). The main exposures include: **individual level factors**: risk perception, community/family support, sexual activity, risk, concerns about drug's side effects and harm on self (pregnancy) and/or infant's health. **Pill regimen and study factors** include: PrEP side effects, time required to participate in study, patient-provider relationship measured from the participants' perspective**. Disease factors** include: stigma around HIV and PrEP, and partner's HIV status (see Table 5 for specific variables).

We will also describe the frequency of **HIV outcomes**, including maternal HIV acquisition and MTCT, and any laboratory or self-reported side effects (e.g. changes in creatinine or self-reported side-effects [GI symptoms, headache, and etc.]). Analyses will include pure-count and person-time approaches; for the latter, confidence intervals will be calculated following the method of Breslow and Day [86]. We will also describe **infant outcomes over time** (including birthweight, gestational age at delivery, pregnancy loss and any infant illness, hospitalization or death). While we expect the frequency of adverse HIV-related outcomes to be low, we will describe characteristics of women who did/did not acquire HIV, and consider further analyses using the approaches outlined above.

Qualitative data analysis considerations

Following our standard practice, study tools including in depth interview guides and ACASI materials will be translated into isiXhosa and Afrikaans, the predominant local languages, with independent back-translation for verification. We will digitally record the IDIs and then have the recordings transcribed verbatim. The recordings will be reviewed and verified for accuracy by the interviewers. Transcripts will then be translated and key quotations back-translated to verify meaning. A subset of 20% of transcripts will be double-coded to examine the inter-rater reliability of the coding process. After coding, Investigators will search by substantive codes and themes identified utilizing matrices to organize and allow for comparisons by group (e.g. age, pregnancy stage, partner status, initiators and non-initiators). Patterns in the matrices will be used to identify themes. Tables of themes will be created using the verbatim quotations as evidence to support the themes that serve as the primary data analyses approach. Conclusions will be based on interpretation of these tables of themes with quotations. Data will be managed using NVivo Software (QSR International).

Data management

Data management will take place at the site following procedures established for other research protocols conducted in Gugulethu. Data collected on paper forms will be entered into a custom designed RedCap database, maintained in a firewall-protected UCT server with nightly backups. The study database will be password-protected following standard password safety procedures. The database will be designed and maintained by a senior data manager who will develop the data dictionary, direct queries, and data quality assurance / quality control activities, and will supervise the data entry clerk. Data quality assurance will be in the form of robust database structure and platform, and "front-end" data checks, including real-time database queries. Quality control will be through data checking scripts to identify out-of-range values, logic violations, and missing observations. Data editing will be based on reference to the form and/or source document in question; all data queries and responses will be logged, and edits will be implemented through separate program files. All study records will contain anonymous participant identification numbers, and no participant names or identifiers will be recorded. Patient routine folder numbers will be stored in a separate password protected database. Once all routine data are linked the folder number will be removed and only the study identification number will be used.

7. Ethical considerations

Ethical review

The study protocol, informed consent form, all data collection tools, and other requested documents will be reviewed and approved by the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (UCT-HREC). After the initial review and approval, UCT-HREC will review progress of the study at least annually. Following the approval, we will submit the protocol and approval to University of California Los Angeles (UCLA) for secondary review and approval. UCLA IRB will also review progress of the study annually and we will report all adverse events or amendments to both Ethics Committees.

Insurance

Currently we propose that this protocol is covered by UCT's no-fault insurance policy as this is non-commercially sponsored interventional research.

Ethics approach for including adolescent girls (16+ years old) in study

As per the Department of Health. Guidelines for Good Practice in the Conduct of Clinical Trials with Human Participants in South Africa [21] we will collect parental or guardian consent to participate in the study as well as assent from the minor.

The risk is justified by the anticipated benefit to the subjects: the risks associated with PrEP-PP study procedures are minor and largely non-invasive (except for phlebotomy) and are justified by the anticipated benefit that PrEP would have on prevention of HIV acquisition in this vulnerable group. Thus, there is the potential for direct benefit associated with participation.

Informed consent

Informed consent for the study and questionnaire is modelled after that used in previous studies and will be delivered in participants' home language (isiXhosa or Afrikaans) by trained interviewers. This ICF details the purpose of the study, study procedures, and the risks and benefits to mothers that participants may encounter at the additional study measurement visit. This consent includes a separate specimen storage section. Participants who do not consent to specimen storage but who consent to the main study visit will still be able to complete the rest of the study.

Here, study staff will emphasize to participants that:

- Participation is entirely voluntary, and their choice regarding participation will in no way influence the quality of routine medical care for mothers or their infants
- Women may exit the study at any time for any reason without compromising the quality of health care received.

English versions of the informed consent documents are provided in the Appendix to this document. Translated isiXhosa and Afrikaans versions (as well as a certification of their translation and back-translation) will be submitted to the HREC before the start of the study.

Risks

The potential risks to participants in the study include:

- Risks associated with collection of self-reported behavioural and psychosocial information, related to psychosocial distress raised by questionnaire items involving social support, mental health, or disclosure of HIV status

- Risks due to loss of confidentiality due to study procedures—for instance, in the process of data collection
- Risk associated with asking participants to disclose their status, and potential for interpersonal violence by the partner resultant from the disclosure.

The potential risks to participants who take PrEP include:

- Risks associated with PrEP side effects (headaches, gastro-intestinal) for women on PrEP
- Risks associated with PrEP adverse events for women on PrEP
- Risks associated with collection of dried blood spots

All participants will be informed of these risks, and the strategies to minimize these, as part of the informed consent process. These strategies draw directly from prior experiences conducting research on HIV prevention and treatment in Gugulethu, Mitchell's Plain and similar communities across Cape Town.

Benefits

Direct benefit

The major potential direct benefit from participating in this study is that pregnant women will receive best possible HIV prevention including ongoing counseling, Hepatitis B screening, STI testing and treatment and PrEP if they choose to take it which can prevent HIV acquisition during pregnancy and breastfeeding periods. If women do not opt to take PrEP, or are not adherent to PrEP, she will still receive the ongoing counseling and STI testing/treatment. Their participation may help us answer our research questions and help us inform health programs for pregnant women in the future. The benefit of participating in the study and preventing HIV acquisition and onward infant transmission is likely to outweigh the risk of PrEP exposure or other risks.

Indirect benefit

By identifying the optimal strategy for delivering PrEP to pregnant women, this study has the potential to lead to improved HIV prevention interventions to protect against HIV acquisition and vertical transmission in HIV-uninfected women and their infants in Cape Town, the Western Cape Province, and across South Africa.

Compensation

Participants will be given up to R250 per visit including reimbursement for the participant's time, transportation and including their refreshments during the study. Visits will correspond to regular ANC or postpartum/well-baby clinical visits wherever possible. All participants will also receive refreshment on the day of their visit.

Confidentiality

The following steps will be taken to minimize the risk of any loss of confidentiality throughout study design and conduct.

- All personnel involved in data collection and management will undergo specific training for the study in confidentiality and related patient protection issues.
- Following standard practice, all patient- and study-related information will be kept in locked cabinets at either the study office in Gugulethu, Mitchell's Plain or at UCT.
- Anonymous participant identification numbers will be used on all study documents. Collection of participant names and other identifiers will be restricted to informed consent documents, patient tracing materials, and a study identification key, all of which will be kept in a locked cabinet in the study office at Gugulethu and at UCT separate from other study documentation and accessible only by the project

coordinator and local PI. No CRF will include participant name, including CRF that may reflect HIV status of women or their children (including STI test results or treatment).

- All electronic records will be kept in password-protected files. All electronic communications of study data will be through password-protected, encrypted files. All data storage at the University of Cape Town will be within a firewall-protected server.

While efforts will be made to minimize the loss of confidentiality, in the event that staff learn that the participant is a threat to themselves or to others or of possible abuse by partners, the proper authorities will be notified. This exception will be included in all study informed consent forms.

Internal monitoring

The purpose of monitoring is to verify the rights and well-being of human subjects are protected; that trial data is accurate, complete and verifiable with source data; that the trial is conducted in compliance with the protocol, GCP and the applicable regulatory requirements. Throughout the conduct of the study, internal study monitoring will be led by the study PIs. We are collaborating with the study Paediatrician, Dr. Lisa Frigati and Obstetrician, Dr. Greg Petro, who will monitor emergent clinical concerns as co-Investigators. They will monitor all adverse events and advise on treatment for all participants who have adverse events.

Throughout the duration of the study, study PIs, co-investigators and the study coordinator will participate in weekly conference calls to monitor the rate of participant enrolment and the integrity of protocol implementation (including the completion of informed consent and quality of study measures). In addition, participant retention and safety endpoints will be discussed as well. We will report all serious maternal and/or infant adverse events, including any laboratory or other measures that require women to stop PrEP, to the study's DSMB and Ethics Committee.

Because of the vulnerable nature of the study population –pregnant women and adolescent girls –, and the innovative nature of providing PrEP to those women, we have chosen to invite an independent DSMB to review study progress. While independent DSMB review is not common in implementation research, we feel that external review of study progress will be critical to maximizing the benefits and minimizing the risks of the PrEP-PP evaluation. Briefly, the DSMB will monitor:

- Study protocol and tools for data collection
- The rate of recruitment at different time points
- Adverse events, including social adverse events, identified during the study
- any missing or spurious data with the Investigator, which should be resolved in a timely manner.

DSMB members:

- Dr. Raphael Landovitz (UCLA) is an infectious disease and HIV clinician with both a clinical and research interest in HIV prevention, particularly the use of chemoprophylaxis as part of HIV prevention - PrEP, PEP, and microbicides - and their impact on risk behavior. He works in the ACTG, HPTN and ATN clinical trials networks.
- Dr. Barbara Moscicki (UCLA) is Professor of Pediatrics, Chief of Adolescent and Young Adult Medicine at UCLA who is a member of the Scientific Leadership Group in Pediatric HIV and AIDS Cohort Study with 20 years of experience conducting research on HIV infected adolescents.
- Dr. Grace Aldrovandi (UCLA) is Chief of Pediatric Infectious Diseases at the David Geffen School of Medicine at UCLA and PI of International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) Laboratory Center and other R01 funded projects.
- Dr. James McIntyre (UCT) Ob-Gyn, is the CEO of the Anova Health Institute and Honorary Professor in the School of Public Health & Family Medicine at UCT, with significant experience in research on PMTCT and PrEP delivery in SA.

- Dr. Sinead Delany-Moretlwe (Wits) is a MD epidemiologist who is a PI on three PrEP demonstration projects for adolescent girls and young women across SA, with a particular focus on evaluating interventions that may address the social and structural barriers to PrEP use in young women.

Use of Information and Publications

Publication or presentation of the results of this study will be agreed upon in collaboration with the study investigators. Note that the funding agency has no input in the decision to present or publish study data or the nature of the data that are presented or published.

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