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Oral pre-exposure prophylaxis delivery among HIV-negative pregnant and postpartum women in antenatal clinics of Cape Town, South Africa: Adolescent Girls and Young Women, Intimate Partner Violence, and Prevention-effective Adherence

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Oral pre-exposure prophylaxis delivery among HIV-negative pregnant and postpartum women in antenatal clinics of Cape Town, South Africa: Adolescent Girls and Young Women, Intimate Partner Violence, and Prevention-effective Adherence

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

by

Nehaa Khadka

2023

ABSTRACT OF THE DISSERTATION

Oral Pre-exposure Prophylaxis Delivery among
HIV-negative pregnant and postpartum women in
antenatal clinics of Cape Town, South Africa:
Adolescent Girls and Young Women,
Intimate Partner Violence, and Prevention-effective Adherence

by

Nehaa Khadka
Doctor of Philosophy in Epidemiology
University of California, Los Angeles, 2023
Professor Pamina M. Gorbach, Chair

HIV acquisition risks remain high for pregnant and breastfeeding populations in South Africa. Oral pre-exposure prophylaxis (PrEP) with tenofovir disoproxil fumarate/emtricitabine (TDF-FTC) can be used daily during periods of sexual activity to prevent HIV infections for cisgender women. In 2021, oral PrEP became the standard of care for HIV prevention during pregnancy and breastfeeding periods. The objective of this dissertation was to evaluate trends in oral PrEP initiation, continuation, and adherence among adolescent girls and young women, women experiencing intimate partner violence, and by sexual behaviors throughout gestational periods and postpartum. We used data from the PrEP in Pregnancy and Postpartum (PrEP-PP)

study, a prospective cohort in Cape Town of 1200 participants without HIV. The PrEP-PP study provided HIV prevention counselling and offered PrEP to pregnant and breastfeeding women.

The first study evaluated the oral PrEP cascade framework among adolescent girls and young women (AGYW) in the PrEP-PP study. Approximately 83% of AGYW initiated PrEP at their first antenatal care (ANC) visit, 34% continued PrEP at 6 months, and 11% stopped and restarted. AGYW with a higher HIV risk had an increased adjusted likelihood of continuing PrEP through 6 months (adjusted odds ratio[aOR]:1.91 [95% CI, 1.15-3.16]). About 7% of AGYW had high adherence to PrEP at 6 months.

The second study examined the relationship between recent and past-year intimate partner violence (IPV) experienced by pregnant and postpartum women and oral PrEP continuation and adherence. Women who experienced past-year IPV were less likely to discontinue PrEP(adjusted hazards ratio: 0.80 (95% CI: 0.61, 1.06) and had higher adherence(quantifiable tenofovir-diphosphate[TFV-DP] in dried blood spots; aOR=1.82 (95% CI: 1.02, 3.25) at 6-month follow-up visits.

The third study evaluated prevention-effective adherence by gestational trimesters of pregnancy and postpartum. Prevention-effective adherence(initiation/quantifiable TFV-DP or reported use during follow-up among those engaging in condomless sex) was 65% overall, with the highest adherence in trimester 1(81%) and lowest at early postpartum(49%). There was a positive association between engaging in condomless sex and PrEP use(quantifiable TFV-DP or self-reported use; adjusted risk ratio:1.88; 95% CI: 1.67, 2.12).

In conclusion, AGYW during pregnancy and postpartum had high oral uptake, but retention in PrEP by 6 months was low. Those with higher HIV risks are more likely to continue PrEP. Pregnant/postpartum women who experienced past-year IPV were more likely to stay in the study and had greater adherence. The findings suggest that pregnant and postpartum women align their PrEP use with their potential HIV risks. Implementing violence screening and

oral PrEP counselling (with conversations about changing HIV risks) at ANC may improve HIV prevention for women during pregnancy and postpartum in South Africa and beyond.

The dissertation of Nehaa Khadka is approved.

Dvora L. Joseph Davey

Roch A. K. Nianogo

Marjan Javanbahkt

Grace M. Aldrovandi

Pamina M. Gorbach, Committee Chair

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2023

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ACRONYMS

Adjusted Hazard Ratio (aHR)

Adjusted Odds Ratio (aOR)

Adjusted Risk Ratio (aRR)

Adolescent Girls and Young Women (AGYW)

Alcohol Use Disorders Identification Test-Concise (AUDIT-C)

Antenatal Care (ANC)

Dried Blood Spots (DBS)

Chlamydia trachomatis (CT)

Confidence Interval (CI)

Hazard ratio (HR)

Human Immunodeficiency Virus (HIV)

Institutional Review Boards (IRB)

Intimate Partner Violence (IPV)

Neisseria gonorrhoeae (NG)

Odds Ratio (OR)

Prenatal Clinics (PNC)

Pre-exposure Prophylaxis (PrEP)

Risk Ratios (RR)

Sexually Transmitted Infection (STI)

Standard Deviation (SD)

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)

PrEP in Pregnancy and Postpartum (PrEP-PP)

Tenofovir disoproxil fumarate/emtricitabine (TDF-FTC)

Tenofovir-diphosphate (TFV-DP)

The Joint United Nations Programme on HIV/AIDS (UNAIDS)

Trichomonas vaginalis (TV)

World Health Organization (WHO)

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Chapter I. Introduction

1.1 Background

South Africa has one of the largest HIV epidemics globally, with over 7.5 million people living with HIV.[1] Despite major strides in testing and viral suppression towards the progress of Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 targets, there were still about 210,000 incident HIV infections in South Africa in 2021.[1] The 2021 Political Declaration on AIDS updated the target to 95-95-95 by 2025, meaning that 95% of individuals living with HIV should be aware of their HIV status through testing, of whom, 95% should have access to treatment and of whom, 95% should have suppressed viral loads across all demographic groups and regions.

Pregnant and breastfeeding populations (PBFP) are at an increased risk of acquiring HIV and subsequently of vertical transmission.[2,3] A pooled estimate from 19 cohort studies found that the risk of incident HIV was 4.7 per 100 person-years during pregnancy and 2.9 per 100 person-years during postpartum, compared to non-pregnant individuals.[4] An updated meta-analysis using data from 37 publications across Sub-Saharan Africa showed that the pooled HIV incidence rate during pregnancy and postpartum was 3.6 per 100 person-years (95% CI: 1.2 to 11.1)[5], meeting the World Health Organization (WHO) threshold for substantial risk.[2] In 2021 alone, over 34,000 new child HIV infections occurred due to vertical transmission from acute HIV acquisition during pregnancy or breastfeeding periods.[6] Without effective oral pre-exposure prophylaxis (PrEP) for HIV prevention, mathematical projections suggest that South Africa will experience over 76,000 new infant HIV infections in the next decade, with one-third of these infections attributable to acute maternal HIV infections during pregnancy and postpartum.[7]

Elevated HIV infection risks during pregnancy and postpartum are driven by both biological and behavioral factors.[8,9] Hormonal changes and genital mucosal alterations during pregnancy can lead to increased inflammation, which may contribute to the higher risk of HIV acquisition.[8,10]

Behavioral factors associated with increased HIV acquisition risk during pregnancy and postpartum period include condomless sex[11], partner HIV testing[12], sexual activity[11], and stigma[13]. As part of combination prevention approaches, the WHO 2015 guidelines recommend oral PrEP with tenofovir-diphosphate (TDF-FTC) for populations at risk of acquiring HIV.[2] Oral PrEP is an antiretroviral medication that, when taken daily by HIV-negative individuals prior to HIV exposure, can prevent acquisition. However, high adherence during periods of sexual activity is critical for the pill to be effective.[14] The 2020 South African National Department of Health guidelines support WHO guidelines on PrEP provision and confirm that PrEP is safe for use in PBFP at substantial risk of HIV infection.[15] However, there are gaps in our research of oral PrEP use behaviors among sub-groups of women during pregnancy and postpartum.

1.2. Focus of the Dissertation

1.2.1. Study 1: Oral PrEP delivery among Adolescent Girls and Young Women during pregnancy and postpartum

Adolescent girls and young women (AGYW) are at a disproportionately higher risk of HIV infection accounting for nearly 25% of all incident HIV infections globally, despite making up only 10% of the population.[6] AGYW (aged 15 to 24) were about 2.4 times more likely to acquire HIV than young men of similar age.[16] According to survey findings administered among a representative sample of South African AGYW, more than half (53%) of cisgender AGYW who reported ever having sex were previously pregnant.[17] Among South African AGYW that reported ever being pregnant, 36% reported that their first pregnancy occurred before age 18, 70% reported their first pregnancy was unintended, and 26% reported they were pregnant more than once.[17] However, there remains a gap in knowledge about PrEP use by pregnant and postpartum AGYW. Thus, this study will describe PrEP initiation, continuation, and adherence among pregnant and postpartum AGYW using the HIV prevention oral PrEP cascade.

1.2.2. Study 2: Intimate Partner Violence and Oral PrEP

Intimate partner violence (IPV) has impacted about 27% (19-37%) of women in southern sub-Saharan Africa in their lifetime and 14% (9-22%) in the past-year.[18] IPV is associated with an elevated HIV risk and has a bi-directional relationship.[19-23] Women with IPV victimization may have increased vulnerability to HIV due to hesitations about having discussions on safer sex and fear that negotiating condom use could lead to violence or retaliation. IPV and oral PrEP use are conflicted. While one study reported PrEP acceptability was lower among women with a history of IPV, another study reported younger women experiencing IPV were more likely to use PrEP.[24] We previously reported that 12% of women experienced emotional, physical, or sexual IPV in the past 12 months and it was correlated with PrEP initiation.[25] However, we know little about how IPV victimization and domains of IPV (physical, psychological, or sexual) affect PrEP continuation and adherence during pregnancy and postpartum. Therefore, in this study, we will evaluate the effect of any past-year and recent IPV and PrEP continuation through 6 months, and PrEP adherence (objective and self-reported). We will also examine IPV by domains and severity and oral PrEP use.

1.2.3. Study 3: Dynamic Sexual Behaviors and Oral PrEP use across gestational periods of pregnancy and postpartum

Finally, prior oral PrEP studies have reported trends of high initiation, but are challenged by discontinuation and adherence.[25-27] Some reasons women may discontinue on PrEP is due to side effects[25], stigma[13], pill burden (size of the pill and overburdened by daily dosing), or forgetting.[25] Another reason women discontinue PrEP is because of changing sexual risks.[14] There are research gaps on how and whether women adjust their PrEP use by sexual behaviors, especially during gestational periods of pregnancy and postpartum. Thus, we will estimate the prevalence of prevention-effective adherence (effective PrEP use during periods of sexual activity) and examine whether sexual behaviors in the last 3 months correlate with oral PrEP use across pregnant/postpartum windows (by trimester and postpartum stage).

1.3. Conceptual Framework

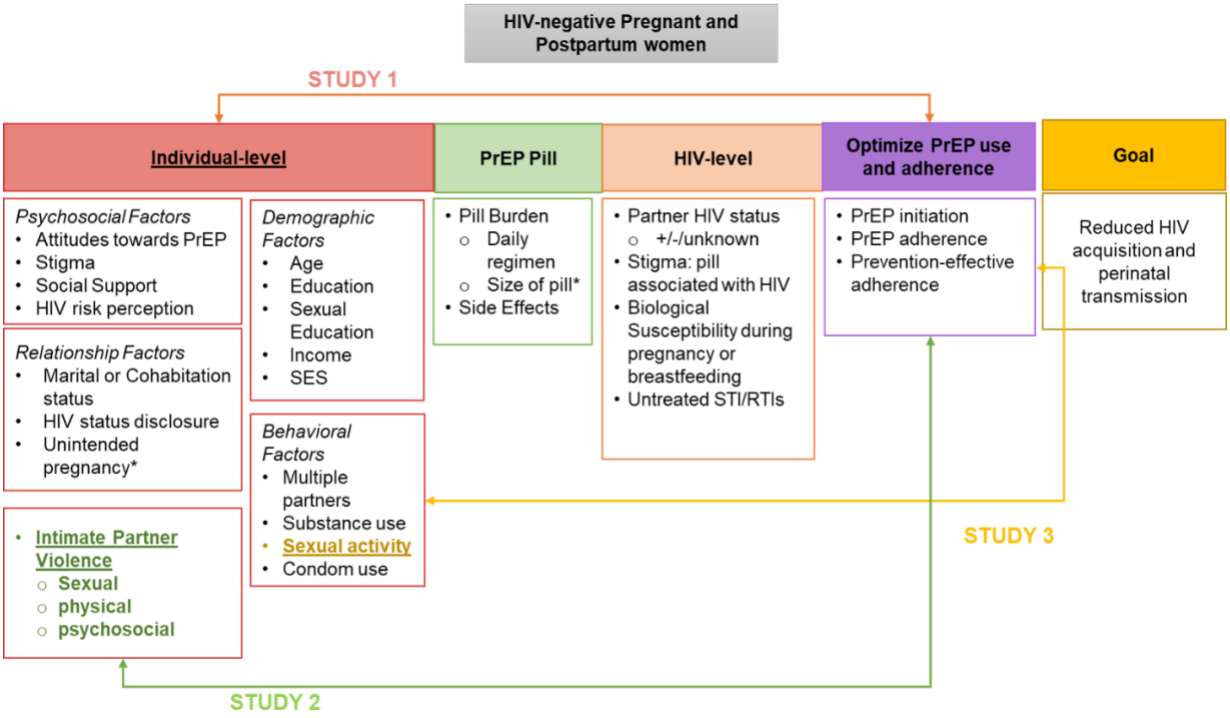
This dissertation is guided by Ickovics and Meisler's conceptual framework for adherence in clinical care.[28] The framework includes multiple factors: individual-level, facility-level, treatment regimens, patient-provider relationship, clinical setting, and disease characteristics that can affect patient adherence. We used an adapted version of this framework to guide our analyses **(Figure 1.1)**, focusing on factors affecting PrEP adherence for HIV prevention. This framework was previously used to guide qualitative studies of PrEP adherence among pregnant/postpartum populations.[29] Information that were not available in our study are shown with an asterisk (*).

Study 1 will describe pregnant and postpartum AGYW by their demographic characteristics (age, education, Socioeconomic status, income) and HIV risk factors (condom use, sexual activity, multiple partners, marital or cohabitation status). We will also use the HIV prevention cascade to quantify the proportion of AGYW using oral PrEP journey (uptake, continuation, adherence, stop/restarting on PrEP) throughout their pregnancy and postpartum.

Study 2 will use similar outcomes (PrEP continuation through 6 months, self-reported and TFV-DP levels for adherence at 3 and 6 months) but will examine factors comparing those experiencing IPV to those that do not experience IPV among pregnant and postpartum women.

Finally, study 3 will examine the association of dynamic sexual activity and condom use and oral PrEP use to estimate prevention-effective adherence throughout pregnancy and postpartum periods. The relevant variables for this dissertation and their relationships with the corresponding outcomes are shown below. This conceptual framework also demonstrates how the three independent papers in this dissertation are related and have a shared aim of preventing HIV acquisition among pregnant and postpartum women and avoiding vertical transmissions.

Figure 1.3. Conceptual Model: Factors associated with PrEP Adherence in HIV-negative pregnant and postpartum women



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Chapter II. Study 1: HIV Pre-exposure Prophylaxis Use Behaviors among pregnant and postpartum Adolescent Girls and Young Women in antenatal care in Cape Town, South Africa

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Abstract

Background: Adolescent girls and young women (AGYW) have elevated risk of incident HIV in South Africa. Despite growing availability of daily oral pre-exposure prophylaxis (PrEP) for HIV prevention, little is known about PrEP use during pregnancy and postpartum serviced at antenatal care (ANC) facility.

Methods: We used data from HIV-uninfected pregnant women aged 16-24 in Cape Town, South Africa enrolled in the PrEP in pregnancy and postpartum (PrEP-PP) cohort study at their 1st ANC visit. Using the PrEP cascade framework, the outcomes were PrEP initiation (prescribed TDF-FTC at baseline), continuation(returned for prescription) and persistence(quantifiable tenofovir diphosphate [TDF-DP] in dried blood). Exposure was baseline HIV risk score (0-5): condomless sex, >1 sexual partner, partner living with HIV/ unknown serostatus, laboratory diagnosed STIs *(Chlamydia trachomatis, Neisseria gonorrhoeae or Trichomonas vaginalis)*, hazardous alcohol use before pregnancy (AUDIT≥3). We used logistic regression to examine associations between HIV risk and PrEP adjusting for *apriori* confounders.

Results: Of 489 pregnant women, 16% were “adolescents” (16-18 years) and 84% were “young women” (19-24 years). ANC initiation was later for adolescents than young women (median=28 weeks [20-35] vs 23 weeks [16-34], P=0.03). Almost half (48%) had STI diagnosis at baseline. Overall, 83% of AGYW initiated PrEP at 1st ANC; PrEP continuation was 63% at 1 month, 53% at 3 months and 34% at 6 months. About 24% consistently continued PrEP through 6 months and 11% stopped and restarted. AGYW with a higher HIV risk (score≥2 vs ≤1) had increased odds of continuing PrEP (aOR, 1.91 [95% CI, 1.15-3.16]) through 6 months adjusting for gestational weeks, maternal age, and whether the baseline visit was before or during/after the enactment of national COVID-19 pandemic lockdowns (March 28, 2020).TDF-DP was detected

among 56% of AGYW reporting PrEP use and 7% had high adherence to PrEP (~7 doses/week) at 6 months.

Conclusions: AGYW had high oral PrEP initiation, but only one-third were retained in the study by 6 months. Higher baseline HIV risk was associated with PrEP continuation. Low persistence of TFV-DP suggests oral PrEP coverage remained inadequate for ample HIV protection. Key barriers persist in HIV prevention efforts for AGYW during pregnancy and postpartum.

Keywords: South Africa; AGYW; adherence; breastfeeding; cohort studies; oral pre-exposure prophylaxis; pregnant.

Introduction

Adolescent girls and young women (AGYW, ages 16-24) have an elevated risk of HIV infection in South Africa. According to UNAIDS, about 250,000 AGYW were infected with HIV worldwide in 2021 and 6 out of 7 incident HIV infections in sub-Saharan Africa among adolescents (age 15-19) were girls.[1] Despite making up only 10% of the population in sub-Saharan Africa, AGYW comprised 25% of all acute HIV infections.[2] AGYW have doubled the risk of living with HIV than men of similar age and were likely to acquire HIV five to seven years earlier.[3] Thus, UNAIDS aims to reduce new HIV infections among AGYW to less than 50,000 by 2025.[1]

HIV acquisition is especially high during pregnancy and postpartum periods. AGYW have a higher proportion of exposed genital mucosa exposure susceptible to HIV due to immature cervix and higher levels of genital inflammation and hormonal effects compared to older women.[4] Among AGYW, behavioral factors associated with higher HIV acquisition include age-disparate sexual partners, multiple partners, unknown partner serostatus, low marriage or cohabitation rates, earlier sexual debut, gender-based violence, lack of sexual education, and frequent condomless sex.[5,6] In South Africa, the prevalence of adolescent pregnancy (age<19) was estimated to be 20%[7] with 76% of pregnancies unintended[8], highlighting the importance of strong HIV testing, prevention, and counseling services in antenatal care settings. Moreover, the risk of vertical transmission is much higher among those with incident HIV infections during pregnancy/postpartum than among those already living with HIV.[9] In 2021, 22,000 incident HIV infections occurred during pregnancy or breastfeeding periods in Eastern and southern Africa.[1] The pooled HIV incidence rate during pregnancy and postpartum was 3.6 per 100 person-years (95% CI: 1.2 to 11.1) in sub-Saharan Africa[9], meeting the UNAIDS threshold of substantial HIV risk[1]. Therefore, prevention of HIV acquisition throughout pregnancy and postpartum periods is especially important for not only maternal health but also pivotal in the elimination of vertical HIV transmission.[9]

The South African National Department of Health supports oral pre-exposure prophylaxis (PrEP) provision and HIV prevention counseling as part of a comprehensive combination prevention strategy for AGYW and pregnant and breastfeeding women at substantial risk of HIV.[1,10] Oral PrEP with tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) is an antiretroviral medication that can be taken daily by HIV-negative persons before HIV exposure to prevent acquisition; however, high adherence during periods of elevated HIV risk is needed for PrEP to be efficacious.[11] The PrEP cascade, an analogous extension of the HIV care cascade [11], provides a quantifiable framework for measuring progress in HIV prevention efforts and PrEP delivery. It illustrates the stages of PrEP delivery: PrEP eligibility, initiation, persistence on PrEP during periods of HIV risk, and adherence to PrEP for sufficient protection from HIV.[12] Moreover, prior studies have reported that PrEP delivery for AGYW poses unique challenges, such as pill burden and stigma from taking an oral PrEP and for being pregnant.[13,14] Studies on pregnant and postpartum women have also identified delivery patterns unique to pregnancy, such as high attrition during postpartum.[15-19] However, there is a gap in knowledge for PrEP cascade and adherence studies among AGYW during pregnancy and postpartum.

We utilized the PrEP cascade among pregnant AGYW to examine PrEP initiation, continuation through 6 months, and persistence to PrEP (measuring TDF-FTC levels) at a busy antenatal care (ANC) facility in Cape Town, South Africa. We also evaluated the association between baseline HIV risk and PrEP delivery outcomes to inform national and regional PrEP programs as they are scaled up for pregnant/postpartum and AGYW.

Methods

Study Population

We used data from the PrEP in Pregnancy and Postpartum (PrEP-PP) study, a prospective cohort of 1,200 women based in Cape Town, South Africa, to evaluate PrEP use, continuation, and persistence among a sub-set of AGYW pregnant and postpartum women at

risk for HIV. The study's methodology has been described in detail elsewhere.[18] In brief, PrEP-PP study participants (age ≥ 16 years) were recruited into the study from their ANC visit at a public health clinic from August 2019 to October 2021 and were followed through 12 months postpartum. Interested study participants provided written informed consent in English or their local language (isiXhosa). Participants were then confirmed to be pregnant, not living with HIV (confirmed by a 4th generation rapid HIV antigen/antibody test from Abbott laboratories), and Hepatitis B surface antigen negative (confirmed by a rapid hepatitis B surface antigen test from Abbott Laboratories) to be eligible for the study.

Enrollment and Measurements

Upon enrollment, study staff administered a baseline survey collecting participant's demographic information, clinical characteristics, and behavioral HIV risk factors using REDCap, a secure web-based application. Participants then provided point-of-care testing for sexually transmitted infections (STI) and those with STIs were provided treatment per South African national STI Guidelines.[20] After, participants received counseling on HIV prevention during pregnancy and were then asked whether they would like to start on PrEP, clarifying that the use of PrEP would not impact their study participation. Study participants interested in starting PrEP had their blood tested to confirm that their baseline creatinine levels (i.e., glomerular filtration rate >60) met clinical eligibility for PrEP. Participants who initiated PrEP were supplied with 1-month Truvada (tenofovir disoproxil fumarate/emtricitabine [TDF-FTC] or 'PrEP').

Follow-up visits were scheduled at 1, 3, and 6 months and were aligned with the women's regular ANC visits until delivery. At 3- and 6-month visits, participants completed brief interviewer-assessed follow-up surveys irrespective of PrEP use and were supplied with additional PrEP prescriptions (for those interested); dried blood spots were also collected for those who reported taking PrEP in the last 30 days during follow-up.

Ethics

The study was approved by the Human Research Ethics Committee at the University of Cape Town (#297/2018) and by the University of California, Los Angeles Institutional Review Board (IRB#18-001622). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Outcomes: PrEP initiation, continuation, and objective persistence

We evaluated PrEP initiation, continuation (1, 3, and 6 months), consistent continuation through 6 months, and objective persistence (3 and 6 months). PrEP initiation was defined as the acceptance and receipt of a PrEP prescription at the baseline visit, which was also their first antenatal care visit. PrEP continuation was defined as receiving a PrEP prescription at each study visit after baseline among those who initiated PrEP at baseline. PrEP continuation through 6 months was defined as attending and receiving a PrEP prescription at all study visits (1, 3, and 6 months) among those who initiated PrEP at baseline compared to those who did not attend or reported discontinuing PrEP. Objective PrEP persistence was measured using erythrocyte intracellular tenofovir-diphosphate (TFV-DP) levels detected by liquid chromatography and mass-spectroscopy, which is a measure of cumulative PrEP adherence over several weeks[21]. We defined objective PrEP persistence as any TFV-DP or 'PrEP' detected in collected dried blood spot (DBS) results at the follow-up study visit (3 and 6 months) among those who initiated PrEP at baseline and of those with DBS collected and analyzed. The DBS were analyzed only for participants that reported taking PrEP in the last 30 days before the study visit. As recommended, we used separate thresholds for those who were pregnant and those who were postpartum. High adherence or daily intake oral PrEP (~7 doses/week) was defined by DBS with TFV-DP ≥600 fmol/punch for pregnant and ≥1000 fmol/punch for postpartum women; moderate adherence (2-6 doses/week) was defined as 200-599 fmol/punch

for pregnant and 400-999 fmol/punch for postpartum women and low adherence (<2 doses/week) was defined as quantifiable but <200 fmol/punch for pregnant and <400 fmol/punch for postpartum women. We then classified them as high, moderate, low, and below the quantifiable TFV-DP concentrations. Due to the low number of women with high TFV-DP (~7 doses/week), this outcome compared those with quantifiable TFV-DP concentrations to those with unquantifiable TFV-DP concentrations.

Exposure: HIV risk score and risk perception

The two primary exposures of this study were baseline HIV risk score and risk perception for HIV. We created a composite baseline risk score based on the number of behavioral HIV risk factors reported (range 0-5), adapted from another study examining HIV risk among AGYW.[14] The HIV risk score is a sum of 5 factors that are scored at 1 point each: condom-less sex, reporting >1 sexual partner, reporting of a primary partner living with HIV or unknown serostatus, laboratory-confirmed STI diagnosis at baseline and hazardous alcohol use (AUDIT-C score≥3) in the year prior to pregnancy. We used this risk score as a continuous variable and created a two-category HIV risk variable (≤1, ≥2) to examine the differences between lower and higher risk scores. We defined risk perception as answering, “no chance”, “low chance”, or “high chance” to the question “How would you describe your chances of getting HIV in the next year?” at baseline.

Covariates

Relevant demographic measures included the highest level of education, socioeconomic status, gravidity, and relationship status, which was collected by an interviewer at each study visit using a survey on REDCap. Clinical characteristics measures included gestational age at the first ANC visit in weeks. Baseline STI diagnosis was determined based on results from a self-collected vaginal swab tested for *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV) (Cepheid Inc., Sunnyvale, CA, USA).

At baseline, participants were asked about their number of sexual acts, condom use at last sex, number of sexual partners in the past 12 months, partner HIV status in the past 12 months, intimate partner violence (IPV) in the past 12 months (WHO IPV scale)[22], and alcohol use in the past 12 months and before finding out about their pregnancy using the Alcohol Use Disorders Identification Test (AUDIT)[23]. Alcohol use was defined as reporting any alcohol use or by a cutoff of AUDIT score ≥3, which was used in our previous study to identify hazardous alcohol use among pregnant women in South Africa.[17] We also reported pregnancy status at 1,3, and 6 months and HIV risk perception and number of sex acts at 3 and 6 months.

Statistical Analysis

For this specific study, we restricted the analytical sample of this study to participants with age 16-24 years at baseline (n=489). First, the baseline characteristics were described overall and stratified by age categories of adolescent girls (16-18) and young women (19-24). We reported the median (interquartile ranges [IQR]) for continuous variables and frequency/percentages for categorical variables. We then compared baseline characteristics by age using student t-tests, chi-squared tests, or Fisher's exact test (when categorical variables had cell counts <10) as appropriate.

We evaluated the PrEP cascade by estimating the cumulative proportion of AGYW who were eligible for PrEP, initiated PrEP, continued PrEP (1, 3, 6 months), and their objective levels of PrEP persistence (3 and 6 months). The cascade was shown as overall, stratified by age categories, and by HIV risk scores. Finally, we ran crude and adjusted logistic regression models to estimate odds ratios for the association between behavioral HIV risk factors and PrEP outcomes using separate models. We reported associated 95% confidence intervals [CI] for each model. In the adjusted analyses, we controlled for maternal age at baseline, gestational age at baseline, and whether the baseline data was collected before or during/after the national COVID-19 lockdowns in South Africa (defined as before/after March 28, 2020).[24] All analyses were performed in SAS version 9.4 (SAS Institute).

Results

Patient Characteristics

Of the 1200 women enrolled in the PrEP-PP study, 489 were AGYW. Specifically,16% (n=79) were aged 16-18 “adolescents” and 84% (n=410) were aged 19-24 years “young women”. Overall, 67% (n=329) were pregnant with their first child and 78% (n=338) were unmarried or not cohabitating with their partner. Adolescent girls were largely unmarried/not cohabitating with a partner (92% vs. 76%, $p<0.01$) than young women.

Clinical Characteristics

The overall median gestational age at first antenatal care visit was 24 weeks (IQR=17-34). The median gestation age at baseline for adolescent girls was later (28 [20-35] weeks) when compared to young women (23 [16-34] weeks, $p=0.03$). Thus, more adolescents attended antenatal care for the first time at over the recommended 14 weeks’ gestation than young women (89% vs. 79%, $p=0.04$). Moreover, almost all the adolescent girls were primigravida compared to the proportion of young women (91% vs. 63%, $p<0.01$). Almost half (48%, n=38) of adolescent girls were diagnosed with an STI at baseline compared to 38% (n=155) of young women. Adolescent girls also had multiple STI co-infections present than young women (19% vs. 9% with multiple STIs, respectively).

Behavioral Risk Factors

Of the 96% (n=472) women sexually active at baseline, the majority (62%, n=294) had condomless sex at baseline and most (81%, n=395) reported having 1 sexual partner. Overall, 65% (n=320) reported having partners who were not living with HIV, 34% (n=166) did not know their partner’s HIV status, and 0.6% (n=3) reported having partners living with HIV at baseline. About 12% of AGYW reported experiencing intimate partner violence in the past 12 months and

over half (55%, n=270) reported alcohol use in the 12 months before pregnancy. Prior to the pregnancy, 34% (n=268) reported hazardous alcohol use (AUDIT-C ≥3).

Compared with adolescent girls, more young women had sex over 5 times per month (19% vs. 36%, *p*=0.40). However, most behavioral risk factors such as condom use during sex (39% vs. 36%, *p*=0.48), multiple sexual partners (18% vs. 20%, *p*=0.71), and composite HIV risk score (63% vs. 63% scoring 2+ on risk score, *p*=0.82) were similar between adolescent girls and young women (all *p*>0.10). More adolescents did not know their partner's HIV serostatus (41% vs. 33%, *p*=0.33) and had less hazardous alcohol use before pregnancy (29% vs. 35%, *p*=0.10) than young women.

PrEP Cascade in Pregnant and Postpartum AGYW

Figure 2.1 displays the HIV PrEP Cascade indicators among pregnant and postpartum AGYW at baseline, 1-, 3-, and 6-month follow-up visits. Of the 83% (405/489) women that initiated PrEP, the percentage of continuation during follow-up was 63% (256/405) at 1 month, 53% (214/405) at 3 months, and 34% (137/405) at 6 months. Adolescent girls and young women had similar PrEP uptake and continuation prevalence across the cascade. About 24% (103/405) consistently attended all visits through 6 months after initiating PrEP (**Table 2.1**) and 11% (34/302) missed either 1- or 3- month visits but restarted on PrEP at 6 months (Data not shown). Among those who restarted on PrEP, most were postpartum at 6 months (76%, n=26). Of those with DBS collected and analyzed, quantifiable TFV-DP was detected among 61% (85/140) at 3 months and 56% (24/43) at 6 months. Disaggregating adherence data further, 7% (n=10) had high adherence (~7 doses/week), 24% (n=34) had medium adherence (~2-5 doses/week), and 29% (n=41) had low adherence (<2 doses/week) and 39% (n=55) had unquantifiable TFV-DP at 3 months. Meanwhile at 6 months, 7% (n=3) had high adherence (~7 doses/week), 26% (n=11) had medium adherence (~2-5 doses/week), and 23% (n=10) had low adherence (<2 doses/week) and 44% (n=19) had unquantifiable TFV-DP.

Most AGYW (97%) were sexually active at baseline and of those who continued on the study, 70% were sexually active at 3 months follow-up and 75% were sexually active at 6 months (**Table 2.2**). At the 3-month visit, 57% (n=122) of AGYW were pregnant and 43% (n=92) were postpartum. A higher proportion of adolescent girls reported being sexually abstinent during postpartum compared to young women (75% vs. 52%, *p*=0.04). However, at 6 months frequency of sexual activity during postpartum was similar AGYW (31% vs. 32%, *p*=0.89). At 3 months, most young women were having sex while pregnant (96%, n=27), but fewer women had sex during postpartum (68%, n=55). Also, more women reported being sexually active while pregnant (73% adolescent girls, 85% young women) than during postpartum (25% adolescent girls, 49% young women). At 3 months, adolescent girls who reported no perceived HIV risk also reported sexual abstinence (56%, n=22); meanwhile, about 57% (n=99) of young girls reported no perceived HIV risk and yet only 30% (n=51) reported sexual abstinence.

Figure 2.2 displays the PrEP cascade indicators among pregnant and postpartum AGYW at baseline, 1-, 3-, and 6-month follow-up visits stratified by their baseline HIV risk score (score ≤1 and ≥2). While the proportion of women that initiated PrEP at baseline were similar (82% vs 82%, *p*=0.79), continuation at 1 (57% vs. 67%, *p*=0.04), 3 (46% vs 57%, *p*=0.03), and 6 (28% vs 37%, *p*=0.08) months were higher among those with greater HIV baseline risk score compared to the lower risk score. However, the proportion of those with any TFV-DP detected in the blood was similar at 3 (60% vs 61%, *p*=0.84) and 6 (60% vs 55%, *p*=0.76) months.

Table 2.3 summarized the associations between HIV risk score, risk perception, and outcomes from the PrEP cascade. AGYW with a higher risk score (score ≥2) had higher odds of PrEP continuation at 1 month (OR,1.54 [95% CI,1.02, 2.34]), 3 months (OR, 1.55 [95% CI, 1.03, 2.32]), 6 months (OR, 1.48 [95% CI, 0.96, 2.29]), and consistently continuing PrEP through 6 months (OR, 2.01 [95% CI, 1.22, 3.31]). Adjusting for maternal age, gestational age at baseline, and whether the baseline data was collected before/after March 28, 2020 (accounting for the

national COVID-19 early pandemic lockdowns), AGYW with a higher risk score had greater adjusted odds of PrEP continuation through 6 months(aOR, 1.91 [95% CI, 1.15, 3.16]). Compared with AGYW that perceived no HIV risk at baseline, those that had a high HIV risk perception had higher odds of PrEP continuation 3 months (OR, 2.22 [95% CI, 1.04, 4.73]) and consistently continuing PrEP through 6 months (OR, 2.38 [95% CI, 1.15, 4.96]). Both associations shifted towards the null after adjustment. However, those who perceived high HIV risk had greater adjusted odds of consistently continuing PrEP through 6 months (aOR 2.13 [95% CI, 1.01, 4.51]) compared to low and no risk even after adjustment.

Compared to those with no STI at baseline, AGYW with a STI diagnosis and treatment at baseline had 1.5 times the adjusted odds of continuing on PrEP at 1 month (STI: aOR, 1.54 [95% CI, 1.01-2.32]) and a similar association was observed at 6 months (STI: aOR, 1.41 [95% CI, 0.92-2.15]) and consistently continuing PrEP through 6 months (STI: aOR, 1.56 [95% CI, 0.99-2.47] **(Supplemental Table 2.3).** Compared with those with no alcohol use at baseline, AGYW that reported alcohol use were at slightly higher odds of PrEP continuation at 1 month (Alcohol use: aOR, 1.41 [95% CI, 0.94-2.12]), 3 months (Alcohol use: aOR, 1.60 [95% CI, 1.07-2.39]), 6 months (Alcohol use: aOR, 1.26 [95% CI, 0.82-1.92]) and consistently continuing on PrEP through 6 months (Alcohol use: aOR, 1.38 [95% CI, 0.87-2.19]). AGYW with a partner living with HIV or unknown serostatus also had slightly higher adjusted odds of consistently continuing PrEP through 6 months compared to those with a partner not living with HIV (HIV+/unknown partner HIV status: aOR, 1.48 [95% CI, 0.93-2.36]).

Discussion

In this cohort study with 489 pregnant and postpartum AGYW, we observed high overall PrEP initiation (>80%). However, continuation in the study rapidly fell with only one-third of those who initiated PrEP retained by 6 months. Meanwhile, among those who discontinued, 11% of AGYW restarted on PrEP by 6 months. PrEP continuation was higher among those with

a greater baseline HIV risk score and a higher perceived risk of HIV. Moreover, we identified important age-specific clinical characteristics between pregnant and postpartum adolescent girls and young women in our study. This study also contributes to the paucity of literature on the PrEP cascades among the pregnant/postpartum AGYW population from health facilities in South Africa.

Clinical characteristics of AGYW at baseline

Most adolescent girls (age <19) attended their first antenatal clinic visit much later at 28 weeks of gestation, which is in the third trimester of pregnancy. This differs from our early paper among the overall PrEP-PP sample with older women, where the median gestation at ANC initiation was 21 weeks (second trimester). Although this timing is still later than the WHO guideline for women to initiate ANC around 12 weeks (first trimester)[25] and 14 weeks of national South African guidelines, it supports previous literature that AGYW access ANC care much later than older women in sub-Saharan Africa.[26] Early timing of ANC initiation is particularly important in HIV prevention efforts as this could impact access to early initiation of PrEP for those at risk, HIV diagnosis, and early treatment of HIV.

Moreover, almost half (48%) of the adolescent girls in our sample were diagnosed with STI at the baseline visit, often with multiple STI co-infections present (19%). STI case management is typically done at a primary care setting and for AGYW, the Southern African HIV Clinicians Society 2022 guideline recommended that STI screening should be conducted at least annually based on risk assessment (ex. multiple sex partners, engagement in transactional sex, sex under the influence of drugs, or STI diagnosis in the past year).[27] Given the late ANC initiation and high STI burden among adolescent girls in our sample, HIV prevention efforts should promote early ANC visits and strengthen interventions to actively test, manage, and treat STIs beyond a primary care setting.[28,29]

PrEP Initiation and Continuation

The prevalence of PrEP initiation in our study was comparable to that of other studies with AGYW in sub-Saharan Africa.[30] Unlike other studies that reported lower PrEP uptake for AGYW[30,31], PrEP uptake in our sample (83%) was similar to the overall PrEP-PP study with older women[18] (84%) and we also did not observe any differences between the age groups of adolescent girls and young women. While PrEP continuation in our sample was low (63% at 1 month, 53% at 3 months, and 34% at 6 months), they were higher than similar studies with AGYW (32% at 1 month and 6% at 3 months) in Kenya.[30] Both studies had oral PrEP-focused projects with PrEP delivered by aligning with health clinics however, our study was comprised of pregnant AGYW that were coming in regularly for their prenatal care, while non-pregnant AGYW may not have had the incentive to return to clinics solely for PrEP.

HIV Risk Score, Risk Perception, and PrEP Continuation

In our analysis, the continuation of PrEP differed by baseline HIV risk score and by self-perceived HIV risk. Risk scores have previously been used to identify those at high risk of HIV acquisition.[32,33] We used a modified risk score to fit the data available in our study and to reflect relevant clinical and behavioral factors (e.g. condomless sex, more than 1 sexual partner, primary partner living with HIV or unknown serostatus, STI diagnosis at baseline and hazardous alcohol use). Despite low overall continuation, we found that those with greater HIV risk had higher odds of consistently continuing PrEP through 6 months. We also found that having a high-risk perception at baseline was correlated with increased odds of consistently continuing PrEP. Although risk scores are objectively calculated on a series of sexual behaviors and risk perception is seemingly subjective, studies have found the concepts overlapping.[34] Hensen et al reported that AGYW made decisions on PrEP based on their HIV risk perception including condom use, number of sexual partners, and married/cohabitating with a partner[34], all of which were used to develop our risk score. Prior studies have also reported that AGYW who initiated

PrEP were motivated by high perceived HIV risk[30]. Use of risk score at baseline may be used to objectively identify those that would benefit the most from HIV prevention methods, like PrEP.

PrEP Persistence (tenofovir levels in dried blood spots)

PrEP persistence, measured using dried blood spots to detect the presence of TFV-DP, was only examined among those who reported PrEP use in the last 30 days and the proportion of those with quantifiable TFV-DP was unsurprisingly low (61% at 3 months and 56% at 6 months). Due to this, a limitation of our adherence data is that this may be under or overreporting the true proportion of women taking oral PrEP. However, similar to other studies, we measured quantifiable versus unquantifiable TFV-DP in our analysis since the number of AGYW with high TFV-DP, consistent with ~7 doses per week, was small (~7% at 3 and 6 months) .[14] We remain concerned that the levels of tenofovir concentrations in our sample were low and inadequate for ample HIV protection even among those reporting recent PrEP use. A strength of our analysis was the use of biomarkers (levels of TFV-DP in the blood) to measure persistence over self-reported adherence, which correlated poorly with each other in our previous study.[19]

Adherence challenges among pregnant/postpartum AGYW

Qualitative assessments among AGYW have described that persisting on PrEP is difficult with dwindling motivations for a preventative pill while healthy citing daily pill burden (size and frequency)[18,35,36] and stigma with taking the pill.[16,35,36] Meanwhile, others indicated the benefits of PrEP citing that they feel safer while on the pill especially with changing risks.[35] In our earlier analysis, we also reported that side effects such as nausea and vomiting may overlap with pregnancy symptoms, which guided PrEP counseling in the clinics.[18] Prior literature has indicated that PrEP adherence may be less among pregnant women due to pregnancy itself and waning could occur during postpartum periods[19], which was also observed among AGYW in our study.

We also recognize that evaluating prevention-effective adherence, which aligns changing HIV risk with PrEP adherence levels, is important in PrEP studies.[14,37,38] Studies have reported that women, including AGYW, may already be starting and stopping PrEP with changing risks.[13] About 11% of AGYW in our sample stopped and restarted on PrEP at 6 months and most (76%) were postpartum. However, we were unable to examine changing sexual risk as those who discontinued PrEP also missed follow-up study visits and therefore, we were unable to obtain changing HIV risk information among those who discontinued the study. However, given that this is a sample of pregnant and postpartum women across different gestational weeks, future studies could examine whether there are patterns in sexual activity (versus abstinence) by gestational weeks and examine prevention-effective adherence to PrEP by gestational timing.

Moreover, implementation of long-acting injectable PrEP (cabotegravir) may improve HIV protection for AGYW given the high interest in PrEP, but notable barriers to sufficient HIV protection due to adherence challenges.[39] Future trials on long-acting PrEP should include pregnant/postpartum populations and adolescent girls and young women so cabotegravir can be widely implemented among those at high risk for HIV.

Limitations

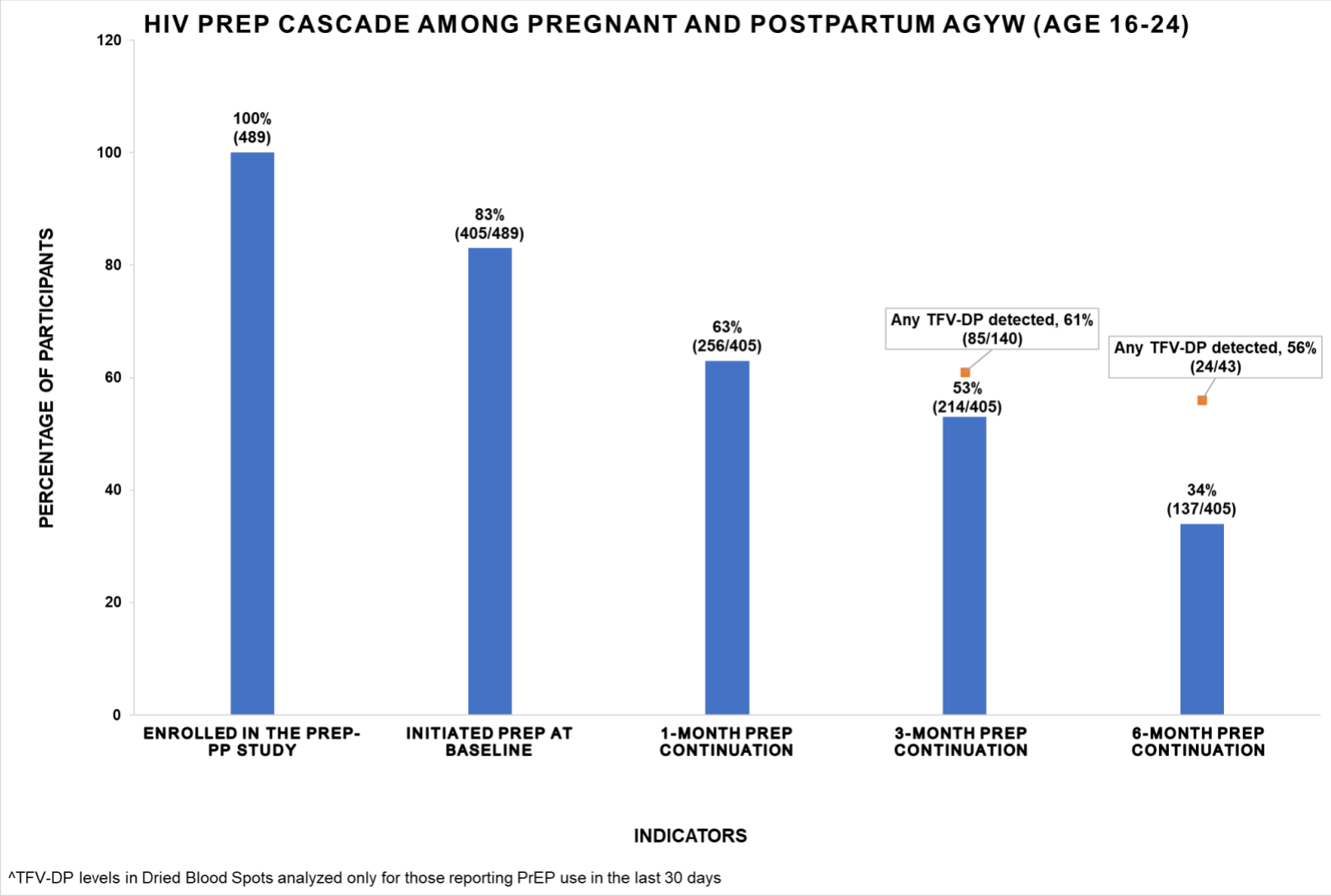
Our study has a few limitations. First, low adherence to PrEP among AGYW could be due to changing HIV risks. Since many of the AGYW are coming into the clinic closer to their child delivery date, they may not be sexually active in late pregnancy or early postpartum. We were unable to examine changing HIV risk due to the collinearity between those who discontinued PrEP and missed study visits. Second, the PrEP-PP study data was collected from one urban ANC clinic in Cape Town, South Africa, it may not be generalizable to other geographical regions or populations. Third, given the surveys were administered by study staff at a health clinic on sensitive information including sexual behaviors, intimate partner violence,

and alcohol use among AGYW, there is potential for reporting errors due to social desirability bias. However, we used biomarkers when feasible, such as for STI diagnosis at baseline and dried blood spots to measure TFV-DP levels.

Conclusion

Using the PrEP cascade for pregnant and postpartum AGYW accessing antenatal care in South Africa, we found high PrEP initiation but retained only one-third of the sample by 6 months. High HIV risk score and high-risk perception were both associated with increased odds of continuing PrEP through 6 months. However, even among AGYW reporting consistent PrEP use, only 56-61% had detectable TFV-DP meaning that PrEP coverage remained inadequate for ample HIV protection. Moreover, AGYW initiated ANC visits much later in pregnancy and with a high burden of untreated STIs. These findings suggest that key barriers exist in HIV prevention efforts for AGYW during pregnancy and postpartum.

Figure 2.1. HIV PrEP Cascade among Pregnant and Postpartum Adolescent Girls and Young Women (Age 16-24) in the PrEP-PP Study (n=489).



^TFV-DP levels in Dried Blood Spots analyzed only for those reporting PrEP use in the last 30 days

Figure 2.2. Baseline HIV Risk Score and HIV PrEP Cascade among Pregnant and Postpartum Adolescent Girls and Young Women (Age 16-24) in the PrEP-PP Study (n=489).

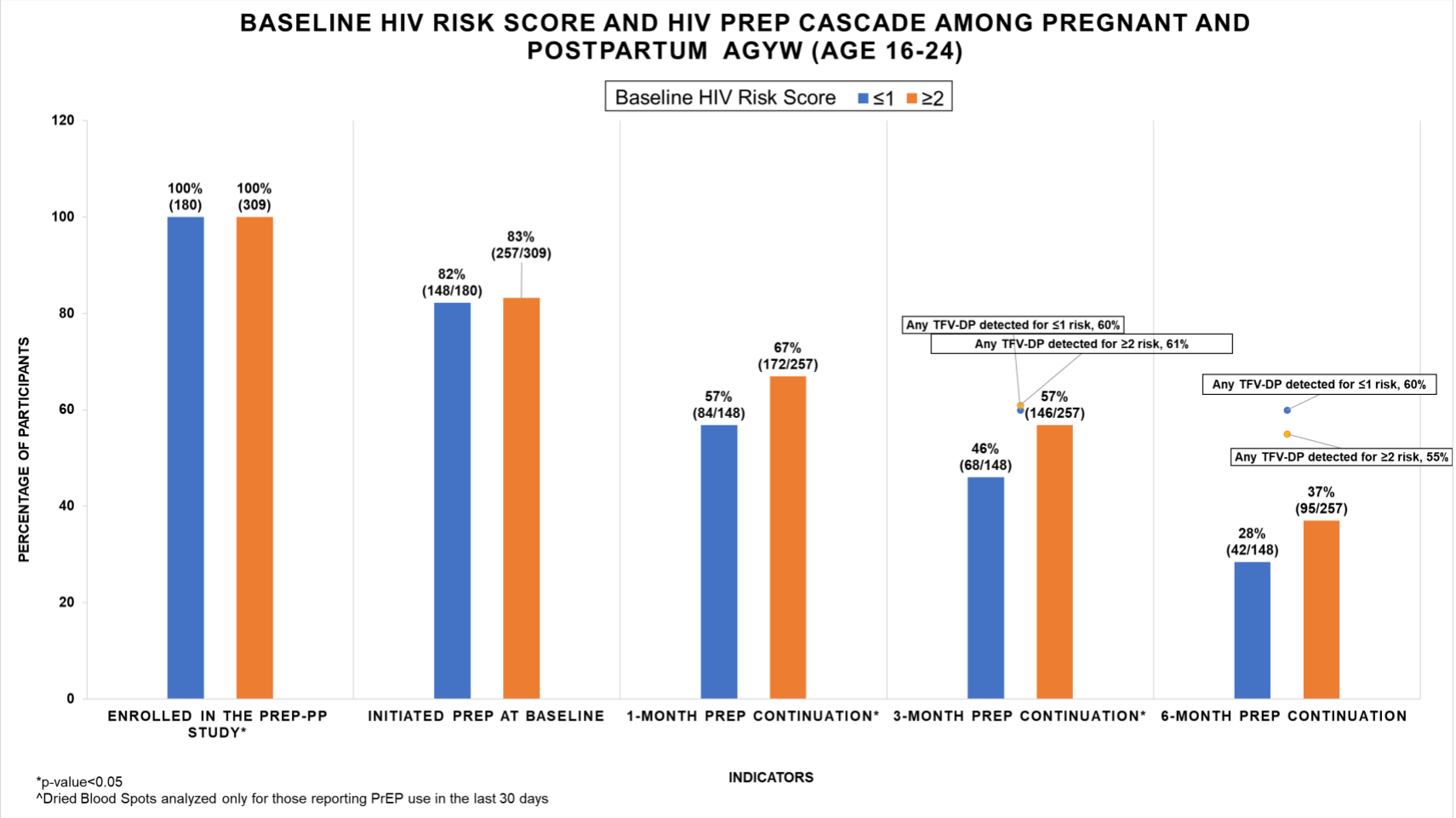


Table 2.1. Baseline characteristics of Pregnant Adolescent Girls and Young Women (aged 16 to 24 years at enrollment) from the PrEP-PP study in Cape Town, South Africa (N = 489).

	Overall	Age 16-18	Age 19-24	P value
	n (%)	n (%)	n (%)	
Total	489 (100.0)	79 (16.2)	410 (83.8)	
Demographics				
Highest Level of Education				
< Grade 12	211 (43.2)	56 (70.9)	155 (37.8)	<.0001
≥ Grade 12	278 (56.9)	23 (29.1)	255 (62.2)	
Socio-economic Status (SES)				
Low SES	161 (32.9)	34 (43.0)	127 (40.0)	0.037
Moderate to high SES	328 (67.1)	45 (57.0)	283 (69.0)	
Gravidity				
Primigravida	329 (67.3)	72 (91.1)	257 (62.7)	<.0001
Multigravida	160 (32.7)	7 (8.9)	153 (37.3)	
Relationship Status				
Married or cohabitating	93 (21.6)	5 (7.7)	88 (24.0)	0.003
Unmarried or not cohabitating	338 (78.4)	60 (92.3)	278 (76.0)	
Clinical Characteristics				
Gestational age at 1st ANC visit in weeks (median, IQR)	24 (17-34)	28 (20-35)	23 (16-34)	0.032
Gestational age at 1st ANC visit in weeks				
≤ 14 weeks	96 (19.6)	9 (11.4)	87 (21.2)	0.044
> 14 weeks	393 (80.4)	70 (88.6)	323 (78.8)	
Any STI Diagnosed (CT, NG and/or TV)				
No STI	296 (60.5)	41 (51.9)	255 (62.2)	0.086
STI diagnosed	193 (39.5)	38 (48.1)	155 (37.8)	
Type of STI diagnosed (CT, NG and/or TV)				
No STI	296 (60.5)	41 (51.9)	255 (62.2)	0.010
CT only	113 (23.1)	19 (24.1)	94 (22.9)	
NG only	13 (2.7)	0 (0.0)	13 (3.2)	
TV only	16 (3.3)	4 (5.1)	12 (2.9)	
CT and NG	30 (6.1)	11 (13.9)	19 (4.6)	
CT and TV	16 (3.3)	2 (2.5)	14 (3.4)	
TV and NG	4 (0.8)	1 (1.3)	3 (0.7)	
CT, NG, and TV	1 (0.20)	1 (1.3)	0 (0.0)	
Behavioral Risk Factors				
Sexually active in pregnancy (at baseline)				
Not Sexually active	17 (3.5)	2 (4.8)	15 (3.4)	0.400

Yes, 1-4 times per month	304 (62.2)	32 (76.2)	272 (60.9)	
Yes, 5+ times per month	168 (34.4)	8 (19.1)	160 (35.8)	
Condom use at last sex (at baseline) *				
Condomless sex	294 (62.3)	44 (55.7)	250 (61.0)	0.480
Condom used	178 (36.4)	31 (39.2)	147 (35.9)	
Number of sexual partners in the past 12 months				
1 sexual partner	395 (80.8)	65 (82.3)	330 (80.5)	0.712
>1 sexual partners	94 (19.2)	14 (17.7)	80 (19.5)	
Partner HIV Status in the past 12 months (at baseline) *				
Do not know	166 (34.0)	32 (40.5)	134 (32.7)	0.334
HIV negative	320 (65.4)	47 (59.5)	273 (66.6)	
HIV positive	3 (0.6)	0 (0.0)	3 (0.7)	
Intimate partner violence (IPV) in the past 12 months**				
No IPV	433 (88.6)	70 (88.6)	363 (88.5)	0.986
Reported IPV	56 (11.5)	9 (11.4)	47 (11.5)	
Alcohol use in the past 12 months before pregnancy				
No Alcohol Use	219 (44.8)	42 (53.2)	177 (43.2)	0.102
Any Alcohol Use	270 (55.2)	37 (46.8)	233 (56.8)	
Hazardous Alcohol Use (AUDIT-C ≥3)	268 (34.4)	23 (29.1)	145 (35.4)	
Baseline HIV Risk*** (Dichotomized)				
No/Low HIV risk (score ≤1)	180 (36.8)	30 (38.0)	150 (26.6)	0.815
Moderate/high HIV risk (score>1)	309 (63.2)	49 (62.0)	260 (63.4)	
Baseline HIV Risk Score***				0.619
0	44 (9.0)	9 (11.4)	35 (8.5)	
1	136 (27.8)	21 (26.6)	115 (28.1)	
2	178 (36.4)	25 (31.7)	153 (37.3)	
3	102 (20.9)	17 (21.5)	85 (20.7)	
4	25 (5.1)	6 (7.6)	19 (4.6)	
5	4 (0.82)	1 (1.3)	3 (0.7)	

Data are n(%) or median (IQR).

Abbreviations. IQR = Interquartile Range; CT =Chlamydia trachomatis. IPV=intimate partner violence, NG =Neisseria gonorrhoeae, PrEP=pre-exposure prophylaxis, STI=sexually transmitted infection, TV=Trichomonas vaginalis, IPV=Intimate Partner Violence
*In women who reported sexual partners

**Participants were considered to have experienced any IPV if they endorsed at least one of four items asking about recent physical, emotional, or sexual violence from a sexual partner

***Defined as reporting at least one of the following at baseline: condomless sex, reporting >1 sexual partner, reporting of a partner living with HIV or unknown partner HIV status, laboratory-confirmed STI diagnosis at baseline, reporting hazardous alcohol use

Table 2.2. The PrEP Cascade Indicators among pregnant and postpartum Adolescent Girls and Young Women (aged 16 to 24 years) from the PrEP-PP study in Cape Town, South Africa (N = 489).

	Overall	Age 16-18	Age 19-24	P value
	n (%)	n (%)	n (%)	
BASELINE				
Total at Baseline	489 (100.0)	79 (16.2)	410 (83.8)	NA
HIV Risk Perception at baseline				
High Chance	42 (8.6)	11 (13.9)	31 (7.6)	0.05
Low Chance	163 (33.3)	19 (24.1)	144 (35.1)	
No Chance	284 (58.1)	49 (62.0)	235 (57.3)	
Sexually active at baseline				
Not Sexually active	17 (3.5)	4 (5.1)	13 (3.2)	0.40
Sexually active	472 (96.5)	75 (94.9)	397 (96.8)	
PrEP initiation at baseline				
Did not initiate PrEP	84 (17.2)	14 (17.7)	70 (17.1)	0.89
Initiated PrEP at baseline	405 (82.8)	65 (82.2)	340 (82.9)	
1 MONTH FOLLOW-UP				
Total at the 1-month follow-up				
Attended and continued PrEP	256 (63.2)	38 (58.5)	218 (64.1)	0.49
Attended and discontinued PrEP	24 (5.9)	3 (4.6)	21 (6.2)	
Missed visit/discontinued PrEP	125 (30.9)	24 (36.9)	101 (29.7)	
Pregnancy Status at 1 month				
Pregnant	217 (84.8)	30 (79.0)	187 (85.8)	0.28
Postpartum	39 (12.2)	8 (21.1)	31 (14.2)	
3 MONTH FOLLOW-UP				
Attended and continued PrEP at 3 months	177 (69.1)	28 (73.7)	149 (68.4)	0.21
Did not attend 3 months and discontinued PrEP	191 (47.2)	26 (40.0)	165 (48.5)	
Total continuing PrEP at 3 months	214 (52.8)	39 (60.0)	175 (51.5)	
Discontinued PrEP at 1 month, re-started at 3 months	37 (9.1)	11 (16.9)	26 (7.7)	
Pregnancy Status at 3 months				
Pregnant	122 (57.0)	15 (38.5)	107 (61.1)	0.01*
Postpartum	92 (43.0)	24 (61.5)	68 (38.9)	
HIV Risk Perception at 3 months				
High Chance	15 (7.0)	5 (12.8)	10 (5.7)	0.26
Low Chance	78 (36.5)	12 (30.8)	66 (37.7)	
No Chance	121 (56.5)	22 (56.4)	99 (56.6)	
Sexually active at 3 months				
Not Sexually active	73 (34.1)	22 (56.4)	51 (29.1)	0.001*
Yes	141 (65.9)	17 (43.6)	124 (70.9)	
Yes, 1-4 times per month	108 (50.5)	13 (33.3)	95 (54.3)	0.01*
Yes, 5+ times per month	33 (15.4)	4 (10.3)	29 (16.6)	
Sexually active during postpartum at 3 months	39 (42.4)	6 (25.0)	33 (48.5)	0.044

Sexually active while pregnant at 3 months	102 (83.6)	11 (73.3)	91 (85.1)	0.268
PrEP persistence at 3 months (30-day self-report)				
High adherence (~7 days)	132 (61.7)	20 (51.3)	112 (64.0)	0.13
Medium adherence (2-6 days)	49 (22.9)	9 (23.1)	40 (22.9)	
Did not adhere to PrEP	33 (15.4)	10 (25.6)	23 (13.1)	
PrEP persistence at 3 months (TFV-DP)				
High adherence (~7 days)	10 (7.1)	1 (3.9)	9 (7.9)	0.79
Medium adherence (2-6 days)	34 (24.3)	8 (30.8)	26 (22.8)	
Low adherence (> BLQ)	41 (29.3)	8 (30.8)	33 (29.0)	
Below the limit of quantification (BLQ)	55 (39.3)	9 (34.6)	46 (40.4)	
PrEP persistence at 3 months (TFV-DP)				
Any TFV-DP detected	85 (60.7)	17 (65.4)	68 (59.7)	0.74
BLQ	55 (39.3)	9 (34.6)	46 (40.4)	
6 MONTH FOLLOW-UP				
Attended and continued PrEP at 6 months	115 (53.7)	25 (64.1)	90 (51.4)	0.15
Did not attend 6 months and discontinued PrEP	268 (66.2)	37 (56.9)	231 (67.9)	
Total continuing PrEP at 6 months	137 (33.8)	28 (43.1)	109 (32.1)	
Discontinued PrEP at 3 months, re-started at 6 months	22 (5.4)	3 (4.6)	19 (5.6)	
Pregnancy Status at 6 months				
Pregnant	30 (21.9)	2 (7.1)	28 (25.7)	0.03*
Postpartum	107 (78.1)	26 (92.9)	81 (74.3)	
HIV Risk Perception at 6 months				
High Chance	3 (2.2)	1 (3.6)	2 (1.8)	0.81
Low Chance	56 (40.9)	12 (42.9)	44 (40.4)	
No Chance	78 (56.9)	15 (53.6)	63 (57.8)	
Sexually active at 6 months				
Not Sexually active	35 (25.6)	8 (28.6)	27 (24.8)	0.68
Yes	102 (74.5)	20 (71.4)	82 (75.2)	
Yes, 1-4 times per month	77 (56.2)	16 (57.1)	61 (56.0)	0.80
Yes, 5+ times per month	25 (18.3)	4 (14.3)	21 (19.3)	
PrEP persistence at 6 months (30-day self-report)				
High adherence (~7 days)	73 (53.3)	16 (57.1)	57 (52.3)	0.89
Medium adherence (2-6 days)	36 (26.3)	7 (25.0)	29 (26.6)	
Did not adhere to PrEP	28 (20.4)	5 (17.9)	23 (21.1)	
PrEP persistence at 6 months (TFV-DP)				
High adherence (~7 days)	3 (7.0)	0 (0.0)	3 (9.1)	1.00
Medium adherence (2-6 days)	11 (25.6)	3 (30.0)	8 (24.2)	
Low adherence (> BLQ)	10 (23.3)	2 (20.0)	8 (24.2)	
BLQ	19 (44.2)	5 (50.0)	14 (42.4)	
PrEP persistence at 6 months (TFV-DP)				

Any TFV-DP detected	24 (55.8)	5 (50.0)	19 (57.6)	0.73
BLQ	19 (44.2)	5 (50.0)	14 (42.4)	

Abbreviations. SD=Standard Deviation; DBS=Dried Blood Spots; BLQ=Below the limit of quantification; TFV-DP=tenofovir disoproxil fumarate/emtricitabine;1M = 1 month, 3M = 3 months, 6M=6 months; *p<0.05

Table 2.3. HIV risk factors, risk perception and outcomes from the PrEP Cascade among pregnant and postpartum Adolescent Girls and Young Women (aged 16 to 24 years) from the PrEP-PP study in Cape Town, South Africa (N = 489).

	PrEP status, Odds Ratio (95% CI)						
	Initiation (Baseline)	**Continuation (1-month)**	**Continuation (3-month)**	**Continuation (6-month)**	**Continued consistently to 6-month visit**	**Any TFV-DP at 3-month**	**Any TFV-DP at 6-month**
Crude							
Baseline HIV Risk Score							
No/Low HIV risk (score ≤1)	Reference						
Moderate/High HIV risk (score ≥2)	1.07 (0.66, 1.74)	**1.54 (1.02, 2.34)**	**1.55 (1.03, 2.32)**	1.48 (0.96, 2.29)	**2.01 (1.22, 3.31)**	1.08 (0.53, 2.20)	0.80 (0.19, 3.37)
Baseline HIV Risk Score (continuous)	1.04 (0.83, 1.30)	1.04 (0.83, 1.30)	**1.29 (1.06, 1.57)**	1.19 (0.99, 1.44)	1.15 (0.94, 1.39)	1.35 (1.09, 1.68)	1.19 (0.88, 1.61)
HIV Risk Perception at baseline							
No Chance	Reference						
Low Chance	0.82 (0.50, 1.36)	1.38 (0.88, 2.15)	1.22 (0.80, 1.87)	1.01 (0.64, 1.59)	0.98 (0.59, 1.61)	1.32 (0.62, 2.79)	2.75 (0.65, 11.62)
High Chance	0.97 (0.41, 2.31)	1.45 (0.68, 3.10)	**2.22 (1.04, 4.73)**	1.98 (0.97, 4.04)	**2.38 (1.15, 4.96)**	0.94 (0.30, 2.95)	0.60 (0.11, 3.21)
Adjusted*							
Baseline HIV Risk Score							
No/Low HIV risk (score ≤1)	Reference						

Moderate/High HIV risk (score ≥2)	1.11 (0.68, 1.82)	**1.50 (0.99, 2.28)**	**1.48 (0.98, 2.23)**	1.40 (0.90, 2.18)	**1.91 (1.15, 3.16)**	1.02 (0.49, 2.13)	1.14 (0.61, 2.11)
Baseline HIV Risk Score (continuous)	1.04 (0.83, 1.31)	1.04 (0.83, 1.31)	**1.28 (1.05, 1.56)**	**1.18 (0.98, 1.43)**	1.13 (0.92, 1.37)	**1.34 (1.08, 1.66)**	1.18 (0.87, 1.60)
HIV Risk Perception at baseline							
No Chance	Reference						
Low Chance	0.85 (0.51, 1.41)	1.39 (0.89, 2.18)	1.23 (0.80, 1.90)	1.03 (0.65, 1.63)	0.99 (0.59, 1.64)	1.39 (0.65, 3.00)	2.41 (0.53, 10.96)
High Chance	1.21 (0.50, 2.92)	1.39 (0.64, 2.99)	**1.96 (0.91, 4.24)**	1.78 (0.86, 3.71)	**2.13 (1.01, 4.51)**	1.12 (0.34, 3.70)	0.45 (0.07, 2.80)

Abbreviations: PrEP, pre-exposure prophylaxis; aOR, adjusted Odds Ratio; TFV-DP=tenofovir disoproxil fumarate/emtricitabine; CT =Chlamydia trachomatis. IPV=intimate partner violence, NG =Neisseria gonorrhoeae, PrEP=pre-exposure prophylaxis, STI=sexually transmitted infection, TV=Trichomonas vaginalis, IPV=Intimate Partner Violence

Bold: statistically significant measures that do not cross the null (1.00).

*adjusted for maternal age, gestational age at baseline, and whether baseline data was collected before or during/after the national COVID-19 pandemic lockdowns in South Africa (defined as before/after March 28, 2020)

**Defined as reporting at least one of the following at baseline: condomless sex, reporting >1 sexual partner, reporting of a partner living with HIV or unknown partner HIV status, laboratory-confirmed STI diagnosis at baseline, reporting hazardous alcohol use

Outcome definitions: a) initiation (baseline) are those who initiated PrEP among those PrEP eligible at baseline visit (n=489); b) continuation at 1, 3, 6 months are those who attended and requested a PrEP prescription among those who initiated PrEP at baseline (n=405); c) continued consistently to 6 months visit are those who attended all study visits (1-,3-, and 6-month follow-up) among those who initiated PrEP at baseline (n=405); d) persisted on PrEP is any TFV-DP detected among those who reported PrEP use in the last 30 days (n=140 at 3 months and n=43 at 6 months).

Supplemental Table 2.1. Clinical and Behavioral Factors by outcomes from the PrEP cascade	
	PrEP status, n (%)

	Overall Sample	Initiation (Baseline)	Continuation (1-month)	Continuation (3-month)	Continuation (6-month)	Continued through 6-month visit	Any TFV-DP at 3-month	Any TFV-DP at 6-month
Attrition across the PrEP Cascade	489 (100.0)	405 (82.8)	256 (63.2)	214 (52.8)	137 (33.8)	103 (24.4)	85 (60.7)	24 (60.0)
Baseline visit before the national COVID-19 lockdown (March 28, 2020)								
Data collected before	144 (29.5)	132 (32.6)	77 (30.1)	59 (27.6)	35 (25.6)	23 (22.3)	35 (41.2)	6 (25.0)
Data collected after	345 (70.6)	273 (67.4)	179 (69.9)	155 (72.4)	102 (74.5)	80 (77.7)	50 (58.8)	18 (75.0)
AGYW age groups								
Adolescent Girls (Age 16-18)	79 (16.2)	65 (82.3)	38 (58.5)	39 (60.0)	28 (43.1)	22 (33.9)	17 (20.0)	5 (20.8)
Young Women (19-24)	410 (83.8)	340 (82.9)	218 (64.1)	175 (51.5)	109 (32.1)	81 (23.8)	68 (80.0)	19 (79.2)
Baseline HIV Risk Score (categorized)								
No/Low HIV risk (score ≤1)	180 (36.8)	148 (82.2)	84 (56.8)	68 (46.0)	42 (28.4)	26 (17.6)	28 (32.9)	6 (25.0)
Moderate/High HIV risk (score ≥2)	309 (63.2)	257 (83.2)	172 (66.9)	146 (56.8)	95 (37.0)	77 (30.0)	57 (67.1)	18 (75.0)

Baseline HIV Risk score, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1.5-3)
Maternal age at baseline, median (IQR)	21 (19-23)	21 (19-23)	21 (19.5-23)	21 (19-23)	21 (19-23)	21 (19-23)	21 (19-23)	21.5 (19-23)
Maternal gestational age at baseline, median (IQR)	24 (17-34)	24 (17-33)	24 (17-32)	24 (17-32)	22 (15-34)	24 (16-33)	23 (17-29)	27 (11.5-37)
Intimate partner violence (IPV) in the past 12 months								
No IPV	433 (88.6)	357 (88.2)	222 (86.7)	183 (85.5)	121 (88.3)	88 (85.4)	71 (83.5)	22 (91.7)
IPV reported	56 (11.5)	48 (11.9)	34 (13.3)	31 (14.5)	16 (11.7)	15 (14.6)	14 (16.5)	2 (8.3)
Baseline STI diagnosis (CT, NG and/or TV)								
No STI	296 (60.5)	243 (60.0)	144 (56.3)	129 (60.3)	75 (54.7)	54 (52.4)	49 (57.7)	12 (50.0)
STI Diagnosed	193 (39.5)	162 (40.0)	112 (43.8)	85 (39.7)	62 (45.3)	49 (47.6)	36 (42.4)	12 (50.0)
Alcohol use in the past 12 months before pregnancy								
No alcohol use	219 (44.8)	182 (44.9)	107 (41.8)	84 (39.3)	56 (40.9)	40 (38.8)	34 (40.0)	9 (37.5)

Alcohol use	270 (55.2)	223 (55.1)	149 (58.2)	130 (60.8)	81 (59.1)	63 (61.2)	51 (60.0)	15 (62.5)
Partner HIV status								
HIV Negative	320 (65.4)	262 (64.7)	164 (64.1)	133 (62.2)	87 (63.5)	60 (58.3)	48 (56.5)	13 (54.2)
Don't Know or HIV Positive	169 (34.6)	143 (35.3)	92 (35.9)	81 (37.9)	50 (36.5)	43 (41.8)	37 (43.5)	11 (45.8)
Number of sexual partners								
1 partner	395 (80.8)	327 (80.7)	202 (78.9)	167 (78.0)	113 (82.5)	84 (81.6)	65 (76.5)	18 (75.0)
>1 partners	94 (19.2)	78 (19.3)	54 (21.1)	47 (22.0)	24 (17.5)	19 (18.5)	20 (23.5)	6 (25.0)
Condom Use								
No	294 (62.3)	239 (61.1)	150 (61.0)	118 (57.8)	79 (61.2)	63 (65.6)	49 (62.0)	14 (63.6)
Yes	178 (37.7)	152 (38.9)	96 (39.0)	86 (42.2)	50 (38.8)	33 (34.4)	30 (38.0)	8 (36.4)
HIV Risk perception at baseline								
No chance	284 (58.1)	238 (58.8)	143 (55.9)	118 (55.1)	77 (56.2)	57 (55.3)	47 (55.3)	10 (41.7
Low chance	163 (33.3)	132 (32.6)	89 (34.8)	72 (33.6)	43 (31.4)	31 (30.1)	30 (35.3)	11 (45.8)
High chance	42 (8.6)	35 (8.6)	24 (9.4)	24 (11.2)	17 (12.4)	15 (14.6)	8 (9.4)	3 (12.5)
Sexually active at baseline								
Not sexually active	17 (3.5)	14 (3.5)	10 (3.9)	10 (4.7)	8 (5.8)	7 (6.8)	6 (7.1)	2 (8.3)
1-4x per month	304 (62.2)	254 (62.7)	155 (60.6)	135 (63.1)	83 (60.6)	61 (59.2)	51 (60.0)	13 (54.2)

>5x per month	168 (34.4)	137 (33.8)	91 (35.6)	69 (32.2)	46 (33.6)	35 (34.0)	28 (32.9)	9 (37.5)

Abbreviations: IPV=Intimate Partner Violence; TFV-DP=tenofovir disoproxil fumarate/emtricitabine; IQR=interquartile range; CT =Chlamydia trachomatis. IPV=intimate partner violence, NG =Neisseria gonorrhoeae, PrEP=pre-exposure prophylaxis, STI=sexually transmitted infection, TV=Trichomonas vaginalis

*NA due to zero cells in the stratum; Data presented as n(%) and median (IQR) reported.

Outcome definitions: a) initiation (baseline) are those who initiated PrEP among those PrEP eligible at baseline visit (n=489); b) continuation at 1, 3, 6 months are those who attended and requested a PrEP prescription among those who initiated PrEP at baseline (n=405); c) continued consistently to 6 months visit are those who attended all study visits (1-,3-, and 6-month follow-up) among those who initiated PrEP at baseline (n=405); d) persisted on PrEP is any TFV-DP detected among those who reported PrEP use in the last 30 days (n=140 at 3 months and n=43 at 6 months).

Supplemental Table 2.2. Clinical and Behavioral Factors associated with outcomes from the PrEP cascade, unadjusted analysis

	PrEP status, Crude Odds Ratio (95% CI)						
	Initiation (Baseline)	**Continuation (1-month)**	**Continuation (3-month)**	**Continuation (6-month)**	**Continued through 6-month visit**	**Any TFV-DP at 3-month**	**Any TFV-DP at 6-month**
Baseline Data Collected prior to national COVID-19 lockdown (March 28, 2020)							
Yes	Reference						
No, data collected after March 28, 2020	0.35 (0.18, 0.66)	1.36 (0.89, 2.08)	**1.63 (1.07, 2.47)**	1**.65 (1.05, 2.61)**	**1.96 (1.17, 3.30)**	0.64 (0.31, 1.31)	0.80 (0.19, 3.37)
Age Groups							
Adolescent Girls (Age 16-18)	Reference						

Young Women (19-24)	1.05 (0.56, 1.97)	1.27 (0.74, 2.18)	0.71 (0.41, 1.21)	0.62 (0.36, 1.07)	0.61 (0.35, 1.08)	0.78 (0.32, 1.91)	1.36 (0.33, 5.61)
Maternal age at baseline	1.04 (0.94, 1.16)	0.99 (0.90, 1.08)	0.94 (0.86, 1.03)	0.91 (0.83, 0.99)	0.90 (0.82, 1.00)	0.91 (0.79, 1.06)	1.10 (0.86, 1.42)
Maternal gestational age at baseline	1.01 (0.99, 1.04)	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)	0.99 (0.96, 1.01)	0.99 (0.96, 1.01)	1.00 (0.97,1.04)	1.01 (0.96, 1.06)
IPV in the past 12 months							
No IPV	Reference						
IPV reported	1.28 (0.58, 2.81)	1.48 (0.77, 2.85)	1.73 (0.93, 3.25)	0.98 (0.52, 1.85)	1.39 (0.72, 2.68)	0.89 (0.36, 2.17)	0.26 (0.04, 1.49)
Baseline STI diagnosis (CT, NG and/or TV)							
No STI	Reference						
STI Diagnosed	1.14 (0.70, 1.85)	**1.54 (1.01, 2.34)**	0.98 (0.66, 1.45)	1.39 (0.92, 2.11)	1.52 (0.97, 2.38)	1.02 (0.51, 2.03)	0.58 (0.17, 1.99)
Alcohol use in the past 12 months before pregnancy							
No alcohol use	Reference						
Alcohol use	0.97 (0.60, 1.55)	1.41 (0.94, 2.12)	**1.63 (1.10, 2.42)**	1.28 (0.85, 1.95)	1.40 (0.89, 2.21)	0.93 (0.46, 1.86)	0.60 (0.16, 2.21)
Partner HIV status							
HIV Negative	Reference						
Don't Know or HIV Positive	1.22 (0.73, 2.02)	1.08 (0.71,1.65)	1.27 (0.84, 1.91)	1.08 (0.70, 1.66)	1.45 (0.92, 2.29)	1.46 (0.72, 2.95)	0.94 (0.28, 3.14)

Number of sexual partners							
1 partner	Reference						
>1 partners	1.01 (0.56, 1.84)	1.39 (0.82, 2.34)	1.45 (0.88, 2.40)	0.84 (0.49, 1.43)	0.93 (0.53, 1.65)	1.39 (0.59, 3.24)	1.78 (0.38, 8.30)
Condom use in last sex							
No	Reference						
Yes	1.35 (0.81, 2.24)	1.02 (0.67, 1.55)	1.34 (0.89, 2.01)	0.99 (0.64, 1.53)	0.78 (0.48, 1.25)	0.71 (0.35, 1.45)	0.57 (0.16, 2.03)
Sexually active at baseline							
Not sexually active	Reference						
1-4 times per month	1.09 (0.30, 3.93)	0.63 (0.19, 2.05)	0.45 (0.14, 1.49)	0.36 (0.12, 1.08)	0.32 (0.11, 0.94)	0.73 (0.17, 3.11)	0.59 (0.05, 7.43)
>5 times per month	0.95 (0.26, 3.50)	0.79 (0.24, 2.66)	0.41 (0.12, 1.36)	0.38 (0.12, 1.16)	0.34 (0.11, 1.05)	0.82 (0.18, 3.73)	0.64 (0.05, 8.62)

Abbreviations: IPV=Intimate Partner Violence; TFV-DP=tenofovir disoproxil fumarate/emtricitabine; IQR=interquartile range; CT =Chlamydia trachomatis. IPV=intimate partner violence, NG =Neisseria gonorrhoeae, PrEP=pre-exposure prophylaxis, STI=sexually transmitted infection, TV=Trichomonas vaginalis

*NA due to zero cells in the stratum; Data presented as n(%) and median (IQR) reported.

Bold: statistically significant measures that do not cross the null (1.00).

Outcome definitions: a) initiation (baseline) are those who initiated PrEP among those PrEP eligible at baseline visit (n=489); b) continuation at 1, 3, 6 months are those who attended and requested a PrEP prescription among those who initiated PrEP at baseline (n=405); c) continued consistently to 6 months visit are those who attended all study visits (1-,3-, and 6-month follow-up) among those who initiated PrEP at baseline (n=405); d) persisted on PrEP is any TFV-DP detected among those who reported PrEP use in the last 30 days (n=140 at 3 months and n=43 at 6 months).

Supplemental Table 2.3. Clinical and Behavioral Factors associated with outcomes from the PrEP cascade, adjusted analysis							
	PrEP status, Adjusted Odds Ratio (95% CI)						
	Initiation (Baseline)	**Continuation (1-month)**	**Continuation (3-month)**	**Continuation (6-month)**	**Continued through 6-month visit**	**Any TFV-DP at 3-month**	**Any TFV-DP at 6-month**
IPV in the past 12 months (prior to baseline)							
No IPV	Reference						
IPV reported	1.31 (0.60, 2.92)	1.48 (0.77, 2.85)	1.70 (0.90, 3.19)	0.95 (0.50, 1.81)	1.36 (0.71, 2.65)	0.88 (0.36, 2.18)	0.25 (0.04, 1.52)
STI in the past 12 months							
No STI	Reference						
STI diagnosed	1.10 (0.68, 1.80)	**1.54 (1.01, 2.32)**	0.98 (0.62, 1.46)	1.41 (0.92, 2.15)	1.56 (0.99, 2.47)	1.06 (0.53, 2.14)	0.54 (0.15, 1.96)
Alcohol use in the past 12 months before pregnancy							
No alcohol use	Reference						
Alcohol use	0.99 (0.61, 1.61)	1.41 (0.94, 2.12)	**1.60 (1.07, 2.39)**	1.26 (0.82, 1.92)	1.38 (0.87, 2.19)	0.87 (0.43, 1.77)	0.61 (0.16, 2.28)
Partner HIV status							
HIV Negative	Reference						
Don't Know/HIV Positive	1.23 (0.74, 2.05)	1.08 (0.71, 1.65)	1.29 (0.85, 1.95)	1.10 (0.71, 1.69)	1.48 (0.93, 2.36)	1.41 (0.69, 2.86)	0.97 (0.28, 3.35)
Number of sexual partners							

1 partner	Reference						
>1 partners	0.99 (0.54, 1.83)	1.39 (0.82, 2.37)	1.47 (0.88, 2.44)	0.84 (0.49, 1.44)	0.94 (0.53, 1.69)	1.40 (0.59, 3.32)	1.93 (0.39, 9.59)
Condom use in last sex							
No	Reference						
Yes	1.25 (0.75, 2.10)	1.02 (0.67, 1.55)	1.41 (0.93, 2.14)	1.04 (0.67, 1.61)	0.81 (0.50, 1.33)	0.68 (0.33, 1.40)	0.55 (0.14, 2.06)
Sexually active at baseline							
Not sexually active	Reference						
1-4x per month	1.04 (0.28, 3.79)	0.63 (0.19, 2.01)	0.45 (0.14, 1.48)	0.36 (0.12, 1.09)	0.32 (0.11, 0.95)	0.64 (0.14, 2.81)	0.54 (0.04, 7.04)
>5x per month	0.90 (0.24, 3.40)	0.79 (0.24, 2.66)	0.39 (0.12, 1.32)	0.37 (0.12, 1.14)	0.34 (0.11, 1.05)	0.74 (0.15, 3.34)	0.63 (0.05, 8.67)

Abbreviations: PrEP, pre-exposure prophylaxis; aOR, adjusted Odds Ratio; TFV-DP=tenofovir disoproxil fumarate/emtricitabine; CT =Chlamydia trachomatis. IPV=intimate partner violence, NG =Neisseria gonorrhoeae, PrEP=pre-exposure prophylaxis, STI=sexually transmitted infection, TV=Trichomonas vaginalis, IPV=Intimate Partner Violence

Bold: statistically significant measures that do not cross the null (1.00).

*adjusted for maternal age, gestational age at baseline, and whether baseline data was collected before or during/after the national COVID-19 pandemic lockdowns in South Africa (defined as before/after March 28, 2020)

**Defined as reporting at least one of the following at baseline: condomless sex, reporting >1 sexual partner, reporting of a partner living with HIV or unknown partner HIV status, laboratory-confirmed STI diagnosis at baseline, reporting hazardous alcohol use

Outcome definitions: a) initiation (baseline) are those who initiated PrEP among those PrEP eligible at baseline visit (n=489); b) continuation at 1, 3, 6 months are those who attended and requested a PrEP prescription among those who initiated PrEP at baseline (n=405); c) continued consistently to 6 months visit are those who attended all study visits (1-,3-, and 6-month follow-up) among those who initiated PrEP at baseline (n=405); d) persisted on PrEP is any TFV-DP detected among those who reported PrEP use in the last 30 days (n=140 at 3 months and n=43 at 6 months).

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Chapter III. Study 2: Higher HIV Pre-exposure Prophylaxis continuation and adherence among pregnant and postpartum women reporting Intimate Partner Violence

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Abstract

Background: Pregnant and postpartum women experiencing intimate partner violence (IPV) may have an elevated risk for HIV acquisition. Effective use of oral pre-exposure prophylaxis (PrEP, TDF-FTC) can prevent HIV. In this study, we evaluated if experiencing IPV was associated with PrEP continuation and adherence during the pregnancy and postpartum period.

Methods: We analyzed data from 1200 women enrolled in the PrEP in pregnancy and postpartum (PrEP-PP) cohort study in Cape Town, South Africa. The exposure variable was reporting any past-year or recent IPV victimization, including emotional, sexual, or physical violence. The outcome measures included PrEP discontinuation, self-reported adherence based on missed pills in the last 30 days, and objective adherence measured by tenofovir diphosphate (TFV-DP) levels in dried blood spots (DBS). To examine the relationship between IPV and PrEP discontinuation, we used a Kaplan-Meier curve to plot time to discontinuation and Cox proportional hazards models to estimate adjusted hazard ratios. We used two cut-offs for PrEP adherence: any detectable TFV-DP (vs. unquantifiable TFV-DP) or moderate/high adherence (vs. low/none), consistent with ≥2 doses/week or <2 doses/week. To assess the association between IPV and PrEP adherence (self-reported and objective), we used logistic regression models adjusting for covariates.

Results: At baseline, 12% of women reported IPV victimization. By 6 months, the proportion of women with IPV experiences in the past 3-months had increased to 15%, with emotional violence being the most common type (13%), followed by physical violence (8%), and both physical and emotional violence (7%). We observed a lower rate of PrEP discontinuation among women who experienced past-year IPV, with an adjusted hazard ratio (aHR) of 0.80 (95% CI: 0.61, 1.06) after adjusting for maternal age, gestational age, cohabitation status, education, and COVID-19 pandemic lockdowns. Furthermore, women with past-year IPV had higher odds of quantifiable TFV-DP in their DBS at both 3- and 6-month follow-up visits, with an adjusted odds

ratio (aOR) of 1.53 (95% CI: 1.00, 2.34) at 3-months and aOR=1.82 (95% CI: 1.02, 3.25) at 6-months after adjusting for the same potential confounders.

Conclusion: Past-year IPV was associated with lower time-to-oral PrEP discontinuation and increased odds of moderate/high levels of TDF-DP in DBS. These findings underscore the importance of violence screening, referrals to counseling services that may address IPV, and HIV prevention counseling, including promotion of oral PrEP, in antenatal clinics.

Introduction

Intimate partner violence (IPV) is defined as any physical, psychological, or sexual harm by a current or former intimate partner.[1] About 27%(19-37%) of women in southern sub-Saharan Africa have experienced IPV in their lifetime and 14%(9-22%) in the past-year.[2] The annual mortality rate from IPV was 8.8 per 100,000 women and half of all female homicides were by their intimate partners.[3]

IPV is associated with an elevated HIV risk, especially during pregnancy, and has a bi-directional relationship.[1,4-7] About 25% of all HIV infections in women were due to IPV and partner controlling behaviors.[8] IPV during pregnancy has been associated with risky sexual behaviors and is more prevalent among younger women and those experiencing poverty.[4] Individuals experiencing IPV may face increased vulnerability to HIV including hesitations about discussing safer sex practices, such as condom use, for fear of violence or retaliation.[4] Additionally, women who test positive for HIV during pregnancy may experience increased abuse and violence.[4] Those perpetuating partner violence are more likely to have multiple sexual partners and engage in unprotected sex, which increases the risk of HIV transmission.[9] Women experiencing IPV also face greater gender inequity in their relationships and have a higher incidence of HIV.[10] In 2021, there were 22,000 new HIV infections that occurred during pregnancy or breastfeeding periods in eastern and southern Africa.[11] The incidence rate of HIV during pregnancy and postpartum in sub-Saharan Africa was 3.6 per 100 person-years (95% CI: 1.2 to 11.1) [9], meeting the UNAIDS threshold for substantial HIV risk.[11] Preventing HIV acquisition during pregnancy and postpartum periods is crucial not only for maternal health but also for eliminating vertical HIV transmission.[7]

Oral pre-exposure prophylaxis (PrEP, tenofovir disoproxil fumarate and emtricitabine [TDF-FTC]) is an important biomedical method for preventing HIV. It is a user-controlled strategy that can be taken discreetly during periods of sexual activity and doesn't require partner cooperation.[12] The South African National Department of Health supports use of daily oral PrEP

as part of a comprehensive combination prevention strategy for pregnant and breastfeeding women at substantial risk of HIV.[12] The relationship between IPV and PrEP are conflicting; while one study reported PrEP acceptability was lower among women with a history of IPV, another study reported younger women experiencing IPV were more likely to use PrEP.[13] We previously reported that 12% of women experienced emotional, physical, or sexual IPV in the past 12 months and it was correlated with PrEP initiation.[14] Adherence challenges among pregnant and postpartum women is well documented[15], but little is known about how IPV victimization affects PrEP continuation and adherence.[16]

This study extends what we know about relationship between how past-year and recent IPV victimization affects PrEP discontinuation and adherence among pregnant and postpartum women.

Methods

Study Population

We used data from the 1,200 women enrolled in the PrEP in Pregnancy and Postpartum (PrEP-PP) study, a prospective cohort based in Cape Town, South Africa. The study's methodology has been described in detail elsewhere.[14] Briefly, women aged 16 years or older were recruited from a public health clinic during their antenatal visit between August 2019 and October 2021. Participants were followed up for 12 months postpartum, with visits scheduled at 1, 3, and 6-months after baseline. Eligibility for the study required a written informed consent in English or the local language (isiXhosa) and confirmed to be pregnant, HIV-negative (confirmed by a 4th generation rapid HIV antigen/antibody test from Abbott laboratories), and Hepatitis-B surface antigen-negative (confirmed by a rapid hepatitis B surface antigen test from Abbott Laboratories). The purpose of this analysis was to investigate how past-year IPV at baseline and IPV in the past 3 months reported during follow-up study visits affects continuation and adherence to PrEP among pregnant and postpartum women in an antenatal care setting.

Enrollment and Measurements

At enrollment, study staff administered a baseline survey collecting participant's demographic information, clinical characteristics, and behavioral HIV risk factors using REDCap, a secure web-based application. Point-of-care testing for sexually transmitted infections (STI) was subsequently performed, and participants with positive test results were treated in compliance with South African national STI Guidelines.[17] Participants received counseling on HIV prevention during pregnancy and were then were offered PrEP. Decision on whether to use PrEP did not impede participants' involvement in the study.

At 3- and 6-month visits, participants completed brief follow-up surveys irrespective of PrEP use and were supplied with additional PrEP prescriptions (for those interested). We also collected dried blood spots (DBS) for those who reported taking PrEP in the last 30 days during follow-up.

Ethics

The study was approved by the Human Research Ethics Committee at the University of Cape Town (#297/2018) and by the University of California, Los Angeles Institutional Review Board (IRB#18-001622).

Outcomes

We evaluated PrEP discontinuation and adherence among women that initiated PrEP at baseline. Discontinuation was defined as not returning to the study or did not refill PrEP when they returned among those who initiated PrEP at the baseline visit.

Cumulative adherence on PrEP (use in the past 30 days) was defined by TFV-DP levels in DBS using a validated liquid chromatography-tandem mass spectrometry assay at the Division of Clinical Pharmacology, University of Cape Town.[18] DBS were analyzed only for participants that reported taking PrEP in the last 30 days before the study visit. As recommended[18], we used separate thresholds for those who were pregnant and postpartum. High adherence or daily intake oral PrEP (~7 doses/week) was defined by DBS with TFV-DP≥600 fmol/punch for

pregnant and ≥1000 fmol/punch for postpartum women; moderate adherence (2-6 doses/week) was 200-599 fmol/punch for pregnant and 400-999 fmol/punch for postpartum women; low adherence (<2 doses/week) was quantifiable but <200 fmol/punch for pregnant and <400 fmol/punch for postpartum women and no adherence was defined as DBS was analyzed but they had unquantifiable TFV-DP concentrations. We then classified them as high, moderate, low, and below the quantifiable TFV-DP concentrations. We used two cut-offs: any TFV-DP present (yes/no) or moderate/high adherence (consistent with ≥2 doses/week vs. <2 doses/week). Those who discontinued PrEP were categorized as "not adherent".

Self-reported PrEP adherence was measured by PrEP intake in the last 30 days at the 3- and 6-month follow-up visits. Poor adherence was defined as missing ≥5 doses in the last 30 days. We divided the number of doses taken by 4 to obtain number of doses per week. We categorized the doses into high adherence as 7 doses/week, moderate adherence as 2-6 doses/week, low adherence as <2 doses/week, and no adherence as 0 doses/week. Then, we confirmed self-reported adherence using biomarker (TFV-DP levels) if available. The reference group was those who discontinued PrEP and those with poor adherence using information from self-report and objective measures.

Exposures

We assessed IPV using a validated questionnaire from the *13-item WHO Violence Against Women Modules.*[19-21] Study staff asked participants about physical, emotional, and sexual IPV using questions in **Table 3.1** at baseline and during follow-up visits. IPV was defined as reporting "yes" to any of the physical, sexual, or emotional IPV questions by current sexual partner in the past year at baseline or in the last 3 months during follow-up. We also examined severity of IPV (moderate and severe).[22]

Covariates

We collected information on potential confounders and mediators **(Supplemental Figure 3.1),** including age(continuous), education attainment, socioeconomic status, relationship/cohabitation status, gravidity, depression (Edinburgh Perinatal Depression Scale, cut-off of ≥11 for probable depression).[23] Baseline STI diagnosis was determined based on results from a self-collected vaginal swab tested for *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Trichomonas vaginalis* (TV) (Cepheid Inc., Sunnyvale, CA,USA). We also described IPV by behavioral risk factors for HIV, including number of sexual acts, condom use at last sex, number of sexual partners in the past 12 months, partner HIV status in the past 12 months and alcohol use prior to pregnancy. Hazardous alcohol use in the 12 months before pregnancy was defined by the Alcohol Use Disorders Identification Test-Consumption with a cutoff of AUDIT-C≥3, previously used among pregnant women in South Africa.[24]

Statistical Analysis

We described baseline characteristics stratified by past-year IPV. Then, we estimated proportion of IPV at baseline and the incidence of IPV and types during 3 and 6-months. We also reported self-reported adherence (confirmed by TFP-DP levels, if available) and objective adherence (TFV-DP in DBS) stratified by past-year IPV. We presented the median (interquartile ranges [IQR]) for continuous variables and frequency/percentages for categorical variables. We then compared baseline characteristics by IPV using student t-tests, chi-squared tests, or Fisher's exact test (when categorical variables had cell counts <5) as appropriate.

Then, we estimated the cumulative proportion of women who discontinued PrEP using a Kaplan-Meier estimator. We limited the analysis to those who initiated PrEP at baseline and calculated follow-up times as difference in months between the date of PrEP and the last follow-up date as participants returned at 1, 3, and 6-months for their prescriptions to continue PrEP. Cox proportional hazard models were used to estimate crude and adjusted hazard ratios(HRs) with 95% CI to examine the associations between IPV at baseline (vs. no IPV) and

discontinuing PrEP. We adjusted for maternal age at baseline, gestational age, and for the national COVID-19 lockdowns that occurred during our study recruitment (before/after March 28, 2020). We censored those who experienced a pregnancy loss/miscarriage, seroconverted to HIV positive, or participants continuing PrEP at 6 months after baseline. We assumed proportional hazards and confirmed that the hazard functions did not cross. The hazard ratios estimate the average impact of any past-year IPV.

Finally, we ran crude and adjusted logistic regression models to estimate odds ratios and 95% confidence intervals [CI] for the association between IPV (past year, by types, reported at follow-up) and adherence to PrEP at 3 and 6 months using separate models. In the adjusted analyses, we controlled for potential confounders as earlier and maternal education, gestational age at baseline, relationship status (cohabitating/married vs not cohabitating/unmarried).[25] All analyses were performed in SAS version 9.4 (SAS Institute).

Results

Of the 1200 women enrolled in the PrEP-PP study, 84%(n=1013) initiated PrEP, with a median gestational age of 21 weeks (IQR=15-31 weeks) at the first ANC visit. **Table 3.2** displays the baseline characteristics of women by past-year IPV victimization. At baseline,12% of pregnant women (n=147) reported physical, emotional, or sexual past-year IPV. Overall, 11% of adolescent and young (16-24 years old) pregnant women (n=56) and 13% (n=91) among older women (age >24 years) were affected by IPV (Not shown). Higher proportion of those with lower socioeconomic status (31% without IPV vs. 42% with IPV, p<0.01) and multigravida (65% without IPV vs. 77% with IPV, p<0.01) experienced past-year IPV. Women experiencing IPV had a higher proportion of condomless sex (68% without IPV vs. 79% with IPV, p=0.01) and more than one sexual partner (15% without IPV vs. 23% with IPV, p=0.02). Furthermore, IPV experiences were higher among women with a higher self-perception of HIV risk (10% without IPV vs. 24% with IPV, p<0.01), recent depression (6% without IPV vs. 17% with IPV, p<0.01), and hazardous alcohol use prior to pregnancy (31% without IPV. vs. 50% with IPV, p<0.01).

By 6 months, 15% of women reported IPV victimization (n=174) **(Figure 3.2).** The most common experiences of IPV included emotional violence (13%, n=155), followed by physical violence (8%, n=96), and sexual violence (2%, n=19). Almost 7% (n=79) reported both physical and emotional IPV **(Supplemental Table 3.1).** Moderate violence was experienced by 4% (n=43) and severe violence by 5% (n=55). Responses to the 13-item WHO modules were reported in **Supplemental Figure 3.2**.

More women who had quantifiable levels of PrEP (TFV-DP) in their DBS experienced IPV in the past year (18%) than those without quantifiable levels of PrEP (12%) during the 3-month visit (p=0.04) **(Table 3.3).** Similarly, at the 6-month visit, women with quantifiable PrEP were more likely to experience IPV (22%) than those with unquantifiable PrEP (13%) (p=0.02).

IPV and PrEP discontinuation

Figure 3.3 displays a Kaplan-Meier plot showing PrEP discontinuation by past-year IPV at baseline. This plot indicates that those who did not experience IPV had higher rates of PrEP discontinuation than those who experienced IPV. The crude HR for women with past-year IPV versus those without IPV, with a 7-month follow-up period, was 0.79 (95% CI=0.61, 1.02) **(Table 3.4).** Adjusting for potential confounders minimally changed the findings (aHR=0.80 (95% CI =0.61, 1.06). Although not statistically significant, the hazard of PrEP discontinuation was lower among women who experienced IPV across age groups and gestational age at baseline (**Supplemental Table 3.2)**.

IPV and PrEP adherence and continuation

Table 3.5 reports the odds ratios between past-year IPV and PrEP adherence at 3- and 6-month visits among women who initiated PrEP at baseline. The odds of quantifiable PrEP (TDF-DP levels) were higher among those who experienced past-year IPV than those who did not (3-months: OR=1.57 [95% CI: 1.03, 2.41]; 6-months: OR=1.99 [95% CI: 1.13, 3.53]). The relationship between IPV and PrEP shifted towards null after adjustment, but the direction of association remained the same (3-months: aOR=1.53 [95% CI: 1.00, 2.34]; 6-months:

aOR=1.82 [95% CI: 1.02, 3.25]). Although statistically nonsignificant, the odds of moderate/high PrEP adherence were greater among those who experienced past-year IPV than those who did not (3-months: OR=1.57 [95% CI: 0.93, 2.65]; 6-months: OR=2.33 [95% CI: 1.10, 4.93]). After adjustment, the relationship is similar but shifted slightly towards the null (3-months: aOR=1.50 [95% CI: 0.89, 2.55]; 6-months: aOR=2.11 [95% CI: 0.98, 4.54]). While the estimates were similar when using missed PrEP doses than TFV-DP levels to measure PrEP, the values shifted closer to the null.

We analyzed recent IPV, measured as experiences in the 3 months before follow-up. We found increased odds of PrEP continuation (missed PrEP doses) among those with recent IPV than those who did not (**Supplemental Table 3.3)**. However, we did not observe a relationship between recent IPV and moderate/high adherence at 3- or 6-months. The sample sizes for objective adherence were too low to model. Moreover, we observed greater crude and adjusted odds of quantifiable PrEP (TDF-DP levels) among those who experienced emotional past-year IPV than those who did not (3-months: aOR=1.47 [95% CI: 0.94, 2.29]; 6-months: aOR=2.09 [95% CI: 1.13, 3.67]) (**Supplemental Table 3.4).** We did not observe this relationship with physical past-year IPV and the sample sizes for sexual IPV were too small to model.

Discussion

This study examined the relationship between experiencing IPV and PrEP use among pregnant and postpartum women enrolled in a cohort study at an antenatal clinic in Cape Town, South Africa. We found that women who experienced past-year IPV had a lower rate of discontinuing PrEP. Moreover, IPV was associated with a greater odds of moderate/high PrEP adherence (TFV-DP levels in DBS) at both 3- and 6-month follow-up visits. Women with past-year IPV victimization had a higher proportion of modifiable risk factors, such as condomless sex, multiple sexual partners, experiencing depression, and engaging in hazardous alcohol use prior to pregnancy. Additionally, more women with IPV victimization had a self-perceived higher risk of HIV than those without.

Past-year IPV victimization in our PrEP-PP study (12%) was comparable to the *Global Database on Prevalence of Violence Against Women* in southern sub-Saharan Africa (14%).[2] Prior study on IPV experiences during pregnancy at a similar antenatal clinic in Cape Town was 21%.[21] IPV victimization increased to 15% by the 6-month follow-up visit in our study. Emotional violence was the most reported form of IPV, followed by physical violence, with 7% of the sample reporting both physical and emotional IPV. Meanwhile, the HPTN 082 trial in Southern Africa estimated a much higher prevalence of past-year IPV (49%) among adolescent girls and young women, however this was a non-pregnant group and may have different risk factors.[16] Our study, which used the same WHO questionnaire, estimated a much lower prevalence of IPV (11%) among participants of the same age group. This discrepancy could also potentially be explained by methodological differences, as the HPTN 082 trial employed a Computer Assisted Self Interview software to collect data, while our study relied on trained study staff to administer the IPV questionnaire. IPV reporting using study staff may have been subject to stigma and social desirability bias resulting in underreporting of IPV.

The relationship between IPV and PrEP adherence in the literature were mixed with studies finding lower self-reported PrEP adherence among women with IPV.[26,27] Although the Roberts et al study found greater adherence to PrEP using plasma tenofovir cut-off of 40 ng/mL among those with acute IPV, this relationship was not observed when examining IPV reported prior to 3 months in the study.[26] Plasma tenofovir levels measure drug adherence in the last 2-7 days[28] and is different from the cumulative measure[18] used in our analysis. Another study reported higher PrEP interruptions among those with IPV, but this study had a different sample population that included men. Our study findings align with the HPTN 082 trial, which reported higher adherence (≥700 fmol/punch of TDF-DP or ~4 doses/week) among young women (age>21) reporting IPV in the past year.[16]

IPV and HIV are interlinked and have a bidirectional relationship.[29] Women who experience abuse and violence are at an increased risk of acquiring HIV due to forced sex and

lack of control in their relationships.[4] Even negotiating condom use can make women more vulnerable to abuse. However, women in violent relationships are a high-risk group with increased vulnerability to HIV.[29] Despite limited control in their relationships, women experiencing IPV may have a higher awareness of their HIV risks and therefore opt for oral PrEP. Our previous study also found that recent alcohol use was associated with PrEP continuation, supporting the theory that higher risk women may continue with oral PrEP more.[24] IPV and PrEP adherence in our study could have been influenced by the HIV prevention counselling that participants received, which included information about the risks of vertical HIV transmission and the importance of taking PrEP for sexually active women. Since our study is comprised of women during their pregnancy and postpartum, they may have unique incentives to continue and adhere to PrEP to protect themselves and their infant from HIV.

Higher use of PrEP in our study is encouraging to reduce risk against HIV and to increase the agency for women's health. However, levels of TFV-DP were still low despite differences in PrEP continuation and adherence. Future interventions should encourage adherence to daily oral PrEP and other HIV prevention methods. The availability of long-acting PrEP (Cabotegravir or Dapivirine vaginal rings) may address some concerns with daily adherence among pregnant and postpartum women who have interest in PrEP but have notable challenges with daily adherence by providing additional prevention options.[30]

Future studies should examine the roles of mediating factors such as HIV risk perceptions, depression, hazardous alcohol use with IPV and PrEP. This could provide valuable insights for designing interventions to improve PrEP adherence among high-risk individuals. Some studies have also explored empowerment counselling with objectives of improving PrEP adherence and decreasing social harms and IPV, but the analysis was underpowered.[31]

Limitations

Our study has some limitations. First, we had a small sample of those with high adherence to oral PrEP irrespective of IPV experiences. This could be partially explained by women adjusting their daily PrEP use due to changing sexual risks against HIV. It could mean there is low coverage against HIV acquisition for those at-risk. Second, we did not have information on frequency of violence incidents or the consequences of IPV on women's behaviors, which may provide further context of violence experienced by the women during pregnancy in these relationships. There were several strengths in our analysis including the use of a validated violence survey administered across the world and the use of biomarkers to quantify levels of TFV-DP in DBS. Those who did not continue on the study were marked as non-adherent to PrEP in our analysis. We reported multiple measures of adherence in this study to show how our results shift, though measuring TFV-DP levels is the gold standard. We also examined IPV by types and during follow-up however, we were limited by sample size. Although our study recruited directly from a busy antenatal clinic in Cape Town, it may not be generalizable to all pregnant/postpartum women in South Africa, including those living in rural areas.

Conclusion

This study provides important evidence on the relationship between experiencing IPV and PrEP continuation and adherence among pregnant and postpartum women in South Africa using longitudinal data. IPV was associated with higher HIV risk behaviors and lower PrEP discontinuation and higher adherence. Since our study population were pregnant and postpartum women attending antenatal care, this presents programmatic opportunities to implement violence screening and IPV interventions at the clinic and to continue promotion of oral PrEP counselling for HIV prevention among sexually active pregnant and postpartum women.

Figure 3.1. Venn diagram of types of intimate partner violence experienced during the last 12 months from study baseline among pregnant and postpartum women (N = 1199).

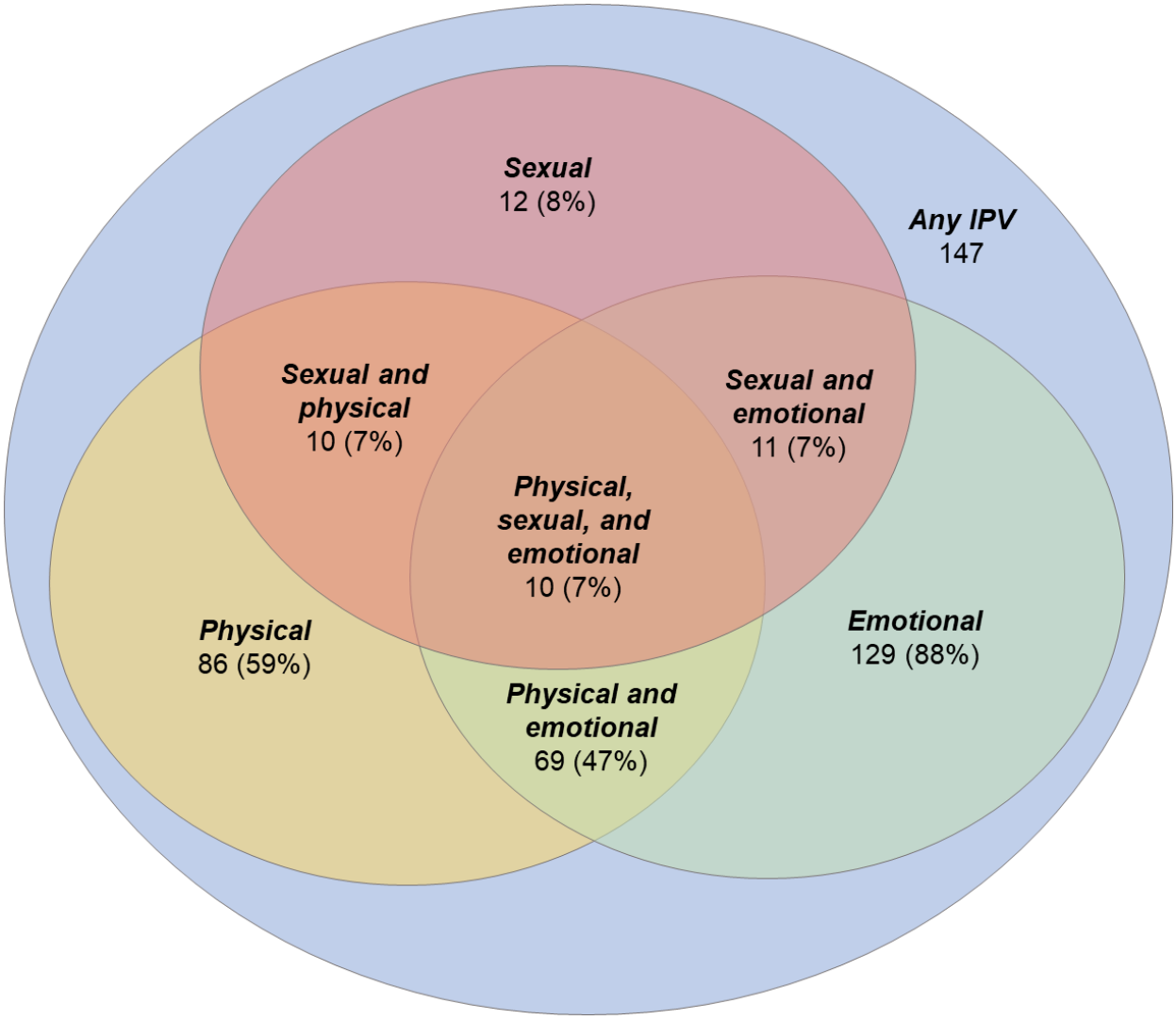


Table 3.1. Definition of IPV types and severity based on the WHO Violence Against Women Modules.

Subtypes of IPV	
Physical IPV	Has your partner: “slapped you or thrown something at you that could hurt you?”, “pushed or shoved you?”, “hit you with a fist or with something else that could hurt you?”, “kicked you, dragged you or beaten you up?”, “choked or burnt you on purpose?”, “threatened to use or used a gun, knife or other weapon against you?”.
Sexual IPV	“Has your partner physically forced you to have sexual intercourse when you did not want to?”, “did you ever have sexual intercourse when you did not want to because you were afraid of what partner might do?”, “has your partner forced you to do something sexual that you found degrading or humiliating?”
Emotional IPV	Has your partner: “insulted you or made you feel bad about yourself?”, “belittled or humiliated you in front of other people?”, “done things to scare or intimidate you on purpose?”, “threatened to hurt you or someone you care about?”.
Severity of IPV	
Moderate IPV	Has he: "slapped you or thrown something at you that could hurt you?” or “pushed you or shoved you?"
Severe IPV	Has he: “hit you with his fist or with something else that could hurt you”, “kicked you, dragged you or beaten you up”, “choked or burnt you on purpose?”, “threatened to use or actually used a gun, knife or other weapon against you?”.

Table 3.2. Baseline characteristics of pregnant and postpartum women from the PrEP-PP study in Cape Town, South Africa (N = 1199).

	Overall	No Past-year IPV Reported at Baseline	Past-year IPV Reported at Baseline	*P value*
	n (%)	n (%)	n (%)	
Total	1199 (100.0)	1052 (87.7)	147 (12.3)	NA
Demographics				
Age				
16-18	79 (6.6)	70 (6.7)	9 (6.1)	0.81
19-24	409 (34.1)	362 (34.4)	47 (32.0)	
25-29	363 (30.3)	320 (30.4)	43 (29.3)	
30-34	201 (17.0)	178 (16.9)	26 (17.7)	
35+	144 (12.0)	122 (11.6)	22 (15.0)	
Age, median (IQR)	26 (22-31)	26 (22-30)	26 (23-31)	0.15
Highest Level of Education				
< Grade 12	584 (48.7)	502 (47.7)	82 (55.8)	0.07
≥ Grade 12	615 (51.3)	550 (52.3)	65 (44.2)	
Highest Level of Education				
Primary	21 (1.8)	17 (1.6)	4 (2.7)	**0.04**
Secondary	1075 (89.7)	937 (89.1)	138 (93.9)	
Tertiary	103 (8.6)	98 (9.3)	5 (3.4)	
Socio-economic Status (SES)				
Low SES	384 (32.0)	322 (30.6)	62 (42.2)	**<0.01**
Moderate to high SES	815 (68.0)	730 (69.4)	85 (57.8)	
Gravidity				
Primigravida	408 (34.0)	374 (35.6)	34 (23.1)	<**0.01**
Multigravida	791 (66.0)	678 (64.5)	113 (76.9)	
Relationship Status				
Married or Cohabitating	443 (37.0)	384 (36.5)	59 (40.1)	0.39
Not married or not cohabiting	756 (63.1)	668 (63.5)	88 (59.9)	
Clinical Characteristics				
Gestational age at baseline in weeks (median, IQR)	21 (15-31)	21 (14-31)	21 (16-27)	0.69
Gestational age at baseline in weeks				
≤ 14 weeks	216 (21.3)	190 (21.5)	26 (19.9)	0.66
> 14 weeks	797 (78.7)	692 (78.5)	105 (80.2)	
Gestational age at baseline in trimesters				

Trimester 1	186 (18.4)	166 (18.8)	20 (15.3)	0.09
Trimester 2	536 (52.9)	455 (51.6)	81 (61.8)	
Trimester 3	287 (28.3)	258 (29.3)	29 (22.1)	
Postpartum	4 (0.39)	3 (0.34)	1 (0.76)	
STI diagnosed (*Chlamydia trachomatis, Neisseria gonorrhoeae* and/or *Trichomonas vaginalis*)				
No STI	820 (68.7)	717 (68.6)	103 (70.1)	0.71
STI diagnosed	373 (31.3)	329 (31.5)	44 (29.9)	
Behavioral Risk Factors				
Sexually active in pregnancy (at baseline)				
Not Sexually active	33 (2.8)	28 (2.7)	5 (3.4)	0.06
Yes, 1-4 times per month	689 (57.5)	618 (58.8)	71 (48.3)	
Yes, 5+ times per month	477 (39.8)	406 (38.6)	71 (48.3)	
Condom Use at last sex (at baseline)				
Condomless sex	802 (68.8)	690 (67.5)	112 (78.9)	**0.01**
Condom used	363 (31.2)	333 (32.6)	30 (21.1)	
Number of Sexual Partners in the past 12 months				
1 sexual partner	1009 (84.3)	895 (85.1)	114 (77.6)	**0.02**
>1 sexual partners	190 (15.9)	157 (14.9)	33 (22.5)	
Partner HIV Status in the past 12 months (at baseline)				
HIV negative	823 (68.6)	723 (68.7)	100 (68.0)	0.93
HIV positive	20 (1.7)	17 (1.6)	3 (2.0)	
Do not know	356 (29.7)	312 (29.7)	44 (29.9)	
HIV Risk Perception				
No chance at all	560 (55.3)	513 (58.2)	47 (35.9)	**<0.01**
Low chance	337 (33.3)	284 (32.2)	53 (40.5)	
High chance	116 (11.5)	85 (9.6)	31 (23.7)	
Self-report of recent depression (EPDS≥11)	78 (7.7)	56 (6.4)	22 (16.8)	**<0.01**
Hazardous Alcohol Use in the past 12 months before pregnancy (AUDIT-C ≥3)	340 (33.6)	274 (31.1)	66 (50.4)	**<0.01**

Data are n(%) or median (IQR). P-values from chi-squared tests or Fisher's exact test (when categorical variables had cell counts <5) as appropriate. P-values<0.05 in bold.

Abbreviations: IQR = Interquartile Range; IPV=intimate partner violence; PrEP=pre-exposure prophylaxis; SES= Socioeconomic Status; STI = sexually transmitted infections; CT =Chlamydia trachomatis; NG =Neisseria gonorrhoeae; TV=Trichomonas vaginalis; PrEP-PP= PrEP in Pregnancy and Postpartum cohort study; EPDS= Edinburgh Perinatal Depression Scale with a cut-off of ≥ 11 for probable depression); AUDIT-C= Alcohol use disorders identification test-consumption with a cut-off of ≥ 3 for hazardous alcohol use.

Figure 3.2. Prevalence and Incidence of Intimate Partner Violence in the PrEP-PP study through 6 months (n=1199).

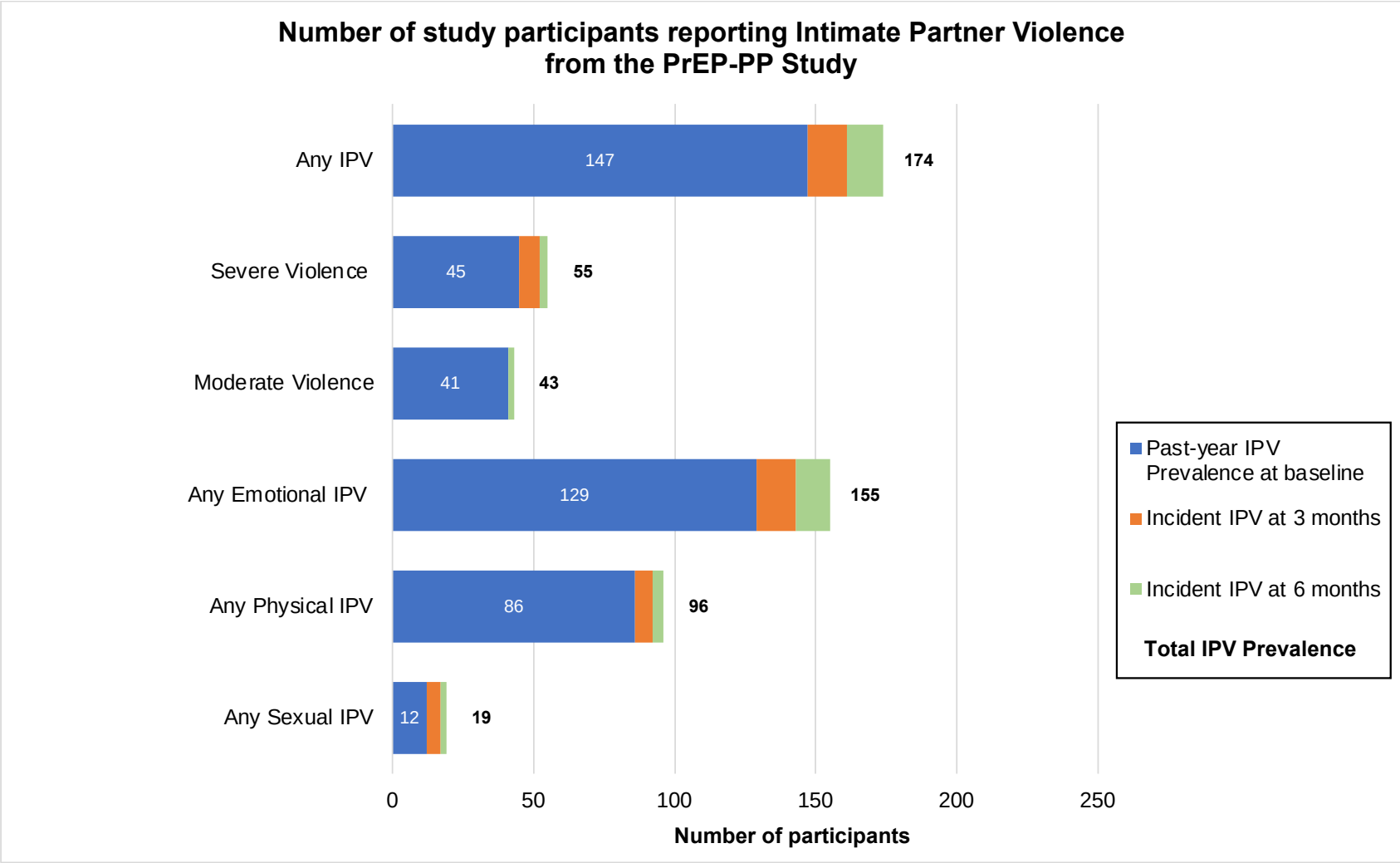


Table 3.3. Pre-exposure prophylaxis adherence at 3- and 6-month visits stratified by past-year intimate partner violence among pregnant and postpartum women that initiated PrEP at baseline (N = 1013).

	self-reported adherence*			Objective adherence** (TFV-DP levels in DBS)		
	No IPV (n=882)	**Any IPV (n=131)**	**P value**	**No IPV (n=711)**	**Any IPV (n=110)**	**P value**
3-month visit						
Any Adherence						
Not adherent/unquantifiable	586 (88.3)	78 (11.8)	0.12	527 (88.1)	71 (11.9)	**0.04**
Any adherence/quantifiable	296 (84.8)	53 (15.2)		184 (82.5)	39 (17.5)	
Adherence						
not adherent	586 (88.3)	78 (11.8)	0.28	527 (88.1)	71 (11.9)	0.16
Low (>BLQ, <2 doses/week)	94 (82.5)	20 (17.5)		91 (83.5)	18 (16.5)	
Moderate (2-6 doses/week)	96 (84.2)	18 (15.8)		73 (83.0)	15 (17.1)	
High (7 doses/week)	106 (87.6)	15 (12.4)		20 (76.9)	6 (23.1)	
6-month visit						
Any Adherence						
Not adherent/unquantifiable	667 (87.7)	94 (12.4)	0.34	607 (87.5)	87 (12.5)	**0.02**
Any adherence/quantifiable	215 (85.3)	37 (14.7)		63 (77.8)	18 (22.2)	
Adherence						
not adherent	667 (87.7)	94 (12.4)	0.65	607 (87.5)	87 (12.5)	0.06
Low (>BLQ, <2 doses/week)	36 (81.8)	8 (18.2)		34 (81.0)	8 (19.1)	
Moderate (2-6 doses/week)	86 (85.2)	15 (14.9)		26 (74.3)	9 (25.7)	
High (7 doses/week)	93 (86.9)	14 (13.1)		3 (75.0)	1 (25.0)	

Data are n(%) or median (IQR). P-values from chi-squared tests or Fisher's exact test (when categorical variables had cell counts <5) as appropriate. P-values<0.05 in bold.

Abbreviations: DBS=Dried Blood Spots; TDF-DP= Tenofovir Diphosphate; IPV=Intimate partner violence; BLQ=below the quantification level for TDF-DP;

*self-reported adherence combined with TFV-DP in dried blood spots when available: If did not attend study visits, then adherence was coded as “not adherent”. If DBS were collected and analyzed, then confirmed TFV-DP levels replaced self-reported adherence data. Not adherent could also be if they had TDF-DP levels below the quantifiable limit on DBS. The lower limit of quantification for TFV-DP was 16.6 fmol/3-mm punch.

**objective adherence: if did not attend study visit, then TFV-DP in DBS was coded as “not adherent”; if attended the study and continued PrEP, but DBS was missing then TFV-DP was coded as “missing”.

Stranix-Chibanda L, et al. Tenofovir Diphosphate Concentrations in Dried Blood Spots From Pregnant and Postpartum Adolescent and Young Women Receiving Daily Observed Pre-exposure Prophylaxis in Sub-Saharan Africa. Clin Infect Dis. 2021. High adherence or daily intake oral PrEP (~7 doses/week) for objective adherence was defined by DBS with TFV-DP ≥600 fmol/punch for pregnant and ≥1000 fmol/punch for postpartum women; moderate adherence (2-6 doses/week) was defined as 200-599 fmol/punch for pregnant and 400-999 fmol/punch for postpartum women; low adherence (<2 doses/week) was defined as quantifiable but <200 fmol/punch for pregnant and <400 fmol/punch for postpartum women and no adherence was defined as DBS was analyzed but they had unquantifiable TFV-DP concentrations. For self-reported adherence, we used number of pills missed to calculate number of doses used per week and categorized them same as for TFV-DP levels in DBS.

Figure 3.3. Kaplan-Meier Curve of time to PrEP Discontinuation by any Past-year Intimate Partner Violence at Baseline among pregnant and postpartum women that initiated PrEP at baseline (N = 1013).

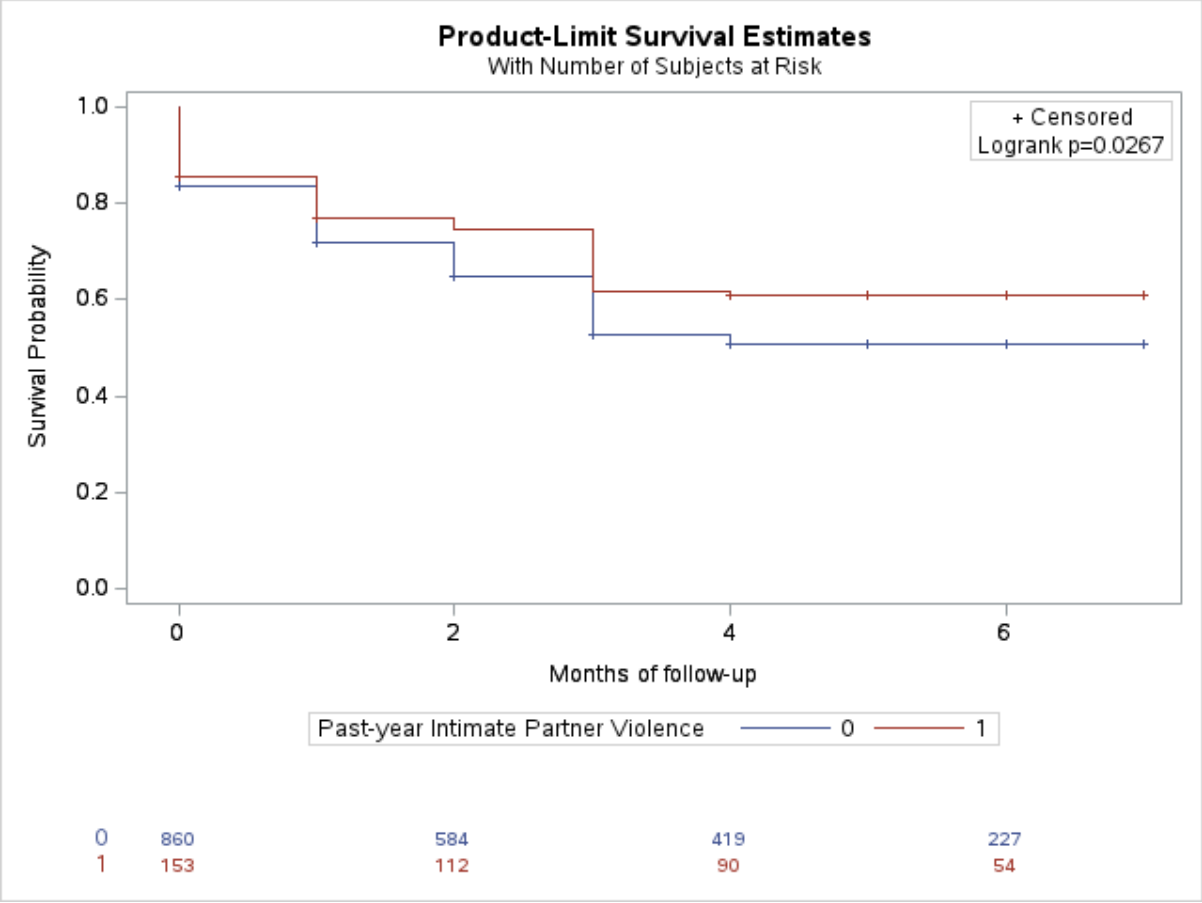


Table 3.4. Cox Models of Past-year Intimate Partner Violence on Pre-exposure prophylaxis Discontinuation (n=1013).

	HR (95% CI)	age-adjusted HR (95% CI)*	adjusted HR (95% CI)**
No IPV	Reference		
Any IPV	0.79 (0.61, 1.02)	0.77 (0.59, 1.02)	0.80 (0.61, 1.06)

*adjusted for maternal age at baseline.
**adjusted for maternal age at baseline, gestational age, cohabitation status, education, and the South African COVID-19 pandemic lockdowns (before/after March 28, 2020).

Abbreviations: HR, Hazard Ratio; aHR, adjusted Hazard Ratio; IPV, intimate partner violence; any IPV, any physical, sexual or emotional IPV in the past year reported at enrollment; PrEP, pre-exposure prophylaxis; PrEP-PP, PrEP in Pregnancy and Postpartum cohort study.

Table 3.5. Past-year Intimate Partner Violence on PrEP adherence at 3- and 6-months among women who initiated PrEP at baseline (N=1013).

	self-reported adherence* (Missed PrEP doses)			Objective adherence** (TFV-DP levels in DBS)		
	Crude OR (95%CI)	**Adjusted OR[1] (95% CI)**	**Adjusted OR[2] (95% CI)**	**Crude OR (95%CI)**	**Adjusted OR[1] (95% CI)**	**Adjusted OR[2] (95% CI)**
3-month visit						
Any PrEP adherence[3]						
No IPV	Reference					
		1.29 (0.88, 1.89)			1.53 (1.00, 2.34)	1.50 (0.98, 2.30)
Any IPV	1.35 (0.92, 1.96)		1.27 (0.86, 1.86)	**1.57 (1.03, 2.41)**		
Moderate/High PrEP adherence[4]						
No IPV	Reference					
		1.06 (0.69, 1.65)			1.50 (0.89, 2.55)	1.47 (0.86, 2.5)
Any IPV	1.13 (0.74, 1.73)		1.04 (0.67, 1.62)	1.57 (0.93, 2.65)		
6-month visit						
Any PrEP adherence[3]						
No IPV	Reference					
		1.13 (0.74, 1.72)			**1.82 (1.02, 3.25**)	1.74 (0.97, 3.11)
Any IPV	1.22 (0.81, 1.84)		1.11 (0.72, 1.69)	**1.99 (1.13, 3.53**)		
Moderate/High PrEP adherence[4]						
No IPV	Reference					
		1.03 (0.65, 1.62)			2.11 (0.98, 4.54)	1.95 (0.90, 4.25)
Any IPV	1.12 (0.72, 1.74)		1.00 (0.64, 1.59)	**2.33 (1.10, 4.93)**		

Abbreviations: OR, Odds Ratio; aOR, adjusted Odds Ratio; IPV, intimate partner violence; TFV-DP, tenofovir-diphosphate; any IPV, any physical, sexual or emotional IPV in the past year reported at enrollment.

*self-reported adherence combined with TFV-DP in dried blood spots when available: If did not attend study visits, then adherence was coded as “not adherent”. If DBS were collected and analyzed, then confirmed TFV-DP levels replaced self-reported adherence data. Not adherent could also be if they had TDF-DP levels below the quantifiable limit on DBS.

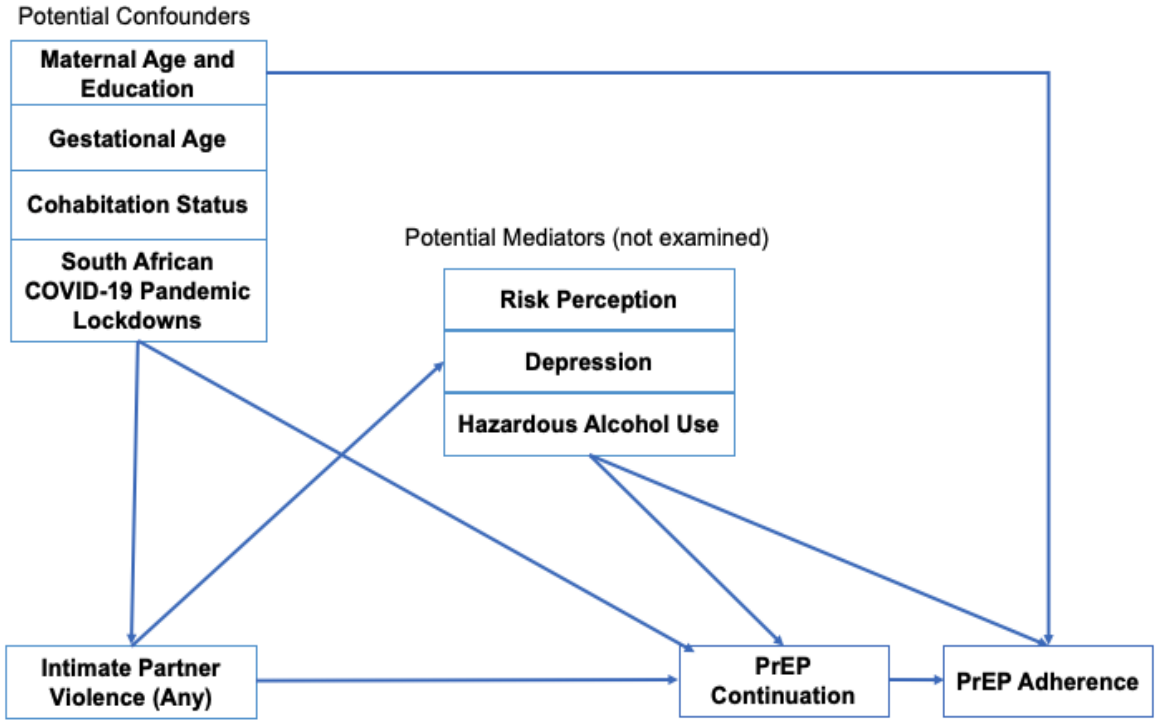
**objective adherence: if did not attend study visit, then TFV-DP in DBS was coded as “not adherent”; if attended the study and continued PrEP, but DBS was missing then TFV-DP was coded as “missing”.

[1]adjusted for maternal age, gestational age at baseline and whether baseline data was collected before or during/after the national COVID-19 pandemic lockdowns in South Africa (defined as before/after March 28, 2020).

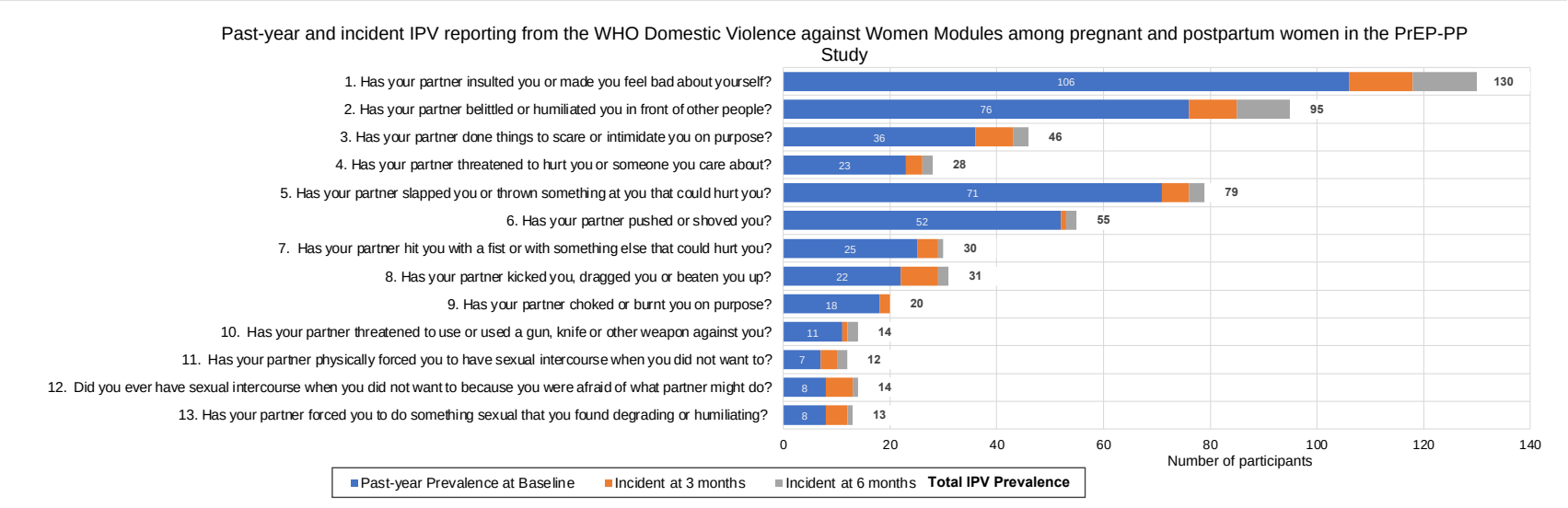
[2]adjusted for maternal age, gestational age at baseline, relationship status, maternal education and whether baseline data was collected before or during/after the national COVID-19 pandemic lockdowns in South Africa (defined as before/after March 28, 2020).

[3]missing <5 doses in the last 30 days or quantifiable TFV-DP in DBS.
[4]High adherence or daily intake oral PrEP (~7 doses/week) for objective adherence was defined by DBS with TFV-DP ≥600 fmol/punch for pregnant and ≥1000 fmol/punch for postpartum women; moderate adherence (2-6 doses/week) was defined as 200-599 fmol/punch for pregnant and 400-999 fmol/punch for postpartum women; low adherence (<2 doses/week) was defined as quantifiable but <200 fmol/punch for pregnant and <400 fmol/punch for postpartum women and no adherence was defined as DBS was analyzed but they had unquantifiable TFV-DP concentrations. For self-reported adherence, we used number of pills missed to calculate number of doses used per week and categorized them same as for TFV-DP levels in DBS.

Supplemental Figure 3.1. Directed Acyclic Graph



Supplemental Figure 3.2. Responses from the WHO Domestic Violence against Women Modules: Prevalence and Incidence among pregnant and postpartum women in the PrEP-PP Study (n=1199).



Supplemental Table 3.1. IPV among pregnant and postpartum women (age ≥ 16) from the PrEP-PP study in Cape Town, South Africa (N = 1199).

	Prevalence of IPV at baseline	Incident 3m	Incident 6m	Any incident IPV after baseline	Prevalence of IPV by 6m*
	n (%)	n (%)	n (%)	n (%)	n (%)
No IPV	1052 (87.74)	--	--	--	1025 (85.5)
Any IPV (Sexual or Emotional or Physical IPV)	147 (12.3)	14/618 (2.3)	13/495 (2.6)	27/509 (5.3)	174 (14.5)
Severe Violence	45 (3.8)	7/684 (1.0)	3/554 (0.5)	10/561 (1.8)	55 (4.6)
Moderate Violence	41 (3.4)	0/690 (0.0)	2/565 (0.4)	2/565 (0.4)	43 (3.6)
Any Emotional IPV	129 (10.8)	14/628 (2.3)	12/503 (2.4)	26/517 (5.0)	155 (12.9)
Any Physical IPV	86 (7.2)	6/664 (0.9)	4/540 (0.7)	10/546 (1.8)	96 (8.0)
Any Sexual IPV	12 (1.0)	5/703 (0.7)	2/572 (0.4)	7/577 (1.2)	19 (1.6)
Physical and Emotional IPV	69 (5.8)	7/673 (1.0)	3/547 (0.6)	10/554 (1.8)	79 (6.6)
Physical and Sexual IPV	10 (0.8)	3/705 (0.4)	2/575 (0.4)	5/578 (0.9)	15 (1.3)
Sexual and Emotional IPV	11 (0.9)	4/704 (0.6)	2/573 (0.4)	6/577 (1.0)	17 (1.4)
Sexual, Emotional, and Physical IPV	10 (0.8)	3/705 (0.4)	2/575 (0.4)	5/578 (0.9)	15 (1.3)
Emotional IPV only	59 (4.9)	11/666 (1.7)	9/535 (1.7)	20/546 (3.7)	79 (6.6)
Physical IPV only	17 (1.4)	1/701 (0.1)	2/571 (0.4)	3/572 (0.5)	20 (1.7)
Sexual IPV only	1 (0.1)	1/709 (0.1)	0/579 (0.0)	1/580 (0.2)	2 (0.2)

*Prevalence of IPV by 6 month includes any reporting of IPV at baseline, 3- and 6-month study visits.

Supplemental Table 3.2. Cox Models of Past-year Intimate Partner Violence on Pre-exposure prophylaxis Discontinuation by Age and Gestational Trimester at Baseline (N =1013).

	HR (95% CI)	Age-adjusted HR (95% CI)*	adjusted HR (95% CI)**
Age Groups			
Age <25			
No IPV	Reference		
Any IPV	0.79 (0.53, 1.20)	0.81 (0.54, 1.22)	0.81 (0.53, 1.23)
Age ≥ 25			
No IPV	Reference		
Any IPV	0.72 (0.50, 1.04)	0.74 (0.51, 1.07)	0.79 (0.55, 1.14)
Gestational Age at Baseline°			
Trimester 1			
No IPV	Reference		
Any IPV	0.59 (0.25, 1.36)	0.58 (0.25, 1.36)	0.58 (0.25, 1.37)
Trimester 2			
No IPV			
Any IPV	0.73 (0.50, 1.05)	0.72 (0.50, 1.04)	0.77 (0.53, 1.11)
Trimester 3			
No IPV	Reference		
Any IPV	0.89 (0.55, 1.45)	0.90 (0.55, 1.47)	0.80 (0.57, 1.54)

*adjusted for maternal age at baseline.

**adjusted for maternal age at baseline, gestational age, cohabitation status, education, and the South African COVID-19 pandemic lockdowns (before/after March 28, 2020).

Abbreviations: HR, Hazard Ratio; aHR, adjusted Hazard Ratio; IPV, intimate partner violence; any IPV, any physical, sexual or emotional IPV in the past year reported at enrollment; PrEP, pre-exposure prophylaxis; PrEP-PP, PrEP in Pregnancy and Postpartum cohort study

°Postpartum sample size too small to model.

Supplemental Table 3.3. Recent Intimate Partner Violence on PrEP adherence at 3- and 6-months (N=1199).

		self-reported adherence* (Missed PrEP doses)			Objective adherence** (TFV-DP levels in DBS)	
	n/N	Crude OR (95%CI)	Adjusted OR[1] (95% CI)	n/N	Crude OR (95%CI)	Adjusted OR[1] (95% CI)
3-month visit						
Any PrEP adherence[2]						
No IPV	341/686	Reference		219/500		
Any IPV	8/24	1.48 (0.95, 2.30)	1.27 (0.86, 1.86)	4/18	***	***
Moderate/High PrEP adherence[3]						
No IPV	227/686	Reference				
Any IPV	8/24	1.15 (0.73, 1.82)	1.04 (0.67, 1.62)	110/500		
6-month visit				4/18	***	***
Any PrEP adherence[2]						
No IPV	260/560	Reference		77/329		
Any IPV	8/20	1.26 (0.80, 1.97)	1.11 (0.72, 1.69)	4/13	***	***
Moderate/High PrEP adherence[3]						
No IPV	213/560	Reference		37/329		
Any IPV	6/20	1.03 (0.64, 1.65)	1.00 (0.64, 1.59)	2/13	***	***

Abbreviations: OR, Odds Ratio; aOR, adjusted Odds Ratio; IPV, intimate partner violence; TFV-DP, tenofovir-diphosphate; any IPV, any physical, sexual or emotional IPV in the past year reported at enrollment. *self-reported adherence combined with TFV-DP in dried blood spots when available: If did not attend study visits, then adherence was coded as "not adherent". If DBS were collected and analyzed, then confirmed TFV-DP levels replaced self-reported adherence data. Not adherent could also be if they had TDF-DP levels below the quantifiable limit on DBS.

**objective adherence: if did not attend study visit, then TFV-DP in DBS was coded as "not adherent"; if attended the study and continued PrEP, but DBS was missing then TFV-DP was coded as "missing".

***limited by small sample size. Since cells <5, we did not model logistic regression.
[1]adjusted for maternal age, gestational age at baseline and whether baseline data was collected before or during/after the national COVID-19 pandemic lockdowns in South Africa (defined as before/after March 28, 2020).

[2]missing <5 doses in the last 30 days or quantifiable TFV-DP in DBS.

[3]High adherence or daily intake oral PrEP (~7 doses/week) for objective adherence was defined by DBS with TFV-DP ≥600 fmol/punch for pregnant and ≥1000 fmol/punch for postpartum women; moderate adherence (2-6 doses/week) was defined as 200-599 fmol/punch for pregnant and 400-999 fmol/punch for postpartum women; low adherence (<2 doses/week) was defined as quantifiable but <200 fmol/punch for pregnant and <400 fmol/punch for postpartum women and no adherence was defined as DBS was analyzed but they had unquantifiable TFV-DP concentrations. For self-reported adherence, we used number of pills missed to calculate number of doses used per week and categorized them same as for TFV-DP levels in DBS.

Supplemental Table 3.4. Past-year Intimate Partner Violence types on PrEP adherence at 3- and 6-months among women who initiated PrEP at baseline (N=1013).

	self-reported adherence* (Missed PrEP doses)			Objective adherence** (TFV-DP levels in DBS)		
	n/N	Crude OR (95%CI)	Adjusted OR[1] (95% CI)	n/N	Crude OR (95%CI)	Adjusted OR[1] (95% CI)
3-month visit						
Any PrEP adherence[2]						
Emotional IPV						
No emotional IPV	304/896	Reference		188/721		
Emotional IPV	45/117	1.22 (0.82, 1.81)	1.14 (0.76, 1.71)	35/100	1.53 (0.98, 2.38)	1.47 (0.94, 2.29)
Physical IPV						
No physical IPV	321/936	Reference		205/756		
Physical IPV	28/77	1.10 (0.68, 1.78)	1.10 (0.67, 1.81)	18/65	1.03 (0.58, 1.81)	1.02 (0.58, 1.81)
Sexual IPV						
No sexual IPV	345/1003	Reference		219/811		
Sexual IPV	4/10	***	***	4/10	***	***
Moderate/High PrEP adherence[3]						
Emotional IPV						
No emotional IPV	207/896	Reference		94/721		
Emotional IPV	28/117	1.05 (0.67, 1.65)	0.96 (0.60, 1.52)	20/100	1.67 (0.98, 2.85)	1.57 (0.91, 2.70)
Physical IPV						
No physical IPV	216/936	Reference		104/756		
Physical IPV	19/77	1.09 (0.64, 1.87)	1.12 (0.64, 1.95)	10/65	1.14 (0.56, 2.31)	1.15 (0.57, 2.35)
Sexual IPV						
No sexual IPV	233/1003	Reference		112/811		
Sexual IPV	2/10	***	***	2/10	***	***
6-month visit						
Any PrEP adherence[2]						
Emotional IPV						
No emotional IPV	218/896	Reference		63/680		
Emotional IPV	34/117	1.27 (0.83, 1.95)	1.15 (0.74, 1.78)	18/95	**2.29 (1.29, 4.07)**	**2.04 (1.13, 3.67)**
Physical IPV						
No physical IPV	234/936	Reference		75/714		

Physical IPV	18/77	0.92 (0.53, 1.58)	0.90 (0.51, 1.58)	6/61	0.93 (0.39, 2.23)	0.87 (0.36, 2.11)
Sexual IPV						
No sexual IPV	249/1003	Reference		79/767		
Sexual IPV	3/10	***	***	2/8	***	***
Moderate/High PrEP adherence[3]						
Emotional IPV						
No emotional IPV	182/896	Reference		29/680		
Emotional IPV	26/117	1.12 (0.70, 1.79)	1.00 (0.62, 1.61)	10/95	**2.64 (1.24, 5.61)**	**2.33 (1.07, 5.06)**
Physical IPV						
No physical IPV	193/936	Reference		36/714		
Physical IPV	15/77	0.92 (0.53, 1.58)	0.92 (0.50, 1.68)	3/61	***	***
Sexual IPV						
No sexual IPV	206/1003	Reference		38/767		
Sexual IPV	2/10	***	***	1/8	***	***

Abbreviations: OR, Odds Ratio; aOR, adjusted Odds Ratio; IPV, intimate partner violence; TFV-DP, tenofovir-diphosphate; any IPV, any physical, sexual or emotional IPV in the past year reported at enrollment.

*self-reported adherence combined with TFV-DP in dried blood spots when available: If did not attend study visits, then adherence was coded as “not adherent”. If DBS were collected and analyzed, then confirmed TFV-DP levels replaced self-reported adherence data. Not adherent could also be if they had TDF-DP levels below the quantifiable limit on DBS.

**objective adherence: if did not attend study visit, then TFV-DP in DBS was coded as “not adherent”; if attended the study and continued PrEP, but DBS was missing then TFV-DP was coded as “missing”.

***limited by small sample size. Since cells <5, we did not model logistic regression.

[1]adjusted for maternal age, gestational age at baseline and whether baseline data was collected before or during/after the national COVID-19 pandemic lockdowns in South Africa (defined as before/after March 28, 2020).

[2]missing <5 doses in the last 30 days or quantifiable TFV-DP in DBS.

[3]High adherence or daily intake oral PrEP (~7 doses/week) for objective adherence was defined by DBS with TFV-DP ≥600 fmol/punch for pregnant and ≥1000 fmol/punch for postpartum women; moderate adherence (2-6 doses/week) was defined as 200-599 fmol/punch for pregnant and 400-999 fmol/punch for postpartum women; low adherence (<2 doses/week) was defined as quantifiable but <200 fmol/punch for pregnant and <400 fmol/punch for postpartum women and no adherence was defined as DBS was analyzed but they had unquantifiable TFV-DP concentrations. For self-reported adherence, we used number of pills missed to calculate number of doses used per week and categorized them same as for TFV-DP levels in DBS.

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Chapter IV. Study 3: Dynamic Sexual Behaviors and Oral PrEP use by gestational trimesters and postpartum status in Cape Town, South Africa

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Abstract

Background

HIV acquisition risks are high during pregnancy and postpartum, but adherence challenges with oral pre-exposure prophylaxis (PrEP) remain. It is important to consider prevention-effective adherence, PrEP use during periods of sexual activity, when evaluating effective PrEP use. We aimed to evaluate patterns of oral PrEP use during periods of sexual activity and condomless sex across gestational periods and postpartum.

Methods

We used data from the PrEP in pregnancy and postpartum (PrEP-PP) study, a prospective cohort of pregnant women without HIV enrolled from their 1st antenatal visit and followed through 12 months postpartum in Cape Town, South Africa. We examined PrEP continuation (initiation/continuation of filled prescriptions for TDF-FTC) and any PrEP use (initiation and quantifiable tenofovir diphosphate [TFV-DP] in dried blood spots or self-reported use with filled prescriptions). Data on sexual behaviors and oral PrEP were collected quarterly. The primary exposure was any condomless sex in the last 3 months. We used group-based trajectory modeling to identify oral PrEP trajectories during the gestational periods to describe the study cohort and reported sexual behaviors and PrEP use by gestational periods. Finally,

we used generalized estimating equations of repeated measures to examine the association between condomless sex in the last 3 months and continuation and any use of PrEP adjusting for maternal age, partner HIV status and gestational age at baseline.

Results

Of the 1200 participants, there were 3367 visits completed with information on sexual behaviors and oral PrEP. We identified three oral PrEP trajectories: consistent PrEP/declining at late postpartum (40%, n=450), initiated/declining PrEP after initiation (50%, n=571), and low/no PrEP (10%, n=113). Prevention-effective adherence (initiation/quantifiable TFV-DP or reported use during follow-up among those engaging in condomless sex) was 65% overall with 81% at trimester 1, 78% at trimester 2, 67% at trimester 3, 49% at early postpartum, and 50% at late postpartum. The adjusted risk of PrEP initiation/continuation (aRR=1.09; 95% CI: 1.01, 1.16) and PrEP initiation/use (quantifiable TFV-DP or self-reported use) (aRR=1.88; 95% CI: 1.67, 2.12) were higher among those who reported condomless sex in the last 3 months (vs. no condomless sex reported) after controlling for potential confounders.

Conclusion

There was an association between engaging in condomless sex and PrEP use, which suggests that pregnant and postpartum women align their PrEP use by potential HIV risks. However, prevention-effective adherence was lowest during postpartum meaning targeted research and interventions are necessary to understand PrEP discontinuation despite HIV risks post child delivery. Our findings encourage providers of oral PrEP to foster discussions about changing HIV risks during PrEP counselling.

Key words: prevention-effective adherence, dynamic sexual behaviors, pregnant, postpartum, South Africa

Introduction

HIV risks continue to remain alarmingly high during pregnancy and postpartum periods in sub-Saharan Africa. In 2021, about 22,000 new HIV infections were reported in eastern and southern Africa during pregnancy or breastfeeding periods.[1] With an incidence rate of 3.6 cases per 100 person-years[2] from a meta-analysis, pregnant and postpartum women fall under the category of "substantial risk" for HIV, according to the World Health Organization.[3]

The heightened risk of HIV transmission during pregnancy and postpartum is attributed to both biological and behavioral factors.[2] During pregnancy, women experience hormonal changes and genital mucosal alterations that can increase inflammation, making them more vulnerable to HIV transmission. Furthermore, condomless sex acts during pregnancy can steadily increase the risk of HIV transmission, with the highest risk occurring during postpartum.[4] In other words, pregnancy (after 14 weeks of gestation) and postpartum periods pose the greatest threat for both maternal HIV acquisition and vertical transmission.[4] Since South Africa has a high national antenatal care (ANC) coverage of >90%, it provides a good setting for HIV testing, prevention, and counselling services for pregnant women.[5]

Oral pre-exposure prophylaxis (PrEP, tenofovir disoproxil fumarate and emtricitabine [TDF-FTC]) is a biomedical prevention method that can be taken daily to prevent HIV.[3] The South African National Department of Health supports oral PrEP as part of a comprehensive combination prevention strategy for pregnant and breastfeeding women at substantial risk of HIV.[6] PrEP should be used during periods where individuals are potentially at risk for HIV acquisition, also called prevention-effective adherence[7]. Prior PrEP studies, including those with pregnant and breastfeeding women, have reported trends of high initiation, but discontinuation from either PrEP or the study citing challenges with PrEP adherence.[8-10] Studies note that women may not adhere to PrEP due to side effects[8], stigma[11], pill burden (size of the pill and overburdened by daily dosing), or forgetting.[8] One explanation for the high drop-offs in the prior

studies could be due to periodic use of PrEP due to changing sexual risks.[7] Qualitative research has reported that women usually stop and restart on PrEP as their sexual risks change.[12,13]

Prior study of sexual activity during the pregnancy and postpartum period reported most women were having sex in the first two trimesters of pregnancy, followed by a substantial drop-off (abstinence period) by third trimester to 6-months postpartum, then increasing again after 6 months.[14] Meanwhile, condom use was low during trimester 1 (10%), but gradually increased with highest use observed during early postpartum (41% at 0-6 months post child delivery). However, research on how and whether women adjust their PrEP use by sexual risks during pregnancy and after delivery are unknown.

In this study, we aim to: a) describe how sexual behaviors change throughout pregnancy and during postpartum in a cohort of pregnant women not living with HIV, b) to estimate prevention-effective adherence of PrEP by quantifying proportion of women using PrEP during periods of condomless sex, and c) to examine the association between sexual behaviors and effective PrEP use.

Methods

Study Population

This study was conducted using the PrEP in Pregnancy and Postpartum (PrEP-PP) cohort study in Cape Town, South Africa.[8] PrEP-PP followed 1,200 pregnant women without HIV that were recruited from their first antenatal visit between August 2019 to October 2021 through 12 months postpartum. Study participants provided informed consent and were 16 years or older in age. The purpose of this analysis was to investigate the relationship between recent sexual activity (reported in the past 3 months) and continuation of PrEP among pregnant and postpartum women in an antenatal care setting.

Enrollment and Measurements

After enrollment, a baseline survey was administered by the study staff on REDCap (a secure web-based application)[15], collecting sociodemographic information, clinical

characteristics and behavioral HIV risk factors. Study participants were tested for sexually transmitted infections (STI) and treated following national guidelines.[16] Participants who decided to start PrEP and met clinical eligibility were supplied with a month's supply of TDF-FTC and follow-up testing was scheduled after 1-month. After, follow-up visits were scheduled every 3 months aligning with their routine ANC visits. During follow-up visits, participants completed surveys on sexual behaviors and PrEP use and were prescribed additional PrEP prescriptions if interested. Dried blood spots were collected during follow-up for those who reported taking PrEP in the last 30 days prior to the visit for tenofovir diphosphate analysis of estimated PrEP adherence in the past month.[17]

Ethics

The study was approved by the Human Research Ethics Committee at the University of Cape Town (#297/2018) and by the University of California, Los Angeles Institutional Review Board (IRB#18-001622).

Exposure

The primary exposure of this analysis was condomless sex in the past 3 months, defined as reporting being sexually active and using condoms every time ("always"). We coded "no" for condomless sex in the past 3 months if participants were not sexually active or reported always used condoms. Data was also collected on frequency of sexual activity, condom use during last sex, and whether the participant had a new sexual partner in the last 3 months.

Outcome

PrEP use was defined as initiating PrEP at baseline or continuing PrEP in the past 3 months. For secondary analysis, we used the quantifiable levels of tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) as a marker for PrEP use.[17] We also used reporting of any self-reported PrEP use when biomarker data was not available. Participant-visits were marked as "discontinued PrEP" if they missed the study visit.

For prevention-effective adherence (use of PrEP during periods of sexual activity), risk for HIV was considered high if participant reported condomless sex in the last 3 months. Risk was considered low if participant did not report condomless sex or was not sexually active.

Covariates

We stratified the data by gestational periods of Trimester 1, 2, or 3 during pregnancy and early or late postpartum. Trimester 1 is defined as gestational age between 1 and ≤12 weeks, trimester 2 is gestational age between >12 and ≤28 weeks, and trimester 3 is gestational age between >28 weeks among those pregnant. Early postpartum is defined as >0 days and ≤ 6 months post-delivery and later postpartum is defined as >6 months and ≤12 months post-delivery.

Statistical Analysis

First, we combined all our study visits and categorized them by gestational periods. We censored data for those that were no longer PrEP-eligible (seroconverted or were no longer pregnant [termination of pregnancy, miscarriage, or stillbirths]). Gestational age in weeks was calculated using the sum of gestational age at baseline and time in months since baseline date and visit date. We then categorized the time into Trimester 1, 2, or 3 as defined above. For gestational age postpartum, we took the time in months between delivery date and visit date and categorized the time into early and late postpartum as defined above.

We used group-based trajectory modeling (GBMTM)[18] to identify oral PrEP trajectories during the gestational periods. GBMTM identifies clusters of individuals within populations that follow distinct trajectories over time and they are semi-parametric, finite mixture models that were fit using maximum likelihood estimation.[18] We used the traj package for GBMTM in STATA (version 14) and followed Nagin's diagnostic criteria to identify the final model.[19] We described baseline individual factors, clinical and partnership characteristics by their GBMTM sub-groups and computed p-values using t-tests, chi-squared tests, or Fisher's exact test (when categorical variables had cell counts <5) as appropriate.

Then, we described sexual behaviors and PrEP use (self-reported or objectively collected via TFV-DP of DBS at the corresponding visit) during each visit by gestational periods using frequency and percentages. We used the Cochran Mantel-Haenszel tests to compute p-values for trend. We also described prevention-effective adherence or PrEP coverage among those reporting condomless sex in the past 3 months by visits.

We utilized the *longCatEDA* package on R Studio to create a sorted horizontal line plot to visually show condomless sex and PrEP usage (filled prescriptions) by gestational periods.[20] Each line in the plot represents a participant's risk and PrEP use throughout the study, starting from when they entered and followed horizontally across gestational trimesters and postpartum. The visits were color-coded based on the following categories: "condomless sex and PrEP use," "condomless sex and no PrEP use," "always uses condoms or not sexually active and PrEP use," "consistent condom use or not sexually active and no PrEP use." Since we did not have information on sexual behaviors among those who discontinued from the study, we coded them as “unknown condom use and no PrEP use”. If a participant did not have a visit at the consecutive trimester, their visit was marked as missing, but the next visit would be shown in the following gestational period. When participants had multiple visits in the same gestational period, only their first visit was represented in the plot.

To estimate the association between condomless sex and PrEP use, we used generalized estimating equations of repeated measures using the PROC GENMOD statement on SAS. Our models were fit using log link and binomial distribution. We controlled all models for repeated measures of patient identification number by visit number. Condomless sex in the last 3 months was paired with PrEP use reported in the last 3 months at the same visit, reflecting self-reported PrEP usage during the same time as reported sexual behavior. To estimate the magnitude of association between sexual behaviors and PrEP use, we computed risk ratios and corresponding 95% confidence intervals. In addition, our adjusted models were controlled for potential confounders, which were maternal age, partner HIV status (tested HIV

negative vs. living with HIV or unknown serostatus) and gestational age at baseline. We conducted data cleaning and analyses using SAS version 9.4 (SAS Institute).

Results

This study included a cohort of 1200 women who were followed for 12 months, with visits occurring every 3 months. Study participants attended 3367 visits where they reported on their sexual behaviors and use of oral PrEP. The median gestation at first ANC visit was 21 (IQR=15-31), with 21% married and cohabitating with their partner and median age of 26 years (IQR=22-31).

Table 4.1 reported the baseline characteristics of study participants by their oral PrEP trajectory identified using GBMTM. We identified three trajectories: consistent PrEP/declining at late postpartum (40%, n=450), initiated/declining PrEP after initiating (50%, n=571), and low/no PrEP (10%, n=113). Those in consistent PrEP/declining at late postpartum trajectory had greater proportion of those with high self-perceived risk for HIV (16% vs 9% or 8%, P=0.01), past-year IPV (16% vs 10% or 11%, P<0.01), and partner living with HIV or unknown serostatus (35% vs. 29% or 28%, P=0.09) in the past 12 months of baseline visit. Those in low/no PrEP trajectory had lower proportion of women with high self-perceived risk for HIV (8% vs. 9% or 16%, P=0.01), more women were married and cohabitating with their partner (29% vs. 19% or 20%, P=0.04), had a much earlier median 1st ANC visit (12 weeks vs 23 or 22 weeks, P<0.01), and no sexual partner with a HIV positive status in the past 12 months (0% vs. 1% or 3%).

Table 4.2 provided sexual behaviors in the past 3 months by gestational periods. While most women reported being sexually active during trimesters 1, 2, and 3 (100%, 96%, and 90% respectively), the sexual activity prevalence decreased to 67% during early postpartum and slightly increased to 71% by late postpartum (*P for trend*<0.001). Meanwhile, condomless sex in the past 3 months decreased throughout the gestational period (~100% at trimester 1, 93% at trimester 2, 83% at trimester 3, 56% at early and late postpartum, *P for trend*<0.001). The proportion of women with new sexual partners in the last 3 months increased with 4% of women

reporting they had new sex partners in trimester 3, 5% at early postpartum and 6.5% at late postpartum (*P for trend*=0.02).

Table 4.3 provided PrEP use in the past 3 months by gestational periods. PrEP use (initiation/ quantifiable TFV-DP or reported use with confirmation of PrEP prescription during follow-up) decreased across gestational periods (81% at trimester 1, 77% at trimester 2, 66% at trimester 3, 52% at early postpartum, and 54% at late postpartum, *P for trend*<0.001). By including those who discontinued from the study (and therefore PrEP), PrEP use was even lower during follow-up, especially in the latter periods (31% at early postpartum and 26% at later postpartum).

Table 4.4 reported prevention-effective adherence (PrEP coverage among those reporting condomless sex in the past 3 months) of the study visit. Prevention-effective adherence, using PrEP initiation or continuation, was 81% of the visits overall with 81% of visits at trimester 1, 85% at trimester 2, 82% at trimester 3, 76% at early postpartum, and 80% at late postpartum. Prevention-effective adherence, using initiation or self-reported use/quantifiable TFV-DP, was 65% overall with 81% at trimester 1, 78% at trimester 2, 67% at trimester 3, 49% at early postpartum, and 50% at late postpartum. The lowest prevention-effective adherence was observed during early postpartum (49% within 6 months after child delivery).

Figure 4.1 displayed a horizontal line plot of condomless sex in the last 3 months and oral PrEP (TDF/FTC) use by gestational periods. This plot shows dynamic risks for HIV across the gestational periods longitudinally. Those in “yellow” who represent participants reporting condomless sex and no PrEP use and “white” representing those who had unknown condom use information and no PrEP use (discontinued from the study) are of the greatest concern for HIV acquisition, and these are most prevalent during postpartum.

Table 4.5 reported the associations between sexual behaviors and any PrEP use accounting for within-participant correlation between repeated measures and potential confounders. The adjusted risk of PrEP initiation/continuation was higher among those who

were sexually active in the last 3 months (vs. sexually abstinent [aRR=1.08; 95% CI: 1.00-1.17]), and reported any condomless sex during last sex (vs using condoms [aRR=1.09; 95% CI: 1.02, 1.17]), and condomless sex in the last 3 months (vs. less than always condom use or sexually abstinent [aRR=1.09; 95% CI 1.01, 1.16]) after controlling for potential confounders. The adjusted risk of PrEP initiation/use (quantifiable TFV-DP or self-reported) was higher among those who reported being sexually active in the last 3 months (vs. sexually abstinent [aRR=1.86; 95% CI: 1.63-2.11]), condomless sex during last sex (vs. consistent use of condoms [aRR=1.51; 95% CI: 1.36, 1.68]), condomless sex in the last 3 months (vs. consistent condom use or sexually abstinent [aRR=1.88; 95% CI 1.67, 2.12]), and reporting a new sexual partner in the last 3 months (vs. no new sexual partner [aRR=1.12; 95% CI: 0.94, 1.33]) after controlling for potential confounders.

Discussion

This longitudinal study investigated the dynamic changes of sexual behaviors and oral PrEP (TDF/FTC) use throughout pregnancy and postpartum. We found that prevention-effective adherence to PrEP was high during trimesters 1 and 2 but declined during trimester 3 and postpartum, with the lowest PrEP coverage observed during early postpartum. While most women were sexually active from trimester 1 to 3, fewer women were sexually active during postpartum. Condomless sex was also least prevalent during postpartum. However, there were numerous women with new sexual partners during postpartum (5.3% at early postpartum and 6.5% at late postpartum). By using group-based trajectory models, we found that those with high self-reported HIV risk perception, IPV victimization in the past-year, and partner of unknown or positive HIV status were largely in the consistent PrEP use trajectory.

The prevalence of prevention-effective adherence (PrEP coverage during periods of condomless sex) differed by the definitions used for measuring PrEP use. We were limited by the small number of high TFV-DP (~ 7 doses/week) in our sample that is needed for adequate protection from HIV exposures for cisgender women. Therefore, we used two indicators of PrEP

instead: continuation (filled prescriptions) and any use (quantifiable TFV-DP or self-reported use) during follow-up visits. Prevention-effective adherence remained high across gestational periods when we used continuation measures (range: 76%-85% of visits), but they were lower when we used self-reported or biomarker indicators for any PrEP use (range: 49%-53% of visits) during follow-up. Moreover, our findings showed a moderate association between sexual behaviors and any oral PrEP use when we used self-reported or biomarkers. While there was still a positive association, the strength of association was weaker for sexual behaviors and continuation (filled prescriptions) of PrEP. Use of various measures of PrEP have their advantages and disadvantages given different settings[21], but using biomarker data is advantageous for clinical practice.[9] We also measured sexual behaviors during follow-up visits every 3 months, but more frequent measures might be better in capturing the shifts between changing sexual behaviors and PrEP adherence (such as by using urine TFV testing to measure recent PrEP use).[22]

Pregnant and postpartum women in our study were more likely to continue using PrEP during periods of sexual activity and condomless sex. Our findings on prevention-effective adherence were consistent with previous literature among other sub-populations.[9,23-25] However, prevention-effective adherence was lowest during postpartum. We also noted there was a high occurrence of new sexual partners during postpartum. PrEP coverage during early postpartum where most women are breastfeeding for the first few months is important to avoid vertical transmission through breastfeeding. This finding also presents opportunities to expand upon existing PrEP guidelines and provide counselling with an emphasis on prevention-effective adherence throughout pregnancy and especially postpartum. Providers counselling on oral PrEP should evaluate patient's need for PrEP by fostering discussions around their patient's HIV risk, including condom use, information about sexual partners such as HIV or antiretroviral status, STI risk, and how/when to stop and restart on PrEP. We also need to provide patients with options for PrEP.[26] With the roll-out of long-acting agents such as vaginal rings (Dapivirine)

and injectables (Cabotegravir), it is important for guidelines and drug licensures to include pregnant women with high risk of HIV, so they have options with biomedical HIV preventions that work best with their lifestyle.[26]

Strengths and Limitations

The PrEP-PP study was uniquely able to prospectively measure changes in sexual behaviors and oral PrEP use measured in multiple modalities (filled prescriptions, TFV-DP in DBS, self-reported use with confirmation of filled prescriptions) across gestational periods (trimester 1 of pregnancy through 12 months postpartum). This study was limited by considerable drop-offs of participants from the study during postpartum, which could be due to periods of low or no sexual activity.[7] It may also be due to less frequent contact with antenatal care facilities after child delivery.[8,27] Women may be more inclined to stay on PrEP with fears of vertical transmission during pregnancy, but less during postpartum. With greater focus on their newborn, women may pay less attention to postnatal care.[28] Future studies should focus on understanding the nuances behind discontinuation of oral PrEP during postpartum. Though greater continuation of PrEP during periods of condomless sex is promising, we were underpowered to examine women with high TFV-DP (~7 doses/week), which is adequate use of PrEP during periods of sexual activity for sufficient protection against HIV.[9] This study also recruited ciswomen from one antenatal clinic and therefore may not be generalizable in a different setting or population.

Conclusion

This study longitudinally evaluated patterns of prevention-effective adherence by gestational periods and postpartum. We found an association between engaging in condomless sex and PrEP use, which suggests that pregnant and postpartum women align their PrEP use by potential HIV risks. However, prevention-effective adherence was lowest during postpartum meaning targeted research and interventions are necessary to understand the nuances behind PrEP discontinuation despite HIV risks after delivery. Our findings encourage providers of oral

PrEP to foster discussions about changing HIV risk during PrEP counselling. Our study contributes to a new understanding about patterns of prevention-effective adherence during gestational periods of pregnancy and postpartum that can inform PrEP delivery in Cape Town and surrounding regions.

Figure 4.1. Horizontal Line Plot of condomless sex in the last 3 months and oral PrEP (TDF/FTC) use by gestational period (n=1199)

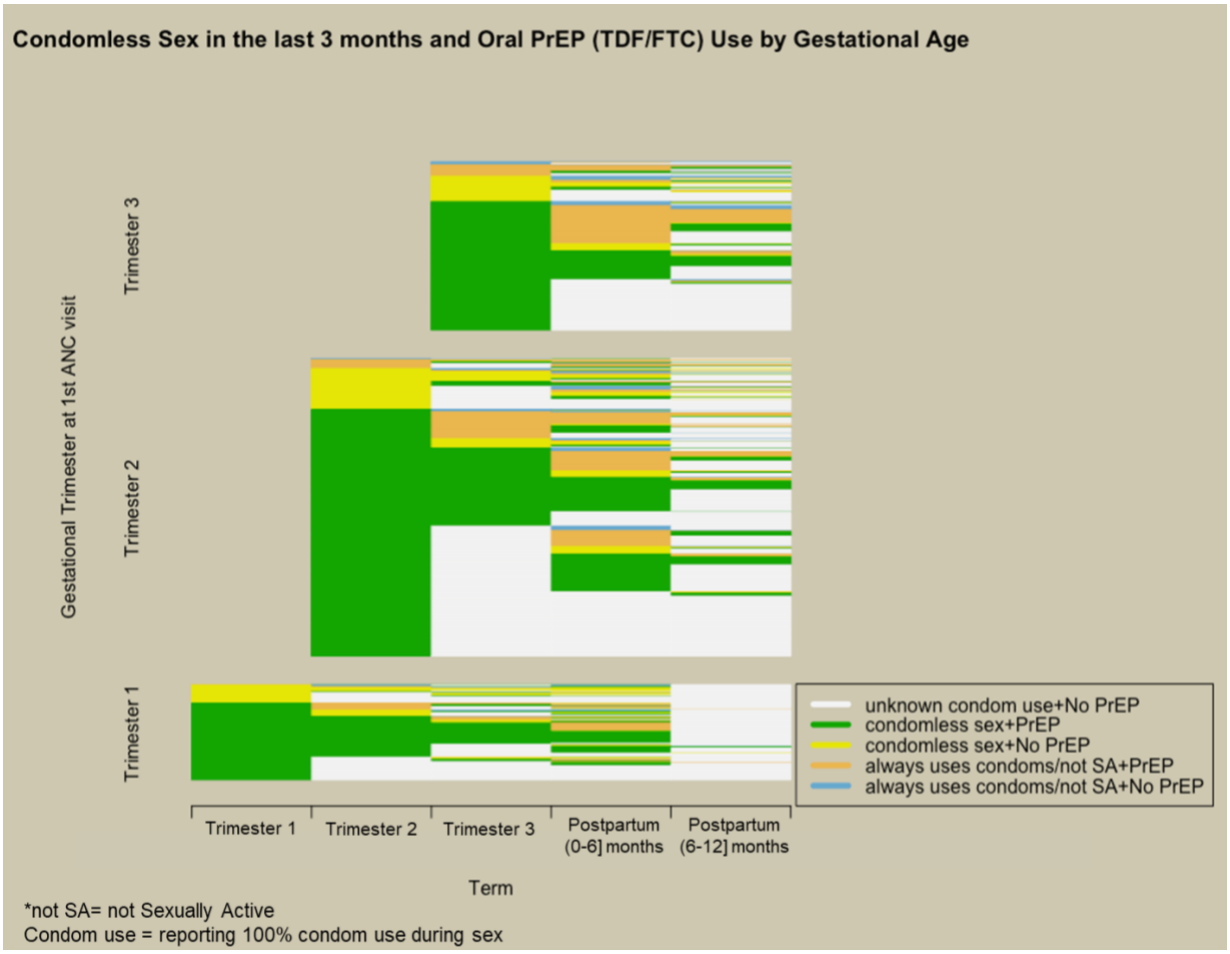


Table 4.1. Baseline characteristics of women by their Oral PrEP trajectory through gestational periods in the PrEP-PP study in Cape town, South Africa (n=1134)

	Overall	Group 1 (Initiated/ Gradually declining PrEP)	Group 2 (Consistent PrEP/declining at late postpartum)	Group 3 (Low/No PrEP)	*P*
	n(%) or median(IQR)	N=571 (50%)	N=450 (40%)	N=113 (10%)	
Individual Factors					
Age, years	26 (22-31)	26 (22-30)	26 (22-31)	27 (22-31)	0.28
Education, >secondary school	584 (51.5)	311 (54.5)	213 (47.3)	60 (53.1)	0.07
Moderate/High socioeconomic status	770 (67.9)	393 (68.8)	295 (65.6)	82 (72.6)	0.29
Risk Perception for HIV as "high"	136 (11.6)	52 (9.1)	70 (15.6)	9 (8.0)	**0.01**
Self-reported recent depression (EPDS≥11)	81 (7.1)	39 (6.8)	36 (8.0)	6 (5.3)	0.56
Clinical characteristics					
Gestational age at 1st ANC visits, weeks	21 (15-31)	23 (17-33)	22 (16-32)	12 (9-21)	**<0.01**
Primigravida	385 (34.0)	208 (36.4)	141 (31.3)	36 (31.9)	0.21
STI diagnosis *(Chlamydia trachomatis, Neisseria gonorrhoeae and/or Trichomonas vaginalis)*	373 (31.2)	180 (31.8)	143 (31.8)	32 (28.3)	0.76
Partnership characteristics					
Married and cohabitating with partner	228 (20.7)	105 (19.7)	77 (19.1)	31 (28.7)	**0.04**
Cohabitating with partner	441 (36.9)	203 (35.6)	163 (36.2)	49 (43.4)	0.28
Past-year Intimate Partner Violence	147 (12.3)	55 (9.6)	74 (16.4)	12 (10.6)	**<0.01**
Partner HIV status in the past 12 months, (unknown/positive)	373 (31.2)	163 (28.6)	156 (34.7)	32 (28.3)	0.09
Partner HIV status in the past 12 months, (positive)	20 (1.7)	7 (1.2)	12 (2.7)	0 (0.0)	NA

Data are n(%) or median (IQR). N= Number of participants at baseline

Abbreviations: IQR = Interquartile Range; PrEP=pre-exposure prophylaxis; STI = sexually transmitted infections; PrEP-PP= PrEP in Pregnancy and Postpartum cohort study; NA= Not Applicable; EPDS= Edinburgh Perinatal Depression Scale with a cut-off of ≥ 11 for probable depression)

Table 4.2. Sexual Behaviors by gestational periods in the PrEP-PP study in Cape Town, South Africa (visits = 3367).

	Trimester 1 (n=192)	Trimester 2 (n=818)	Trimester 3 (n=746)	Postpartum (0-6] months (n=1241)	Postpartum (6-12] months (n=370)	P for trend†
	n (%)	n (%)	n (%)	n (%)	n (%)	
Sexually active in the past 3 months						
No	0 (0.0)	32 (3.9)	72 (9.7)	416 (33.5)	108 (29.2)	<.0001
Yes	192 (100.0)	786 (96.1)	674 (90.4)	825 (66.5)	262 (70.8)	
Condom use frequency in the past 3 months*						
Never	132 (69.1)	535 (68.1)	428 (63.5)	454 (55.0)	121 (46.2)	<.0001
Sometimes	58 (30.4)	229 (29.1)	192 (28.5)	246 (29.8)	86 (32.8)	
Always	1 (0.52)	22 (2.8)	54 (8.0)	125 (15.2)	55 (21.0)	
Condomless sex in the past 3 months						
No	1 (0.5)	54 (6.6)	126 (16.9)	541 (43.6)	163 (44.1)	<.0001
Yes	191 (99.5)	764 (93.4)	620 (83.1)	700 (56.4)	207 (56.0)	
Condomless sex during last sex						
No	9 (4.7)	95 (12.1)	108 (16.0)	224 (27.2)	98 (37.4)	<.0001
Yes	182 (95.3)	691 (87.9)	566 (84.0)	601 (72.9)	164 (62.6)	
Frequency of sexual acts in the past 3 months						
Once a month or less often	16 (8.3)	90 (11.5)	104 (15.4)	172 (20.9)	35 (13.4)	
2-4 times a month	89 (46.4)	385 (49.0)	338 (50.2)	424 (51.4)	123 (47.0)	<.0001
5-20 times per month	70 (36.5)	257 (32.7)	204 (30.3)	189 (22.9)	85 (32.4)	

More than 20 times per month	17 (8.9)	54 (6.9)	28 (4.2)	40 (4.9)	19 (7.3)	
New sexual partners in the past 3 months						
No	186 (96.9)	785 (97.3)	684 (95.8)	999 (94.7)	273 (93.5)	0.0220
Yes	6 (3.1)	22 (2.7)	30 (4.2)	56 (5.3)	19 (6.5)	

n= number of visits. Data are n(col%) or median (IQR). †P-values for trend were calculated with the use of Cochran Mantel-Haenszel tests, where appropriate. *among those sexually active.

Condomless sex in the past 3 months: 'No' defined as always used condoms or was not sexually active and 'Yes' defined as did not always use condoms when sexually active.New sexual partners= >1 sexual partner for baseline visit and new partners since the last study visit for follow-up
Abbreviations: PrEP=pre-exposure prophylaxis; PrEP-PP= PrEP in Pregnancy and Postpartum cohort study

Table 4.3a. PrEP use by gestational periods in the PrEP-PP study in Cape Town, South Africa (visits = 3367).

	Trimester 1 (n=192)	**Trimester 2 (n=818)**	**Trimester 3 (n=746)**	**Postpartum (0-6] months (n=1241)**	**Postpartum (6-12] months (n=370)**	**P for trend†**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Any PrEP use (initiation for baseline and continuation for follow-up visits)						
No	36 (18.8)	120 (14.7)	135 (18.2)	275 (22.2)	76 (20.5)	0.0010
Yes	156 (81.3)	694 (85.3)	606 (81.8)	964 (77.8)	294 (79.5)	
Any PrEP use (initiation for baseline and any TFV-DP levels or self-reported use)						
No	36 (18.8)	187 (22.9)	255 (34.2)	601 (48.4)	170 (46.0)	<.0001
Yes	156 (81.3)	631 (77.1)	491 (65.8)	640 (51.6)	200 (54.1)	

n=number of visits. Data are n(col%) or median (IQR). †P-values for trend were calculated with the use of Cochran Mantel-Haenszel tests, where appropriate.

Abbreviations: PrEP=pre-exposure prophylaxis; PrEP-PP= PrEP in Pregnancy and Postpartum cohort study

Table 4.3b. PrEP use by gestational periods among study participants from the PrEP-PP study in Cape Town, South Africa (visits = 4929) - including those who discontinued from the study.

	Trimester 1 (n=192)	Trimester 2 (n=918)	Trimester 3 (n=946)	Postpartum (0-6] months (n=2102)	Postpartum (6-12] months (n=771)	P for trend†
	n (%)	n (%)	n (%)	n (%)	n (%)	
Any PrEP use (initiation for baseline and continuation for follow-up visits)						
No	36 (18.8)	220 (24.1)	335 (35.6)	1136 (54.1)	477 (61.9)	<.0001
Yes	156 (81.3)	694 (75.9)	606 (64.4)	964 (45.9)	294 (38.1)	
Any PrEP use (initiation for baseline and any TFV-DP levels or self-reported use)						
No	36 (18.8)	287 (31.3)	455 (48.1)	1460 (69.5)	570 (74.0)	<.0001
Yes	156 (81.3)	631 (68.7)	491 (51.9)	640 (30.5)	200 (26.0)	

Table 4.4. Prevention-effective adherence: PrEP coverage among those reporting condomless sex in the past 3 months by gestational periods (visits=2482).

	Participant-visits reporting condomless sex	Overall P(PrEP=1|condomless sex=1)	Trimester 1	Trimester 2	Trimester 3	Postpartum (0-6] months	Postpartum (6-12] months
All visits			**n=191**	**n=760**	**n=615**	**n=700**	**n=207**
Initiated or continued on PrEP	2473	81%	81%	85%	82%	76%	80%
Initiated PrEP, had quantifiable TFV-DP levels, or self-reported PrEP use	2480	65%	81%	78%	67%	49%	50%
Excludes Baseline Visit			**n=0**	**n=181**	**n=305**	**n=70**	**n=207**
Continued PrEP	1404	78%	NA	83%	80%	76%	80%

Quantifiable TFV-DP levels or self-reported PrEP use	1403	50%	NA	53%	51%	49%	50%
Quantifiable TFV-DP levels only	448	53%	NA	57%	61%	43%	52%

n=Participant-visits of condomless sex in the past 3 months
; Abbreviations: PrEP=pre-exposure prophylaxis; TFV-DP = Tenofovir-Diphosphate; DBS= Dried Blood Spots

Table 4.5. Associations between sexual behaviors and any PrEP use (visits=3367).

	PrEP initiation and continuation					**PrEP initiation and use (any quantifiable TFV-DP in DBS or self-reported PrEP use)**				
Sexual Behaviors	**% of visits**	**RR**	**95% CI**	**aRR***	**95% CI**	**% of visits**	**RR**	**95% CI**	**aRR***	**95% CI**
Sexually Active in the last 3 months										
No	499 (18.4)	1		1		343 (16.2)	1		1	
Yes	2215 (81.6)	0.95	(0.87, 1.04)	**1.08**	**(1.00, 1.17)**	1775 (83.8)	**2.14**	**(1.74, 2.64)**	**1.86**	**(1.63, 2.11)**
Condomless sex during last sex										
No	447 (20.2)	1		1		344 (19.4)	1		1	
Yes	1768 (79.8)	1.08	(0.99, 1.18)	**1.09**	**(1.02, 1.17)**	1431 (80.6)	**1.25**	**(1.08, 1.45)**	**1.51**	**(1.36, 1.68)**
Condomless sex in the last 3 months**										
No	712 (26.2)	1.00		1.00		505 (23.8)	1		1	

Yes	2002 (73.8)	**0.96**	**(0.95, 0.97)**	**1.09**	**(1.01, 1.16)**	1613 (76.2)	**2.12**	**(1.79, 2.50)**	**1.88**	**(1.67, 2.12)**
New sexual partners in the past 3 months***										
No	2392 (96.1)	1		1		1880 (96.1)	1		1	
Yes	96 (3.9)	1.05	(0.88, 1.26)	1.06	(0.89, 1.26)	77 (3.9)	1.03	(0.90, 1.17)	1.12	(0.94, 1.33)

PrEP=pre-exposure prophylaxis; RR=risk ratio; aRR=adjusted risk ratio.*adjusted for potential confounders and repeated measures of pid by visit number. Potential confounders were maternal age, partner HIV status (negative vs. positive/unknown) and gestational period.** Condomless sex in the past 3 months: 'No' defined as always used condoms or was not sexually active and 'Yes' defined as did not always use condoms when sexually active.*** New sexual partners= >1 sexual partner for baseline visit and new partners since the last study visit for follow-up **** Model did not converge so this model did not control for partner HIV status (small sample size).

Supplemental Table 4.1. Number of study visits by gestational periods from baseline to 12-month follow-up in the PrEP-PP study in Cape Town, South Africa (Visits=3367).

	Overall	**Trimester 1**	**Trimester 2**	**Trimester 3**	**Postpartum (0-6] months**	**Postpartum (6-12] months**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Baseline	1138	192 (17.0)	599 (53.0)	339 (30.0)	0 (0.0)	0 (0.0)
3-month visit	694	0 (0.0)	212 (30.6)	255 (36.7)	227 (32.7)	0 (0.0)
6-month visit	579	0 (0.0)	7 (1.2)	146 (25.2)	426 (73.6)	0 (0.0)
9-month visit	517	0 (0.0)	0 (0.0)	5 (1.0)	402 (77.8)	110 (21.3)
12-month visit	447	0 (0.0)	0 (0.0)	1 (0.2)	186 (41.6)	260 (58.2)
Total visits	3367	192 (5.7)	818 (24.3)	746 (22.2)	1241 (36.9)	370 (11.0)
Total with follow-up visits only	2237	0 (0.0)	219 (9.8)	407 (18.2)	1241 (55.5)	370 (16.5)

*Row percents; n=visits.

Supplemental Table 4.2. Number of study visits by gestational periods in the PrEP-PP study in Cape Town, South Africa (Visits = 4929) - Including those who discontinued the study.

	Overall	Trimester 1	Trimester 2	Trimester 3	Postpartum (0-6] months	Postpartum (6-12] months
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Baseline	1130	192 (17.0)	599 (53.0)	339 (30.0)	0 (0.0)	0 (0.0)
3-month visit	1077	0 (0.0)	311 (28.9)	363 (33.7)	403 (37.4)	0 (0.0)
6-month visit	1052	0 (0.0)	8 (0.8)	231 (22)	813 (77.3)	0 (0.0)
9-month visit	900	0 (0.0)	0 (0.0)	10 (1.1)	633 (70.3)	257 (28.6)
12-month visit	770	0 (0.0)	0 (0.0)	3 (0.4)	253 (32.9)	514 (66.8)
Total visits	4929	192 (3.9)	918 (18.6)	946 (19.2)	2102 (42.7)	771 (15.6)
Total with follow-up visits only	3799	0 (0.0)	319 (8.4)	607 (16.0)	2102 (55.3)	771 (20.3)

*Row percents; n=visits.

Supplemental Table 4.3. Sexual Behaviors and PrEP use by gestational periods, combined Baseline and follow-up visits through 12 months (visits = 4929) - Includes those who discontinued the PrEP-PP study.

	Trimester 1 (n=192) %	Trimester 2 (n=918) %	Trimester 3 (n=946) %	Postpartum (0-6] months (n=2102) %	Postpartum (6-12] months (n=771) %
Sexually active in the past 3 months					
No	0 (0.0)	32 (3.5)	72 (7.6)	416 (19.8)	108 (14.0)
Yes	192 (100.0)	786 (85.6)	674 (71.3)	825 (39.3)	262 (34.0)
Unknown	0 (0.0)	100 (10.9)	200 (21.1)	861 (41.0)	401 (52.0)
Condom use frequency in the past 3 months					
Never (Not at all)	132 (68.8)	535 (58.3)	428 (45.2)	454 (21.6)	121 (15.7)
Sometimes (Rarely/sometimes)	57 (29.7)	206 (22.4)	176 (18.6)	220 (10.5)	82 (10.6)
Always (always/almost always)	2 (1)	45 (4.9)	70 (7.4)	151 (7.2)	59 (7.7)
Unknown	1 (0.5)	132 (14.4)	272 (28.8)	1277 (60.8)	509 (66)
Condomless sex in the past 3 months (always used condoms)					
No	1 (0.5)	54 (5.9)	126 (13.3)	541 (25.7)	163 (21.1)

Yes	191 (99.5)	764 (83.2)	620 (65.5)	700 (33.3)	207 (26.9)
Unknown	0 (0.0)	100 (10.9)	200 (21.1)	861 (41)	401 (52.0)
Condomless sex during last sex					
No	9 (4.7)	95 (10.4)	108 (11.4)	224 (10.7)	98 (12.7)
Yes	182 (94.8)	691 (75.3)	566 (59.8)	601 (28.6)	164 (21.3)
Unknown	1 (0.5)	132 (14.4)	272 (28.8)	1277 (60.8)	509 (66.0)
Frequency of sexual acts in the past 3 months					
Once a month or less often	16 (8.3)	90 (9.8)	104 (11.0)	172 (8.2)	35 (4.5)
2-4 times a month	89 (46.4)	385 (41.9)	338 (35.7)	424 (20.2)	123 (16.0)
5-20 times per month	70 (36.5)	257 (28.0)	204 (21.6)	189 (9.0)	85 (11.0)
More than 20 times per month	17 (8.9)	54 (5.9)	28 (3.0)	40 (1.9)	19 (2.5)
Unknown	0 (0.0)	132 (14.4)	272 (28.8)	1277 (60.8)	509 (66)

Data are n(col%) or median (IQR). †P-values for trend were calculated with the use of Cochran Mantel-Haenszel tests, where appropriate. **n= number of visits.** Condom use determined as "almost always or always" = yes; Unknown= missing data because of discontinuation from the study; Abbreviations: PrEP=pre-exposure prophylaxis; PrEP-PP= PrEP in Pregnancy and Postpartum cohort study

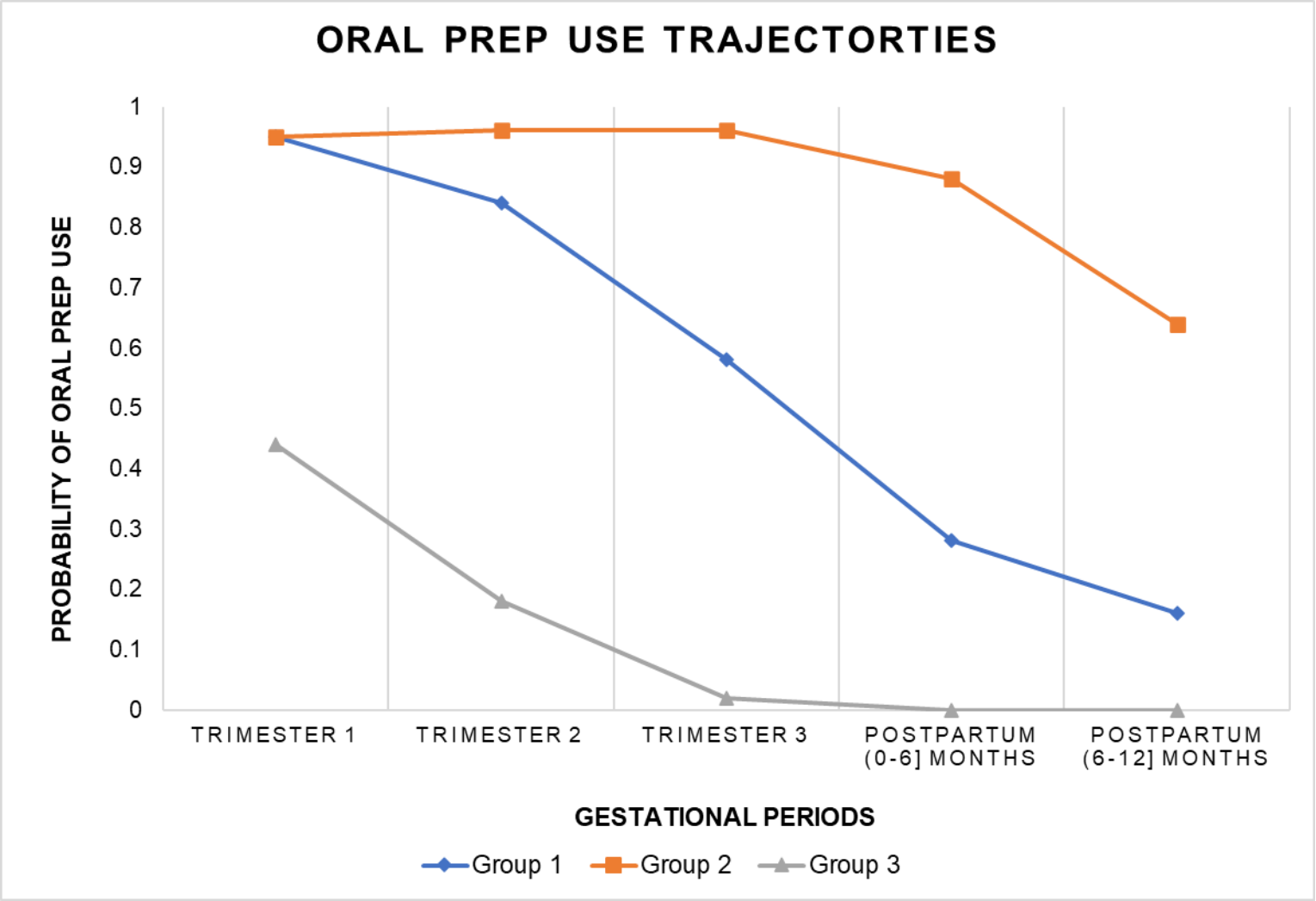
Supplemental Table 4.4. Prevention-effective adherence: PrEP coverage among those reporting condomless sex in the past 3 months by gestational periods (visits=2482).

	Participant-visits reporting condomless sex	Overall P(PrEP=1|condomless sex=1)	Trimester 1	Trimester 2	Trimester 3	Postpartum (0-6] months	Postpartum (6-12] months
All visits			**n=191**	**n=760**	**n=615**	**n=700**	**n=207**
Initiated or continued on PrEP	2473	81%	81%	85%	82%	76%	80%
Initiated PrEP, had quantifiable TFV-DP levels, or self-reported PrEP use among those without DBS analyzed	2480	65%	81%	78%	67%	49%	50%

Excludes Baseline Visit			**n=0**	**n=181**	**n=305**	**n=70**	**n=207**
Continued PrEP	1393	78%	NA	83%	80%	76%	80%
Quantifiable TFV-DP levels or self-reported PrEP use among those without DBS analyzed	1400	50%	NA	53%	51%	49%	50%
Quantifiable TFV-DP levels only	448	53%	NA	57%	61%	43%	52%

n=Participant-visits of condomless sex in the past 3 months
; Abbreviations: PrEP=pre-exposure prophylaxis; TFV-DP = Tenofovir-Diphosphate; DBS= Dried Blood Spots

Supplemental Figure 4.1. Oral PrEP Use Trajectories in the PrEP-PP Study (N=1134)



Oral PrEP use trajectories among 1134 HIV-negative PrEP in Pregnancy and Postpartum (PrEP-PP) participants. Oral PrEP (TDF-FTC) was defined as initiation and continuation using filled prescriptions for PrEP. The identified groups represent those who Initiated/declining PrEP (N=571, 50.4%), Consistent PrEP/declining at late postpartum (N=540, 39.7%), and low/no PrEP (N=113, 10.0%) trajectories over time.

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Chapter V. Public Health Importance

HIV acquisition rates among women during pregnancy and postpartum remain alarmingly high.[1,2] Oral pre-exposure prophylaxis (PrEP; TDF/FTC) can be used to prevent HIV acquisition[3], but its benefits are often hindered by challenges related to continuation and adherence.[4,5] This dissertation sheds light on the factors that influence the uptake and adherence of oral PrEP among pregnant and postpartum women, including adolescent girls and young women (AGYW) who are at higher risk of HIV infection, experiencing intimate partner violence (IPV), or during periods of unprotected condomless sex. The findings of this dissertation suggest that pregnant and postpartum women with a higher risk of HIV acquisition are more likely to continue and adhere to oral PrEP, particularly during periods of condomless

sex and IPV victimization. Despite these encouraging results, cisgender women still face significant challenges in achieving adequate adherence to oral PrEP, which requires taking seven doses per week during periods of sexual activity.

Our first study investigated behavioral patterns of AGYW in accessing oral PrEP at antenatal care (ANC) facility. This study was among the first to describe the HIV Prevention/oral PrEP cascade for AGYW during pregnancy and postpartum. Our findings indicate that AGYW had a high rate of PrEP initiation (83%), but continuation rates rapidly decreased over time, with 63% retained at the 1-month visit, 53% at the 3-month visit, and only 34% at the 6-month visit, which is consistent with older women. Encouragingly, AGYW with greater actual HIV risk and risk perceptions were more likely to consistently continue PrEP through 6 months. However, we also identified unique factors that put AGYW, especially adolescent girls, at greater risk of HIV infection. For instance, adolescent girls presented for their first antenatal visit at 28 weeks, which is 3rd trimester of pregnancy and much later than the recommended time of 14 weeks by the South African national guidelines. Adolescent girls also had a high burden of treatable sexually transmitted infections (STIs) (48%) and 19% with co-infections at their first visit. While STI management is a standard of care during primary care visits, our study suggests that coupled with late ANC initiation, there are gaps in HIV prevention efforts for pregnant adolescent girls. We advocate for the promotion of early prenatal care and strengthening interventions to test, manage, and treat STIs beyond primary care settings for adolescent girls.

During pregnancy, women are also at risk of experiencing IPV. Our second study found that 12% of pregnant women experienced physical, emotional, or sexual IPV in the past year, and 5% had incident IPV. Emotional violence was the most common form of IPV, followed by physical and sexual violence. Women with past-year IPV victimization were more likely to report engaging in condomless sex, having multiple sexual partners, experiencing depression, and engaging in hazardous alcohol use before pregnancy, and they also perceived themselves to be at higher risk for HIV. Given the elevated HIV risk among women experiencing IPV, we

investigated the effects of recent or past-year IPV on oral PrEP continuation and adherence. We found that women with past-year IPV had higher rates of PrEP continuation and higher odds of moderate/high tenofovir-diphosphate levels (an indicator of PrEP adherence) than those who did not report IPV. This finding is encouraging, as it suggests that PrEP can be an effective tool for reducing HIV risk and increasing women's agency over their health, even in the context of IPV. We recommend that ANC clinics implement violence screening and provide interventions as needed while continuing to promote oral PrEP for HIV prevention among sexually active pregnant and postpartum women.

In our third study, we longitudinally examined the dynamic changes in sexual behaviors and oral PrEP use throughout the gestations of pregnancy and postpartum. Pregnant and postpartum women in our study were more likely to continue using PrEP during periods of sexual activity and condomless sex. We found that while most women had condomless sex during trimesters 1 through 3, fewer women were sexually active or having condomless sex during early and late postpartum. Among those having condomless sex, PrEP use was high during trimesters 1 and 2 but declined during trimester 3 through postpartum. We also identified 3 oral PrEP trajectories participants had in the study with the majority in the initiated/declining PrEP (50%) group or consistently used PrEP/declining late postpartum (40%) group and fewer (10%) in the low/no prep trajectory. Those with high self-reported HIV risk perception, IPV victimization in the past-year, or sexual partners of unknown or positive HIV status were largely in the consistent PrEP use trajectory. Our findings indicate that women are already practicing prevention-effective adherence (i.e., altering PrEP use during periods of sexual activity) during pregnancy. During postpartum, we observed lower prevention-effective adherence and higher discontinuation from PrEP and the study. Thus, we need more understanding of barriers to PrEP use or why women discontinue PrEP during postpartum. Findings from this study support current literature[6] for oral PrEP counseling to promote open discussions about changing HIV

risks and how to properly stop and restart PrEP with dynamic sexual behaviors for adequate protection against HIV exposures.

While this dissertation focused on oral PrEP (TDF-FTC), we recognize that the rollout of long-acting methods for preventing HIV is underway[7], offering the potential to overcome current adherence challenges. We advocate for the licensure and guidelines for new and emerging PrEP modalities, such as long-acting injectables (Cabotegravir) and vaginal rings (Dapivirine), to include pregnant and postpartum women.[8] This will provide those with high interest in oral PrEP, such as AGYW, those experiencing IPV, and those with dynamic sexual behaviors to have options for better adherence for sufficient protection against HIV. It also provides pregnant and postpartum women with a range of biomedical options for prevention against the risks of HIV. Even with these options, women will continue to opt for oral PrEP and findings from this dissertation have the potential to improve PrEP delivery in South Africa and surrounding regions.

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