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Improving the delivery of pre-exposure prophylaxis (PrEP) to eliminate vertical HIV transmission

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Improving the delivery of pre-exposure prophylaxis (PrEP) to eliminate vertical HIV transmission

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Editorial: Improving the delivery of pre-exposure prophylaxis (PrEP) to eliminate vertical HIV transmission

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pre-exposure prophylaxis (PrEP), HIV, pregnancy and lactation, prevention of vertical transmission of HIV, PrEP implementation

Editorial on the Research Topic
Improving the delivery of pre-exposure prophylaxis (PrEP) to eliminate vertical HIV transmission

HIV pre-exposure prophylaxis (PrEP) significantly reduces new HIV infections (1). Among pregnant and lactating cisgender women in high HIV prevalence settings PrEP offers dual benefits for maternal and infant HIV prevention and is increasingly integral to vertical transmission prevention programs (2, 3). Many countries in East and Southern Africa with high HIV burden have integrated oral PrEP into HIV prevention programs (4), in the form of daily oral tenofovir disoproxil fumarate (TDF) containing regimens. While daily oral TDF-based PrEP use in pregnancy and lactation is considered safe and effective (5), only recently are data on PrEP implementation and extended safety emerging (6–8). As additional PrEP options become available (9), there is a need for more evidence on how to ensure effective antenatal and postnatal use (10).

Because of its high relevance to public health—and to global goals to eliminate pediatric HIV—we sought to highlight new research in this field. The result is this collection, which includes 13 articles of work done in sub-Saharan Africa (South Africa, Kenya, Eswatini, Zambia, Malawi, Lesotho, and Uganda) and the United States, demonstrating the importance of the topic globally. This body of work followed four major themes: (1) client knowledge, attitudes, and beliefs about PrEP (2) the PrEP care continuum, (3) healthcare provider experiences and attitudes and (4) PrEP safety, effectiveness, and delivery in pregnancy (Table 1). This work spanned the periconceptional period, pregnancy, and lactation. From this collection, we take away important lessons that will assist in advancing the field of PrEP provision of pregnant and lactating people.

Firstly, community PrEP education is critical to reducing stigma and increasing support for PrEP. Three studies explored PrEP knowledge, attitudes, and beliefs among pregnant and postpartum women and their partners. PrEP was viewed as safe and

TABLE 1 Summary of studies on PrEP in pregnant and lactating women in this collection.

Theme/Summary topic	Authors	Setting	Study design	Objective(s)	Population
Client knowledge, attitudes and believes about PrEP in pregnant or lactating people	Hamoonga et al.	Zambia	Qualitative	To explore attitudes and beliefs about PrEP among PLP	In depth interviews (IDIs) with purposively sampled 24 HIV negative pregnant and breastfeeding women (50% under 24 years)
	Young et al.	Malawi	Qualitative	To understand, from the perspective of both women and men, how male partners were involved in supporting women's oral PrEP use during pregnancy and postpartum and the impact this support had on their PrEP adherence. To understand the bidirectional impact of women's PrEP use on antiretroviral therapy (ART) use among male partners living with HIV.	IDIs with purposively recruited pregnant women and their partners (30 women and 20 men)—mix of the male population to include men living with HIV, unknown male HIV status. Women included met HIV risk indications for PrEP.
	Khumalo et al.	Eswatini	Cross sectional survey	To determine PrEP related levels of knowledge, attitudes, intentions and practices and to determine factors associated with use and intention to use PrEP	1,149 HIV negative pregnant and postpartum women
Health Care Worker (HCW) experiences and attitudes of PrEP	Pleaner et al.	South Africa	Qualitative	Understand health care worker experiences of and attitudes towards introduction of PrEP as a new HIV prevention method, and its integration within broader sexual and reproductive health (SRH) services for youth	Free text responses from 48 purposively sampled health care workers in primary health care and mobile clinics
	Wagner et al.	Kenya	Qualitative	To explore health care worker perspectives on barriers to PrEP delivery and strategies for overcoming those barriers that can be empirically tested in future studies as programs seek to integrate PrEP into existing clinical services.	Focus group discussions with 50 health care workers
	Hicks et al.	Kenya	Quantitative survey	To document available services and commodities via a modified service availability and readiness assessment (SARA) survey in PrEP experienced clinics	Health care workers with experience delivering PrEP to pregnant and postpartum women in 55 facilities
PrEP delivery	Sila et al.	Kenya	Difference-in-differences design	To test a combination of three implementation strategies (video education, HIV self-testing for repeat HIV testing, and PrEP dispensing in maternal can child health clinics) to decrease client waiting time, improve coverage of PrEP education and PrEP offer, improve PrEP knowledge, and maintain satisfaction for clients and HCWs.	960 pre-intervention (480 in comparison and 480 in intervention sites) and 959 during the intervention (478 in comparison and 481 in intervention sites)- All pregnant
	Masenyetse et al.	Lesotho	Retrospective cohort	To characterize the PrEP cascade and use patterns among pregnant and postpartum women	Routine PrEP health records of 4,098 participants in 26 health facilities—389 pregnant and postpartum women data included in analysis
	Khadka et al.	South Africa	Cohort	To examine PrEP initiation, continuation through 6 months, and persistence and evaluate the association between baseline HIV risk and PrEP delivery outcomes	486 pregnant women were included in the study, of which 16% were "adolescents" (aged 16–18 years) and 84% were "young women" (aged 19–24 years).
	Hurwitz et al.	South Africa	Single arm longitudinal	To evaluate the use of TDF/FTC as PrEP among women with potential for HIV-exposure and planning for pregnancy using group-based trajectory models	Women aged 18–35 with intention to get pregnant and partner living with HIV or of unknown HIV status (periconceptional PrEP)
PrEP Safety/Effectiveness and delivery	Scott et al.	Clinical trial data from Kenya Uganda and USA	Pharmacokinetic study	To evaluate upward-adjustment of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) PrEP dosing during pregnancy	Modeling study
	Zewdie et al.	Uganda	Cohort	To evaluate the impact of TDF-based PrEP use on bone mineral density loss during pregnancy and investigate the effect of pregnancy on daily oral PrEP adherence and continuation.	499 HIV negative women aged 16–25 including pregnant women
	Fairlie et al.	LMICs	Review/ Commentary	Review safety profiles of currently available PrEP candidates in women of child-bearing potential, pregnancy and breastfeeding and discuss pragmatic approaches for such surveillance in HIV-endemic LMICs.	Review study

effective; however, Hamoonga et al. highlighted important concerns about side effects and potential negative impact on pregnancy and infant health. Fear of stigma was an important determinant of effective PrEP use with women without HIV including concern that partners or the community may perceive women as living with HIV or having multiple sex partners. In Eswatini (Khumalo et al.), PrEP awareness was high but accurate PrEP knowledge was incomplete. Young et al. identified PrEP misconceptions among clients who reported that PrEP improved health and could be used to treat sexually transmitted infections. Partner support was identified across several studies as a key determinant of PrEP uptake and continuation. Having a partner living with HIV was a major reason for initiating PrEP and was associated with higher adherence to both PrEP and ART. Routine data from Lesotho (Masenyetse et al.) identified a 2-fold higher follow-up among PrEP users in relationships where one partner was living with HIV. Similarly, having multiple sex partners was a common reason for PrEP use and a determinant of PrEP continuation.

Secondly, we learned about barriers and facilitators of the PrEP care continuum. Previous work has highlighted significant challenges with PrEP adherence which is critical for efficacy (11). Khadka et al. found that over 80% of pregnant adolescent girls and young women initiated PrEP in the first antenatal care visit. However, PrEP continuation reduced significantly with time and was <40% at 6-months despite the high prevalence of STIs. Similarly, Masenyetse et al. found that 40% of PrEP initiators in routine care among pregnant and postpartum had no follow-up visit, signally that barriers to PrEP continuation persist. Hurwitz et al. estimated overall PrEP adherence at 63% and identified several patterns of PrEP adherence during periconception among HIV-exposed South African women. Changes in perceived HIV risk over time may impact PrEP adherence; however, the large drop-offs and poorer PrEP persistence among women who become pregnant while on PrEP are concerning.

Thirdly, we derive insights from healthcare providers' experiences in delivering PrEP. Among providers who had no training or experience delivering PrEP (Pleaner et al.), there were significant concerns about burdening already busy clinics and the impact on other service delivery. However, in Kenya (Wagner et al.), among providers with experience delivering PrEP, delivery was viewed more favorably, as adaptable and meeting patient needs. However, PrEP delivery required provider training, was more complex compared to other services and required additional resources (Hicks et al.). Additionally, daily dosing for PrEP requiring frequent refills and access to services (e.g., long distances to clinics and waiting time) were important barriers (Hamoonga et al.). Sila et al. found that an intervention package including video education, HIV self-testing, and PrEP dispensing delivered at maternal and child health clinics significantly increased the proportion of clients counselled about PrEP and client satisfaction but was associated with increased waiting time. These findings demonstrate the need for continued research to optimize PrEP delivery.

Finally, this collection addresses PrEP effectiveness and safety in pregnancy. Fairlie et al. reviewed data on the safety profiles of available PrEP candidates including oral TDF-containing regimens, long-acting cabotegravir and the dapivirine ring. Except TDF-containing regimens, safety data on other PrEP agents is very limited in pregnancy and postpartum. They also reviewed existing drug surveillance systems in high- and low-income settings and suggested that PrEP surveillance be integrated into multiple surveillance systems. While the cost of building such systems is high, they argue that the extent of PrEP use warrants investment. Scott et al., found an increase in tenofovir/emtricitabine drug clearance throughout pregnancy, suggesting current dosing schedules may be inadequate to provide protective drug levels. Zewdie et al. found significant bone mineral density loss among pregnant women using oral TDF-based PrEP, which was likely attributed to pregnancy and not PrEP. This study was limited by small numbers of pregnant women not exposed to PrEP. Additional research is needed for robust comparisons between PrEP-exposed and unexposed populations.

In conclusion, this collection highlights important gaps in PrEP delivery among pregnant and lactating people. Ongoing discovery research will likely address pharmacokinetics and expand PrEP options; however, understanding how to scale-up PrEP delivery will require continued evaluation and adaptation to meet the needs of pregnant and postpartum women and in different regions.

Author contributions

IN: Conceptualization, Writing – original draft, Writing – review & editing. FS: Conceptualization, Writing – original draft, Writing – review & editing. DJ: Conceptualization, Writing – review & editing. BC: Writing – review & editing. JP: Conceptualization, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Introduction and integration of PrEP and sexual and reproductive health services for young people: Health provider perspectives from South Africa

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South Africa has one of the largest HIV epidemics in the world, with particularly high prevalence among adolescent girls and young women (AGYW). Oral PrEP was introduced in the public sector in 2016 in a phased manner. Given the important role played by health providers, research was undertaken to understand their experiences of and attitudes towards introduction of PrEP as a new HIV prevention method, and its integration within broader sexual and reproductive health (SRH) services for youth. A survey was undertaken with 48 purposively sampled health providers working in primary health care facilities and mobile clinics in three provinces in South Africa. Qualitative analysis was performed on free-text responses to open-ended questions in the survey, using an inductive approach to code the data in NVivo v.12 software. Health providers expressed concerns about adding a new service to an already overburdened health system, and worried that young people seeking PrEP would divert staff from other critical services. While most recognised the benefits and opportunities afforded by HIV and SRH service integration, providers highlighted the extra time and resources such integration would require. Many were anxious that PrEP would encourage disinhibition and increase unprotected sex among AGYW, and held judgemental attitudes about young people, seen as largely incapable of taking responsibility for their health. Findings underscore the importance of consulting health providers about implementation design and providing channels for them to express their misgivings and concerns, and training needs to be designed to address provider attitudes and values. Opportunities need to be sought to strengthen the provision of adolescent and youth friendly services—including adolescent-health provider dialogues. Insights from this study can assist in guiding the introduction of new HIV prevention methods into the future.

KEYWORDS

oral PrEP, health providers, health systems, HIV prevention, sexual and reproductive health (SRH), integration, adolescent girls, young women (AGYW)

Introduction

South Africa has one of the largest HIV epidemics in the world, with 38% of new infections in 2017 occurring among youth aged 15–24 years. Prevalence among adolescent girls and young women (AGYW) in this group is particularly high: nearly four times greater than that of young men (1, 2). This disparity is largely driven by cross-cutting factors such as poverty and unemployment, age disparate sex (3, 4), and transactional sex (4, 5), against a background of harmful gender norms and unequal gender power dynamics, where the rights, safety and choices of AGYW are severely compromised (6, 7).

Oral pre-exposure prophylaxis (PrEP), comprising the antiretrovirals emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF), has provided a much-needed HIV prevention option globally, and is over 90% effective when used correctly (8). Oral PrEP was introduced into South Africa in 2016 in a phased manner, with initial provision in demonstration and study sites, followed by expanded provision to sex workers, men who have sex with men, and AGYW project sites. It was subsequently rolled out to include public sector primary healthcare clinics, and is supported by national Department of Health guidelines (9).

Health providers play a critical role in the introduction and promotion of new services and are recognised as important catalysts for change. Indeed, their willingness to make adaptations to existing services and their creativity in integrating appropriate changes may determine the success or failure of new health technologies. But health providers may lack the necessary motivation to introduce new methods. Among other factors, this may result from a misalignment between professional roles and expectations on the one hand, and personally held values on the other (10).

Indeed, the introduction of new products is not always supported by the requisite health systems. We can draw lessons from the introduction of other interventions within the public health sector—such as the early introduction of antiretroviral treatment and the subdermal contraceptive implant. Similarly, as PrEP is scaled up in national programmes around the world, lessons are being learnt about the need for robust and appropriate health systems required to support quality of care to ensure optimal health benefits for adolescent clients (11, 12).

Encouragingly, integration with sexual and reproductive health (SRH) services has been shown to improve effective use of PrEP (11), in addition to generating other benefits, such as creating opportunities to promote both HIV and SRH services (13). From a health provider's perspective, integration brings expanded skills development, improved job satisfaction, a reduction in workload (14), improved efficiency, and increased staff motivation (15).

Health providers may feel ambivalent about providing integrated services, however. A study from Kenya looking at health providers' experience of integration of HIV and SRH services identified a number of challenges. These included poor health systems to support service delivery, limited physical space, equipment, drugs and other medical supplies, and perceptions of increased occupational stress and workload (15). Training, capacity building and ongoing support for health providers were found to be crucial components of the health systems strengthening needed to improve health providers' performance and attitudes.

There is growing recognition of the need for HIV and SRH programmes to be responsive to the needs of young people (16, 17) and—given their heightened vulnerability—to AGYW in particular. Substantial work has been undertaken to define what constitutes quality of care for adolescent and youth friendly services (AYFS) (12, 16, 18). There is global consensus that the cornerstone of AYFS is the provision of services which are accessible, acceptable, equitable, appropriate, and effective, with a key focus on the provision of evidence-based, non-judgmental and non-discriminatory care (18, 19). Again, health providers' attitudes are key: if these attitudes discourage young people from accessing PrEP and other SRH services, this will directly impact on service utilisation and health outcomes (10, 20–22). South Africa has generated standards and tools to benchmark quality AYFS, which foreground staff attitudes as critical to the successful provision of these services (23–25). A recent evaluation of facilities in two health sub-districts in the country found that overall, they failed to meet many of the criteria for youth-friendly service provision, suggesting that we still have a long way to go in this regard (26).

Notably, it is in this institutional context that PrEP is being introduced in South Africa, as an additional female-controlled option to prevent HIV (11). PrEP has been an important breakthrough for AGYW and has formed the centre-point of several national AGYW-focused programmes in the country, such as "She Conquers" (27) and DREAMS (28). Yet there is limited evidence on implementation strategies for providing PrEP to AGYW as part of an integrated package of AYFS (29).

In this article, we analyse health providers' views and experiences of the introduction of PrEP into integrated, adolescent- and youth-friendly HIV and SRH services, as well as their perceptions of PrEP as an appropriate HIV prevention method for young people and for AGYW in particular. We draw on data from the Unitaid funded "Project PrEP", which hosted this research. Implemented since December 2018, the project aimed to identify and develop models of integrated service delivery for quality HIV and SRH services, with a focus on AGYW. It generated real world evidence on the introduction and integration of PrEP as it was being rolled out in primary healthcare (PHC) clinics and mobile services in four provinces of South Africa.

Materials and methods

Study design

Qualitative data for this analysis were collected as part of Project PrEP's exploration of the perceptions and experiences of health providers in relation to the introduction of PrEP into comprehensive services for AGYW in South Africa. We analysed free-text responses to open-ended questions in a semi-structured survey undertaken between February 2019 and May 2020 with health providers working in participating PHC facilities and mobile services. The survey coincided with the National Department of Health (NDoH) roll-out of PrEP in public health clinics, which targeted people at substantial risk of HIV infection, including AGYW. At the time of data collection, many of the sites had only just begun to provide PrEP and some health providers had not yet been trained.

Setting

South Africa's health system is two-tiered and highly unequal. The underfunded public sector is accessed by the majority of the population, which largely cannot afford the health insurance needed to access the well-resourced private sector (30). Primary care service provision in the public sector is dominated by chronic long-term care (HIV and non-communicable diseases), with additional service streams focused on acute care (minor ailments), preventive and promotive services (maternal and child health and SRH) and health support services. Although service utilisation may vary by site and depending on the local burden of disease, research among primary care facilities in Kwa Zulu Natal has indicated that in 2020, clinic visits for ART follow-up care accounted for almost half of all clinic visits (43%), followed by visits for minor ailments (18%), child health (11%) and hypertension (10%) (31).

The study was undertaken in four diverse (urban, peri-urban, and rural) geographical clusters in three provinces in South Africa (Gauteng, KwaZulu-Natal and Eastern Cape). Each project cluster consists of two fixed-site, primary care facilities and a project mobile clinic to extend the reach of services within the surrounding community. Participating facilities offer a range of integrated services for AGYW, including HIV testing, contraception, sexually transmitted infection (STI) and PrEP services, and linkages to HIV treatment services as required. Project facilities were selected based on their burden of HIV, teenage pregnancy, STIs and gender-based violence, as well as their proximity to secondary and tertiary educational facilities where adolescents and youth may be reached.

Recruitment and sampling

Health providers were purposively sampled from the eight participating facilities and four mobile services, based on their expertise, experience and role in planning the PrEP roll-out or in providing SRH or PrEP services to adolescents. Only health providers working in the project sites and willing to consent to the survey and to administration of the survey being audio-recorded were eligible for recruitment. Participants were eligible irrespective of gender, health provider cadre, or number of years of experience.

The study team worked with facility managers, who suggested other eligible healthcare providers within their facility who could be invited to participate in the study. Participants were recruited face-to-face by members of the project team. We also made use of snowball sampling among recruited participants to identify additional participants and build a sample large enough to obtain a diversity of views. Some participants were interviewed twice, in order to capture reflections on the implementation process after the roll-out. Recruitment continued until data saturation was reached, at which point 48 participants had been interviewed across the study sites.

Data collection

Surveys were administered face-to-face and telephonically (the latter for participants who were too busy to meet in person and when COVID-19 restrictions were in place in 2020). Interviewers were trained in research ethics and in the skills required to conduct high-quality, reliable surveys, including how to handle open-ended questions. The survey was administered in the language of participants' choice (English, isiZulu or seSotho), and open-ended responses were audio-recorded. Participants were assigned a unique number to ensure anonymity when identifying themselves for the audio recording.

The open-ended questions in the survey (roughly one-fifth of the tool) focused on a range of topics including: training received on PrEP provision, demand creation strategies, uptake and consistent use of PrEP, major programme challenges and successes, and lessons learned in providing integrated services to adolescents and youth.

Data analysis

Descriptive analysis of demographic data was conducted. Audio recordings were translated into English, where necessary, and transcribed verbatim for analysis. A team of three analysts open-coded the transcripts using NVivo software (version 12, QSR International, Melbourne,

Australia), using an inductive coding approach influenced by Grounded Theory (32). Analysts consulted with one another throughout the process to build consensus on the coding framework and ensure consistent application of codes. Key themes emerging from the coding were identified and further developed through the writing of detailed coding summaries, which formed the basis of the manuscript.

Ethical approval

The study was approved by the Human Research Ethics Committee at the University of the Witwatersrand (M180806) and by the World Health Organization (WHO) Ethics Research Committee (Wits-PrEP-AGYW). All participants provided written informed consent before taking part in the interviews.

Results

A total of 48 health providers participated in the interviews. The majority were female (93.7%) and professional nurses (68.7%), with the remainder consisting of doctors, lay counsellors and administrators. This gendered and professional bias is largely reflective of the fact that in South Africa, health providers are mostly female, especially at nurse level, and that PrEP services at PHC facilities are generally provided by professional nurses (31). **Table 1** summarises key demographic characteristics of these participants.

Our analysis of the interview data identified three broad themes in health providers' perspectives on the PrEP roll-out. These included views on (1) challenges, concerns, and anticipated benefits of integrating PrEP into existing SRH services for young people; (2) health system requirements to support PrEP delivery; and (3) attitudes towards PrEP as an appropriate HIV prevention method for youth, and for AGYW specifically.

TABLE 1 Demographic characteristics of the sample of health providers (n = 48).

Variable	n (%)
Gender	
Female	45 (93.7)
Male	3 (6.2)
Age group (years)	
26–35	14 (29.1)
36–45	17 (35.4)
46–55	8 (16.6)
56+	9 (18.7)
Years of experience*	
<5	4 (8.5)
6–10	17 (36.1)
11–15	7 (14.8)
16–20	6 (12.7)
20+	13 (27.6)
Health care provider category	
Professional nurse	33 (68.7)
Lay counsellor	10 (20.8)
Medical doctor	2 (4.1)
Admin staff	3 (6.2)
Geographical location	
Urban formal	40 (83.3)
Rural	8 (16.6)
Providing PrEP at time of survey	45 (93.7)

*Data for 1 participant missing.

Introducing PrEP as an integrated service: Challenges and benefits

When health providers were asked how they felt about absorbing the provision of PrEP into existing services, many described PrEP as an extra, add-on service that was problematic in a context where the health system is already overburdened. There was concern that HIV prevention services were receiving priority over other services, and some confusion about where PrEP services should ideally be located within the clinic structure.

Participants complained about heavy caseloads of ill clients and saw PrEP-users as an additional burden on a health system that could not absorb any more clients—especially clients who are fundamentally well, and not "*sick*" or requiring treatment. This was a view that was apparently held by many of the participants' colleagues as well. Reflecting on what she saw as an increased workload for health providers, one participant complained, "*it's too much, I don't want to lie*" (42-year-old female professional nurse, Eastern Cape). Another participant admitted:

> *It's a bit scary and daunting, because as you say the training won't last forever…at some point we will have to start rolling out ourselves and obviously it's gonna be stats and a lot of paperwork. It's very daunting, it's like an additional workload on our HIV programme* (33-year-old female professional nurse, KwaZulu-Natal).

Some had observed a growing demand for PrEP that was proving difficult to manage. One participant in KwaZulu-Natal said, "*They (youth) are bringing their people for PrEP. I am overwhelmed*" (43-year-old female professional nurse, KwaZulu-Natal).

A number of participants from facilities where the PrEP roll-out was well underway claimed that PrEP service provision was impacting negatively on other essential services. Participants in Gauteng spoke of how other programmes in the clinic "*are suffering*" because health providers are expected to focus on PrEP initiation. In sites where PrEP was already being provided, there were complaints that PrEP was diverting nurses from other PHC services. This problem was said to be further exacerbated by the regulatory requirement in South Africa that only nurses trained as NIMART (Nurse Initiated Management of Antiretroviral Therapy) providers are allowed to administer PrEP. A NIMART nurse in Gauteng complained that she was regularly called away from ART services to deal with initiating new PrEP users: "*We have a shortage of staff as it is. So, for people to leave whatever they are doing, to come and assist with PrEP is very difficult…*" (43-year-old female professional nurse, Gauteng). Similarly, an Eastern Cape participant working as a lone nurse in antenatal care (ANC) described how her ANC clients were frequently left waiting while she was called away to initiate other clients onto PrEP.

There was uncertainty about how to classify PrEP users within the spectrum of clients accessing their facilities—and therefore how to position PrEP services in relation to existing services. Conflicting views were expressed about offering PrEP as an integrated versus a vertical service, and concern about how this decision may impact on PrEP uptake and quality of care.

> *Are they [PrEP clients] chronic or acute? So where do they stay? Even if they come to the clinic, they are the priority, or they must follow the line [queue]? That's where we will lose them. If they follow the long queues yet they know that they came for PrEP only, that's how we can lose them* (43-year-old male professional nurse, KwaZulu-Natal).

Some health providers felt that PrEP services should be offered by a dedicated health provider—separate from PHC services—to ensure that PrEP clients do not swamp the already long queues. Rather than reducing waiting times, there was a feeling that integration had the opposite effect. One participant in Gauteng pointed out that "*clients are in a hurry, [and integration] requires longer consultation times*" (40-year-old female lay counsellor, Gauteng). Another regarded the comprehensive counselling needed at PrEP initiation as too time-consuming:

> *You have to educate and counsel, counsel, counsel. To say [to clients], "these are the disadvantages of not taking [PrEP]" – that takes time. [Meanwhile], the ones outside are complaining* (49-year-old female professional nurse, Eastern Cape).

Numerous participants felt that a range of training, skills and experience was needed for health providers to render integrated services—in addition to the PrEP-specific training that accompanied the roll-out. There were additional concerns about whether facilities could support the one-stop-shop concept when aspects of the service were still fragmented. For example, clients could receive PrEP tablets directly from a provider but if prescribed STI treatment they still had to queue up at the dispensary for the latter.

Overall, however, most health providers in the study supported integration of PrEP with other services and saw the "one-stop shop" approach as reducing waiting times, among other benefits. Some pointed out that dealing with PrEP "*in isolation*" would in fact be challenging since clients themselves bring multiple issues to their consultations. Furthermore, it was believed that referral to multiple health providers for different services—as necessitated by vertically arranged services—would become a barrier for young people accessing PrEP. As one provider put it, "*Youth don't like going around*" (29-year-old female peer educator, Gauteng).

Those who supported integrating PrEP into existing SRH services recognised that this would provide more opportunities to reach young people and improve their health outcomes, especially in relation to averting unplanned pregnancies, identifying and managing STIs, increasing HIV testing and promoting dual protection and condom use. PrEP integration could therefore be an opportunity to go beyond HIV prevention and improve uptake of other SRH services, in other words. One nurse claimed:

> *I always advise people who are on PrEP to use one of the family planning methods. I always encourage everyone, and say: "Are you sexually active?" They say, "Yes"… "Are you using contraceptives?" "No, I'm not"… I give them all the options… they leave with PrEP and family planning. And my family planning stats are increasing because of that* (43-year-old male professional nurse, KwaZulu-Natal).

As this quote suggests, the beneficial knock-on effects of PrEP integration were already becoming evident in some facilities. One nurse reported that since offering PrEP as a service integrated with broader SRH services in her facility, there has been an increase in uptake of HIV testing, which in turn has increased ART initiation. Some providers also favoured integration of PrEP and ART services as a strategy that would help to de-stigmatise HIV services: "*It won't be clear if you are a [HIV] positive somebody or you are a negative somebody, [because] everything will be in the same room*" (34-year-old female professional nurse, KwaZulu-Natal).

Other potential benefits of integration identified by participants included the protection of client privacy, which was deemed to be especially important for young people, who are at risk of stigma if seen by other clients to be accessing SRH services. Furthermore, when clients were not referred to multiple members of staff, they could build trust with a single health provider instead—something that was regarded as essential when dealing with SRH and HIV.

Questions about offering PrEP as integrated versus vertical service surfaced again in discussions about the wisdom of integrating the PrEP roll-out with adolescent and youth friendly services (AYFS). In facilities where there is no dedicated youth-specific zones or rooms, participants pointed out that young people must join the often long queue for clients seeking PHC services. In addition to eschewing referral to multiple providers, it was said that young people also "*don't want to wait*" (38-year-old female professional nurse, Eastern Cape). Participants were concerned that long queues would be even more of a deterrent in the case of PrEP, because the population seeking PrEP are generally healthy:

> *Maybe the youth will end up saying, 'since I am not positive for now, I was just protecting myself, then let me go and come back another day'* (34-year-old female professional nurse, KwaZulu-Natal).

One health provider, who expressed a preference for a stand-alone, prefabricated set of rooms for adolescent and youth services, explained that this separate space would not only remove healthy PrEP clients from the PHC queue, it would also avoid a situation where "*other clients will complain that 'why are PrEP clients coming in and being served before us?'*" (27-year-old female professional nurse, Gauteng).

In other words, the impetus to offer separate services for young people was borne out of a desire to avoid swamping the clinic queues and not necessarily from a recognition that young people want discretion and privacy when seeking sexual health services. This, in turn, motivated some healthcare providers to call for PrEP to be provided as a stand-alone service rather than being integrated into PHC, with dedicated PrEP staff in a youth-friendly environment.

Health systems required to support the provision of PrEP services

A key focus of our inquiry was to explore views relating to aspects of the health system which need strengthening to support the delivery of PrEP and integration, and where the gaps may be in this regard. A number of participants expressed concerns about the ability of the South African health system to support PrEP services, pointing to likely challenges with access and coverage, training, systems to support drug storage and supply, and demand creation.

Notwithstanding the existence of mobile clinic services, many health providers felt that distances from and transport costs to clinics, and the limited scope of the roll-out could deter those seeking PrEP services. Staff shortages in some facilities were seen as potentially affecting PrEP access, particularly in the afternoons when fewer staff are on duty—at precisely the time when youth tend to access services, after school hours.

Health providers across all provinces identified lack of staff training as a potential barrier to PrEP uptake. In some facilities only some staff members had been trained; this was linked to weak buy-in and commitment from staff to embrace PrEP. One nurse reflected on her experience of this kind of uneven training:

> *It is just me who attended [PrEP training] and the professional nurse, you know. It is not the majority of them – in such a way that when it comes [to providing PrEP to clients] they are having some doubts, to say "Do we really? Are we supposed [to provide PrEP]?* (59-year-old female professional nurse, Gauteng).

It was felt that there was a danger that the one PrEP-trained provider in a facility would become labelled as the "*PrEP nurse*", thereby removing the incentive for untrained staff to sign up for training or inform themselves about PrEP. One provider in the Eastern Cape believed this should be avoided at all costs:

> *If all the professional nurses in this section were trained, they would easily give the information to the clients without sending them to somebody else, you see* (58-year-old female professional nurse, Eastern Cape).

Aside from underlining the value of integration of services, her comments raise the question of how respective roles and responsibilities within the provision of PrEP are outlined to the staff team. The need for all staff members in a facility to receive at least some PrEP orientation was considered essential but appeared to not be happening in practice. Indeed, it was not always clear who was responsible for the training of staff, as a DoH training plan for PrEP introduction was expected but did not always materialise. DoH training of more NIMART nurses was specifically requested, but there was also a general call for more comprehensive training of health providers, covering not only the clinical provision of PrEP, but also the integrated provision of other SRH services:

> *… the only challenge will be if we don't have clinicians…who are having all [skills], like NIMART, family planning, SRH. So, you need to have somebody who has all these small… skills* (59-year-old female professional nurse, KwaZulu-Natal).

Additional health system weaknesses that participants highlighted as relevant for PrEP provision revolved around space and infrastructure in clinics, which had implications for issues such as privacy, multiple service delivery points, waiting times, and drug storage. This latter point was an important consideration for PrEP, which was described as medication "*to be kept under a lock and key… in a safe place*" (43-year-old female professional nurse, Gauteng). Furthermore, health providers' experience with contraceptive commodity shortages raised similar concerns about possible stock-outs of PrEP.

Finally, there was recognition that a successful PrEP roll-out required intensive demand creation efforts. Several health providers expressed a desire to do more demand creation but complained that there was not enough time available for it. Two participants in KwaZulu-Natal lamented the fact that demand creation was beyond their reach. One said, "*we don't have dedicated staff members that can do school health, that's where we can identify these teenagers*" (55-year-old female professional nurse). The other, a 34-year-old female professional nurse in a nearby facility, said,

> *We don't get enough time to talk to them… in the clinics it's just, you have to work, work, work. So, if maybe we had an opportunity to go to schools, universities, as our target market is [there], they could allow the nurses to go and initiate PrEP. That's the only barrier because once they know [about PrEP], they start.*

Health provider attitudes toward offering PrEP to young people

A fundamental aspect of the provision (and integration) of PrEP to maximise access for young people is the nature of health providers' attitudes towards young clients. We were interested to know whether healthcare providers saw PrEP as an appropriate HIV prevention method for youth and for AGYW specifically, what kinds of attitudes participants had observed among their colleagues and how these were affecting service provision.

Some participants were somewhat defensive, claiming that young people tended to misunderstand health providers' responses to them and often incorrectly assumed that they would be met with hostility.

> *Eish, our youth… (laughs), when they see nurses… they think nurses are rude and all that… they are perceiving nurses as those horrible people.* (43-year-old female professional nurse, Gauteng).

> *I think ya, they are afraid because of that myth about nurses, that nurses are rude. Some of them become scared to come to us* (28-year-old professional nurse, Eastern Cape).

A larger proportion of participants recognised that many healthcare providers were indeed judgemental of young people, however, and recognised how this would become a barrier to services. There were multiple descriptions of how colleagues in their facilities displayed indifference to the needs of the youth, at best:

> *[Some healthcare providers] just say "aah, nxh! I don't care about them. Let's go that side, these kids are troublesome"… That is your attitude towards PrEP and the youth. But if you have a positive attitude, you will even call them as they walk there, [saying] "come, come, come"* (55-year-old female professional nurse, Gauteng).

Concerns were raised about how negative staff attitudes could impact on both service utilisation and effective PrEP use. Describing one young woman who started PrEP but did not return to the clinic for follow-up appointments, a peer educator said,

> *A few months later she came back and when you ask, "why you stopped PrEP?", they say "because of the attitude that I get here, [it] makes me afraid to come back. I was not treated fairly"* (29-year-old female peer educator, Gauteng).

Some health providers spoke about colleagues who are actively against PrEP, saying they "*don't wanna know about it*" and there were even accounts of clients asking for PrEP but being chased away by health providers. Others speculated that the reason for 'anti-PrEP' attitudes among health providers may be a lack of training and knowledge, or even an underlying suspicion about the motives for PrEP introduction:

> *I think the other health care providers, they are incompetent in terms of PrEP. They have this mentality that has negative thoughts behind PrEP. They are not sure, they think this drug is just there for statistics, money-wise something, something, somebody will benefit at the end"* (30-year-old female professional nurse, KwaZulu-Natal).

A number of participants had much to say about the kind of approach health providers should take with young clients, and the need to communicate in a non-judgemental and youth sensitive manner. As one participant put it:

> *"When you are facing young people, you [should] take your mind, your brain away, your grudges and your elderly mind,*

> *and you just go down and meet the needs of this person."* (63-year-old female professional nurse, Eastern Cape)

Despite the willingness to call out judgemental staff attitudes and an apparent familiarity with the principles of providing AYFS, these same participants at times readily criticised young people and were openly dismissive of their ability to practise safe sex. In part, this reflected a deeper scepticism about the wisdom of supplying young people with PrEP. A large majority of healthcare providers interviewed considered the behaviour of young people to be inherently problematic because of their lack of self-efficacy to take responsibility for their own health. One participant exclaimed, "*Ya! Adolescents can be dumb!*" when this issue came up in the interview. Young people were described as "*irresponsible*", "*careless*", and "*reckless*", routinely engaging in "*sexual unruly behaviour*", which many participants believed would increase once they start taking PrEP. Young people were characterised as having a "*mentality in them that is not mature enough*" for stable relationships (42-year-old female professional nurse, KwaZulu-Natal). A number of participants labelled youth "*promiscuous*", saying that they were "*just sleeping around*"—a characterisation that was implicitly gendered, as it turned out that they were in fact referring to AGYW. On the subject of risk and sexual behaviour, for example, one provider said:

> *"They will do it. They will have unprotected sex. They did that even before PrEP came, for money and when they are with their partners. They cannot stand firm and ask for a condom"* (55-year-old female lay counsellor, KwaZulu-Natal).

A dominant view in the interviews was that PrEP use would inevitably lead to sexual disinhibition among AGYW. A number of participants—both young and older—were concerned that giving PrEP to AGYW at clinics would be seen as effectively "*legitimising*" sex and offering them "*a free pass*" (26-year-old female medical doctor, Eastern Cape). A common perspective on this matter was the belief that:

> *…they will go, knowing that "I'm taking this PrEP medications so I can sleep around whatever without getting infected"* (43-year-old female professional nurse, Gauteng).

There was concern that condom use would decline, while several health providers worried that PrEP usage would be followed by an increase in STIs and unplanned pregnancies.

> *"It will increase the rate of unplanned pregnancies. As it is, they come to the clinic, already pregnant from all these universities. So, if they take PrEP, and not condomise as we advise them to, they will continue getting pregnant"* (55-year-old female lay counsellor, KwaZulu-Natal).

One provider believed that young people would even go so far as to deliberately indulge in risky sex purely to "*test*" the efficacy of PrEP, and thus to "*test*" the credibility of health providers themselves.

> *"They will actually want to test whether the healthcare providers are lying or are they telling the truth that I cannot get HIV by using PrEP"* (38-year-old female professional nurse, Gauteng).

A common explanation for this risk-taking behaviour was that youth were "*not well informed*", and consequently, more education was the only way to remedy the situation. There were calls for "*continuous education, continuous counselling*" (59-year-old female professional nurse, Eastern Cape) to encourage adherence, together with motivational strategies to encourage behaviour change: "*We must counsel them and motivate them to use condoms all the time*" (46-year-old female lay counsellor, Eastern Cape).

Only a small minority of participants expressed more positive views of how PrEP may be empowering for young people, giving them a tool to protect themselves against HIV. One health provider said that PrEP will make young people feel "*very proud*" of themselves, that they will feel the same as if they had "*got a new job or had bought new shoes*" (63-year-old female professional nurse, Eastern Cape). A second health provider challenged the popular, moralistic belief that health technologies could lead to disinhibition of the very behaviour they are designed to prevent, drawing an analogy with contraception myths:

> *At the beginning, a long time ago, there were people [who] were not accepting family planning methods, saying it encourages people to promiscuity, you see! So, it [PrEP] can be the [same] concept as that…I don't think that it can, [that] it will allow them to do that [behave promiscuously]* (59-year-old female professional nurse, Gauteng).

Ultimately, however, young people were presented as fundamentally incapable of using preventative technologies, with responsibility for this 'failure' resting with youth themselves—as one put it, "*it's the failure of youth to know what is right for them*" (34-year-old female professional nurse, KwaZulu-Natal)—rather than with the technologies or with the unsupportive environments in which they are introduced.

Discussion

Health providers are at the heart of service delivery and their perspectives on the barriers and enabling factors that support or hinder the provision of quality, integrated youth-

friendly PrEP and SRH services are therefore important to understand. This study provided in-depth, granular insights into issues that need to be considered when planning for new prevention methods to become part of integrated services. We found that health providers in rural, peri-urban and urban facilities across three provinces in South Africa were ambivalent about integrating PrEP with SRH services. Our findings echoed those of other studies on the topic of HIV and SRH services integration—in which health providers have supported integration as beneficial but also had misgivings about the possibility of extra work (11, 14, 15).

On the one hand, health providers in our study recognised a certain logic to PrEP being offered as part of this integrated package—given the interconnectedness of clients' HIV and SRH needs—and believed such integration would benefit both health providers and clients. On the other hand, providers expressed uncertainty and confusion as to where PrEP fits into the PHC and the HIV care continuum, whether PrEP should be integrated or provided as a vertical service, and how existing staffing arrangements will affect facilities' capacity to absorb this new service. When introducing PrEP services at site level, there is a need for careful engagement with both management and frontline workers on issues such as points of entry for clients, location of PrEP services within clinic structures, and staff training. Health providers need opportunities to express their concerns regarding the additional capacity, time and resources required to integrate PrEP into existing services.

The challenges facing Nurse Initiated and Management of Antiretroviral Treatment (NIMART) trained nurses has been well documented (33–35). The Department of Health pharmaceutical guidelines for the provision of PrEP are the same as for ART (Schedule 4), and as such, require NIMART nurses to be available for the provision thereof (9). As the country introduces new ART-based PrEP methods, this pressure will increase. The training of NIMART nurses needs to be scaled up, not only to meet existing demand but also to ensure that PrEP services become fully part of mainstream PHC provision, with enough trained staff to meet this expanding area.

As countries gear up for the introduction of a range of new biomedical HIV prevention products, there are some useful insights which have implications for expanded oral PrEP provision as well as implementation and integration of future products. If PrEP is to be integrated as an integral part of the PHC and HIV care package, rather than as a marginal vertical service, then we need to build on and expand the use of tools already developed to reduce workload. For example, the waiting times and staff shortages could potentially be addressed by digital tools providing information and encouraging informed choice prior to linkage to services or at the service, thereby contributing to decreasing provider time whilst ensuring accurate information on choices aligned to lifestyle (36).

On a more individual level, health providers play a vital role throughout the PrEP journey taken by AGYW, and their attitudes have the potential to promote or hinder access to these services. What we do know is that a substantial proportion of AGYW do not persist with PrEP, and strategies are needed to help them assess their level of risk (and therefore their need for PrEP), and to deal with the everyday challenges they face in taking PrEP (11, 37). Initiation, continuation and effective use of PrEP may be affected by health providers' lack of evidence-based knowledge about PrEP and reticence about discussing sexual risk (38, 39). Training needs to equip health providers with a solid understanding of how PrEP works, and the confidence to initiate clients onto PrEP and motivate them to continue with this method while their risk remains high. This in turn requires an attitude that holds PrEP in positive regard for what it may offer to young people—which makes our findings on judgemental attitudes about adolescent sexuality very concerning. Such attitudes have a real potential to undermine promotion and delivery of PrEP to young people in South Africa.

To counterbalance these negative views, healthcare worker training needs to explore real-life examples of how stereotypes and prejudicial thinking impact on service delivery and build skills to promote self-care with young clients (40). This could be done through unpacking how PrEP and other HIV prevention options provide tools for young people to take responsibility for their own health and how self-care can contribute to resilience and self-efficacy within an assets based paradigm (41–43). In addition, healthcare workers need to be equipped with a deeper awareness of and sensitivity to the complex contextual dynamics at play for AGYW in terms of gender norms in relationships that set up double standards for them and severely restrict their agency (4, 5, 44). Understanding patterns of sexual behaviour and how these may create barriers to effective PrEP use needs to become an integral part of provider training and guide the messaging conveyed to AGYW (11, 45, 46).

The design and framework for youth-sensitive and youth-responsive services need to consciously factor in the specific needs of AGYW seeking PrEP and other SRH services. This means, for example, not only accommodating the needs of learners who can only access facilities after-hours, but also being sensitive to the needs of young women with work and/or childcare responsibilities. The gender of peer educators, navigators and health promoters should also be taken into account, with due sensitivity to the preference of AGYW wherever possible (17, 28, 47). Alongside training, there is a need for support mechanisms to allow health providers to discuss challenges they grapple with in providing services to young people. Both training and support requires that staff perceptions are addressed in a more deliberate manner, and not as a one-off event but re-visited over time.

The belief that PrEP use will encourage sexual disinhibition, thereby increasing unplanned pregnancies, HIV and STIs, was voiced by a number of healthcare workers in our study and has similarly been documented in other settings (22, 48, 49). Finding ways to deal with judgemental and sometimes prejudicial attitudes is important, including looking at replacing personally held views with evidence, as well as other approaches such as motivational counselling (50) and values clarification and attitude transformation processes (51). In a US-based study, PrEP providers described how their initial ambiguity about PrEP—based partly on a concern about risk compensation—evolved over time as they came to understand their role as helping clients to make informed decisions about their sexual behaviour and use of HIV prevention methods (52). It is possible that such shifts in attitude may be hastened by greater and more meaningful participation of young people in the design and implementation of health services, together with the promotion of dialogues between young people, health providers and programme planners. This needs to take place with a recognition and understanding of young people's rights, within the framework of accessible and acceptable health care (10), and be at the centre of PrEP and SRH service planning and implementation (19).

Finally, while these implications pertain to both Project PrEP and the expanded provision of PrEP in public health facilities in South Africa, the findings highlight the following lessons for Project PrEP: the importance of training including greater gender awareness of AGYWs' prevention needs; the need to proactively problem solve and strategize with the Department of Health with regards to expanded NIMART and PrEP training; and a need for more engagement with management and frontline health workers concerning the integration of service provision into the life and systems within a clinic. The latter point will become even more important as new PrEP methods are introduced.

There were limitations to the study. The qualitative data analysed here were obtained using a structured survey format, which—in spite of training—may have reduced interviewers' probing of superficial or incomplete responses. High staff turnover in study sites made it difficult to re-interview participants, as originally planned, limiting our ability to track whether perspectives shifted once health providers had direct experience of PrEP delivery.

Conclusion

Health providers play a critical role throughout young clients' PrEP journey, and their attitudes have the potential to influence access, health seeking behaviour, effective method utilisation, and ultimately SRH and HIV health outcomes. The insights gained from this paper underscore the importance of firstly, providing channels to explore health providers attitudes, misgivings and misperceptions and consult about implementation design; secondly, ensuring training includes a purposeful, focussed section on attitudes and values, and sensitisation with all staff clients encounter; thirdly, for programme planners and implementers to engage with managers and health providers about structuring and adapting health systems to support HIV prevention and SRH integration, and for integration to be cross cutting—including HIV and SRH, and the embracing of HIV prevention as an integral part of PHC service provision; and fourthly, providing opportunities for the meaningful participation of young people, feedback mechanisms, and health provider-client dialogues. These are important insights to guide the introduction of new HIV prevention methods as they are introduced into the future.

Data availability statement

The datasets presented in this article are not readily available due to the conditions of the ethics approval of the study. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by University of the Witwatersrand (M180806) and the World Health Organization (WHO) Ethics Research Committee (Wits-PrEP-AGYW). The patients/participants provided their written informed consent to participate in this study.

Author contributions

The paper was written by MP, with technical support from FS. FS and LM extracted and coded the interviews and did the statistical analysis. MP, FS and LM analysed the data. VB and MM reviewed the paper and provided input from a Project PrEP implementation perspective. FS, CM, SM provided detailed reviews and editorial support. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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"*PrEP protects us*": Behavioural, normative, and control beliefs influencing pre-exposure prophylaxis uptake among pregnant and breastfeeding women in Zambia

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Background: Although pre-exposure prophylaxis (PrEP) is recommended for pregnant and breastfeeding women at elevated HIV risk, uptake has been low in Zambia.
Methods: In in-depth interviews, we explored beliefs about PrEP among 24 HIV-negative pregnant and breastfeeding Zambian women. Thematic analysis was used to identify behavioural, normative and control beliefs likely to influence PrEP uptake.
Results: Most women viewed PrEP as a good method of protecting themselves and their babies from HIV infection. Partners were cited as key referents in decision making about PrEP use. Many women felt that PrEP use was not entirely in their control. Most reported that they would not use PrEP if their partners did not approve. Health care providers with negative attitudes, long distance to clinics, and extended waiting times were cited as barriers to PrEP uptake.
Conclusion: HIV-negative pregnant and breastfeeding women had a positive attitude towards PrEP but barriers to uptake are multifaceted.

KEYWORDS

PrEP, beliefs, pregnant, breastfeeding, theory of planned behaviour, intention, Zambia, sub-Saharan Africa

Introduction

In sub-Saharan Africa, pregnancy and breastfeeding are periods of increased risk for HIV acquisition. In two meta-analyses, HIV incidence during these periods were at or above the World Health Organization's threshold for high risk (3.0 infections per 100 person-years) (1, 2). The risk of HIV acquisition during pregnancy has been attributed in part to health facility-related factors (e.g., inadequate education about HIV prevention among antenatal care (ANC) attendees (3, 4)), social and behavioral factors [e.g., low condom utilization (5–8)] and low rates of HIV status disclosure to sexual partners (9, 10). Biological, physiological and immunologic alterations also contribute to the elevated HIV risk observed in pregnant and postpartum populations (11–16).

Biomedical interventions such as pre-exposure prophylaxis (PrEP) have the potential to reduce the risk of maternal HIV acquisition (17) and may play an important role in the elimination of HIV mother-to-child-transmission. The World Health Organization (WHO) endorses the use of PrEP during pregnancy and breastfeeding for HIV-negative women who are at higher risk of HIV acquisition, depending on individual behaviour and the characteristics of sexual partners (17). This recommendation is based on PrEP's efficacy and its safety track record across numerous studies in pregnancy (18). While many national programs have introduced PrEP for pregnant and breastfeeding populations (19), there is need to identify and engage people at risk for HIV and further improve demand for PrEP (20, 21).

The Zambia Ministry of Health first introduced PrEP as a key strategy for HIV prevention in 2016 (22). In line with WHO recommendations, the country's 2020 HIV treatment and prevention guidelines extended the provision of PrEP to HIV-negative pregnant and breastfeeding women at substantial risk for HIV acquisition (23). However, to date, uptake of these services in antenatal and postnatal populations has been limited, with some studies reporting rates as low as 1% (24), despite the high rate of mother-to-child transmission (25). The increasing burden of new infant HIV infections can be traced to incident maternal HIV during pregnancy and breastfeeding (26) which may go undiagnosed and therefore untreated. Taking PrEP during pregnancy and breastfeeding has the potential to reduce the risk of maternal seroconversion and onward mother-to-child transmission of HIV. However, factors that may influence uptake of PrEP in this population largely remain unknown.

To better understand facilitators and barriers to PrEP uptake in antenatal settings, we conducted a qualitative study guided by the Theory of Planned Behaviour (TPB) framework. We applied the TPB to understand behavioural, normative and control beliefs that pregnant and breastfeeding women have about PrEP. The TPB assumes that individuals act rationally, according to their attitudes, subjective norms, and perceived behavioral control. According to this theory, in order to predict whether a person intends to engage in a health behaviour, it is important to know whether the person is in favour of doing it (attitude), how much the person feels social pressure to do it (subjective norm), and whether the person feels in control of the behaviour in question (perceived behavioural control) (27). Strategies that are able to modify these three factors can raise a woman's intention to take PrEP and, by doing so, increase the likelihood that she actually takes up the intervention (28).

Materials and methods

Study design and population

In this qualitative study, we recruited HIV-negative pregnant and breastfeeding women from Chipata Level 1 Hospital in Lusaka, Zambia. This government health facility has a catchment population of over 100,000 and an antenatal clinic that attends to about 400–450 new ANC attendees each month. The HIV prevalence among pregnant women attended to at this health facility is approximately 16%, similar to the national prevalence for women (29). Purposive sampling was used to recruit study participants from the Maternal and Child Health clinic, where they were receiving either antenatal or postnatal care services. Pregnant and breastfeeding women aged 18 years or older and with a documented HIV-negative result in their antenatal record, were eligible. We enrolled 24 participants between November 2020 and March 2021. The sample size was determined using the principle of theoretical saturation, the point where additional interviews did not add any new insights on beliefs that women held about PrEP (30).

Data collection

We used a semi-structured questionnaire which had two components: the first part which was structured was used to collect data on socio-demographic characteristics of study participants (i.e., age, educational attainment, employment status and marital status), risky sexual behaviour as well as knowledge about PrEP. The second part which took the form of an interview guide was developed based on the Theory of Planned Behaviour questionnaire (27). The Theory of Planned Behaviour questionnaire has been used in several studies focusing on health-related behaviour to predict both intention and actual behaviour (31–36). The interview guide focused on behavioural beliefs (beliefs about advantages and disadvantages of taking PrEP), normative beliefs (beliefs about how other people expect pregnant and breastfeeding women to behave with respect to whether or not to take PrEP), and control beliefs (how much control pregnant and breastfeeding women have over taking PrEP) (28). Women in our study were asked what they believed were the advantages and disadvantages of taking PrEP during pregnancy and breastfeeding; who they believed would approve or disapprove of their decision to take PrEP; and what they believed were potential facilitators and barriers to PrEP use. The interview guide also included questions aimed at exploring preferences for PrEP delivery in the target population.

The interview guide was piloted to ensure that questions were appropriately phrased and understood. Minor revisions were made based on this feedback and the revised guide was translated into two local languages (Nyanja and Bemba). SSIs were conducted by trained research assistants fluent in English, Nyanja, and Bemba. Prior to enrollment, interviewers described the study and emphasized the voluntary nature of participation. Written informed consent was obtained prior to any study activities. At the beginning of the interview, study staff described PrEP as medicine that HIV-negative people who feel that they might be at risk of acquiring HIV could take to prevent new infections. The following description was read to participants: "PrEP is the use of anti-retroviral drugs by HIV-uninfected people to protect them from getting infected with HIV. Daily oral PrEP is effective in preventing HIV infection when taken consistently." Interviews were conducted in English and local languages (Nyanja, and

Bemba), based on the participant's preference. All interviews were audio-recorded, and later transcribed and translated to English.

Data analysis

Thematic analysis (37, 38), was used to identify beliefs and preferences that may influence PrEP uptake in antenatal and postnatal settings. Two study team members developed independent codebooks; differences were resolved through consensus and consolidated into a final version. Prior to data coding, we engaged in an iterative process of reading transcripts, which was accompanied by memoing, to identify common and unique content from the transcripts. This process was followed by categorizing content from each transcript under the sub-themes that were identified and later the broad themes (Theory of Planned Behavior constructs) based on the final codebook that was developed. Codes relating to advantages and disadvantages of using PrEP were categorized under attitude towards PrEP while codes relating to people who would approve or disapprove of the women's decision to use PrEP were categorized under subjective norm. Control beliefs comprised codes relating to presence of factors that would make it easy or difficult for women to use PrEP during pregnancy or breastfeeding. We also had several codes representing preferences for PrEP delivery during pregnancy and breastfeeding. Data were summarized using a framework matrix. The main themes and sub-themes are presented in Table 1. We used NVIVO v.12 (QSR International, Burlington, MA, USA) for data management and analysis.

Ethical approval

The study received approval from the University of Zambia Biomedical Research Ethics Committee (Lusaka, Zambia) and the Human Research Ethics Committee at the University of the Witwatersrand (Johannesburg, South Africa). Additional approvals were obtained from the Zambia National Health Research Authority and the Lusaka District Medical Office prior to study activation.

Results

We conducted in-depth interviews with 24 HIV-negative pregnant and breastfeeding women. Baseline characteristics of study participants are presented in Table 1. Fifty percent of the women were aged below 24 years (IQR: 22–30 years) and the majority were married and living with their partners (18 of 24). Few women perceived themselves to be at high risk for HIV infection, the majority knew their partner's HIV status.

TABLE 1 Respondent characteristics: HIV-negative pregnant and breastfeeding women ($N = 24$).

Characteristic	*n* (%)
Age in years, median (IQR)	24 (22–30)
Length of interview in minutes, median (range)	14 (8–43)
Marital status	
Never been married before	5 (21)
Married (living with partner)	18 (75)
Married (not living with partner)	1 (4)
Educational attainment	
Primary	7 (29)
Secondary	17 (71)
Employment	
Not working	17 (71)
Working for wages	1 (4)
Self employed	6 (25)
Maternal status	
Pregnant	13 (54)
Breastfeeding	11 (46)
Condom use in the last 30 days	
Never	18 (75)
Sometimes	6 (25)
Transactional sex in the last 30 days	
Yes	2 (8)
No	22 (92)
Partner HIV status	
Known	21 (88)
Unknown	3 (12)
Perceived HIV risk	
No risk	3 (13)
Low risk	13 (54)
Moderate risk	6 (25)
High risk	2 (8)
PrEP awareness before interview	
Yes	10 (42)
No	14 (58)

Beliefs about PrEP

Most women (14 of 24) did not know about PrEP prior to the interview. Among the few that reported having knowledge about PrEP, some mistook PrEP for post-exposure prophylaxis while others described PrEP as treatment for sexually transmitted diseases. Beliefs that women held about PrEP were categorized into three broad themes based on the Theory of Planned Behaviour framework: (1) behavioural beliefs; (2) normative beliefs, and (3) control beliefs. We also asked specific questions about service delivery preferences for PrEP. Because these are related to control beliefs, these perspectives were included in that latter section. Table 2 is a summary of the broad and sub-themes from the interviews.

Behavioural beliefs about PrEP

Participants were asked what they thought were the advantages and disadvantages of taking oral PrEP every day during pregnancy and breastfeeding. The women expressed both positive and negative views. After learning about PrEP from the interviewer, participants felt that PrEP was good for them and their babies as it had the potential to protect them from acquiring HIV.

TABLE 2 Main themes and sub-themes from the study.

Behavioral beliefs	**Advantages of taking PrEP** • Protects pregnant/ breastfeeding woman from contracting HIV • Protects the baby from contracting HIV **Disadvantages of taking PrEP** • Concerns about side effects to the woman • Concerns about side effects to the baby • Pill burden • Stigma/labelling from family, friends and community members	*"I would want to protect myself, and my baby as well, so that we do not contract HIV…. as you know…you can't just be trusting him just because you live with him… it's important to just drink the medicine so that you protect yourself." (Participant 007).* *"I think I can be scared of taking this medication in the sense that I can be taking it [PrEP] without being sick and yet experiencing side effects like weight gain and so on. This can discourage me from taking this medication…" (Married, pregnant).*
Normative beliefs	**People who would approve or disapprove** • Partner • Other family members **What other people would think** • Stigma associated with HIV status • Promiscuity	*"My grandmother can disapprove, even my parents, like my mother… she would say no, you should just be using protection [condoms], things like that (Single, pregnant).* *"…my husband can disapprove. He can think that I can be sleeping around since I know that I won't get sick because of taking PrEP. This would make it difficult for me to take PrEP." (Married, breastfeeding).*
Control beliefs and preferences for PrEP service delivery	**Facilitators and Barriers to PrEP use** • Support from family and the community • Community awareness of PrE **Preferences for PrEP delivery** • Attitude of health care providers • Venue for collecting PrEP • Distance to the facility • Waiting time in the queue • Gender of health worker giving PrEP	*"There is too much stigma! If I tell my friend that I am taking this medication, she will go round telling people that I am sick [HIV positive]. This is what happens in our communities…the community does not support in any way." (Married, breastfeeding).* "*Their attitude should be good; it just has to be good! Otherwise I would stop coming to collect PrEP if I found rude health care providers." (Married, pregnant).* "*Any [whether male or female] is okay with me, as long as they have a good attitude." (Participant 007).*

> "*What I feel is the advantage of taking PrEP is that, PrEP protects us. It is good in the sense that one cannot easily be infected with HIV/AIDS. For example, my husband can have sex with another woman who may be HIV positive but when he sleeps with me, I may not be infected because PrEP will protect me from getting sick. So I feel oral PREP is good." (Married, breastfeeding).*

In addition, lack of trust for the partner was seen as a motivating factor to initiate PrEP during pregnancy and breastfeeding as a way of ensuring that they remained HIV-negative. According to some participants, trusting anyone, including one's own husband was a difficult thing to do. They argued that it was impossible for a woman to know all the whereabouts of her partner, adding that men would engage in multiple sexual relationships and in some instances, they would not even disclose to their spouses that they are on antiretroviral therapy. Women were of the view that, in such circumstances, PrEP could protect them from HIV infection if they had an unfaithful partner or had sex with someone who was HIV positive.

> *"… it is so hard to trust someone these days. It is also hard to trust your own husband. This world is cruel, you can find that your husband is on ARVs [HIV treatment] and you do not know about it. So it is better for me to be taking PrEP in order to protect myself from contracting HIV/AIDS… taking PrEP can protect me from contracting HIV/AIDS." (Married, pregnant).*

Despite the positive impressions about PrEP in general, some women raised concerns about its use during pregnancy or breastfeeding. Fear of side effects, pill burden, and forgetfulness were some of the major issues that were seen as disadvantages of taking PrEP during pregnancy and breastfeeding. Women reported that they were given several other medications during pregnancy (e.g., iron supplements) and that adding more medications could be burdensome. They also reported that they did not want to deal with the side effects of PrEP.

> *"I think I can be scared of taking this medication in the sense that I can be taking it [PrEP] without being sick and yet experiencing side effects like weight gain and so on. This can discourage me from taking this medication because I wouldn't want to experience side effects when I know that I am not sick." (Married, pregnant).*

> *"I think I have some reservations because I fear that my baby can be born prematurely because of taking PrEP." (Single, pregnant)*

Other women did not view PrEP negatively in itself. The disadvantage they reported was linked to how others might view women who take PrEP when they are not sick [HIV-negative]

> *I have not seen any disadvantage of taking PrEP. The only problem is with people who may end up laughing at you that you are taking medication yet you are not sick. This can discourage someone from taking PrEP (Participant 02).*

Normative beliefs about PrEP use

We asked women to tell us about who they thought would approve and/or disapprove of their decision to take PrEP during pregnancy. Community and family members, especially male partners, were often cited. Stigma and being labeled to be on ART seemed to be a major concern that would hinder uptake of PrEP by pregnant and breastfeeding women.

> *"There is too much stigmatization in the community. If I tell my friend that I am taking this medication, she will go round telling people that I am sick [HIV positive] and that is why am taking the medication when in the actual sense, I am protecting myself. This is what happens in our communities, we are used. The community does not support in any way." (Married, breastfeeding).*

Women also felt that people in their communities did not know much about PrEP, and that most community members would mistake PrEP for HIV treatment. The alleged lack of knowledge and stigma were seen as factors that would lead to pregnant and breastfeeding women being labeled as being HIV-positive once seen taking PrEP.

> *"Sometimes you can decide to share with your friends about the medicine you are drinking [PrEP], they can think that you are taking ARVs [HIV treatment] and not PrEP, as you know knowledge levels are different among people in the community. There are people who are educated and those that are not educated and wouldn't understand how PrEP works. They would say that PrEP is just the same as ARVs [HIV treatment] and that the difference is just the colour [of the pills]." (Married, pregnant).*

Other participants viewed PrEP as something that would promote promiscuity among women. They argued that the mere knowledge that PrEP would protect one from contracting HIV would make women engage in risky behaviour including having multiple sexual partners.

> *"I think people can take advantage of the fact that PrEP protects them from contracting HIV/AIDS. They can start misbehaving because they know that they will not get sick. This is the disadvantage I can think of." (Married, breastfeeding).*

Control beliefs about PrEP use

Pregnant and breastfeeding women were asked to describe circumstances that would make it easy and those that would make it difficult for them to take PrEP. For most women, whether or not to take PrEP would depend on approval from family members, including their male partners. In most cases, approval and support from their partners was seen as an important consideration when deciding to take PrEP. Women viewed the lack of support or approval from family members as a possible barrier to taking PrEP during pregnancy and breastfeeding.

> *"I think my husband can make it difficult for me to take this PrEP. It can be difficult in that I do not take any pills. He may ask why I am taking PrEP because he knows I do not take any pills and he also knows that I use the injection as my contraceptive…he would wonder why I am taking this medication. He may also seek advice from his family and friends who could end up misleading him by making him believe that I am taking ARVs [HIV treatment]and not PrEP." (Married, breastfeeding).*

Some of the women stated that they would not take PrEP if their partners did not first approve.

> *"…my husband can disapprove. He can think that I can be sleeping around since I know that I won"t get sick because of taking PrEP. I will need to explain to him the benefits of taking PrEP and if he is to understand then I can go ahead… but I would not drink it if he were to disapprove." (Married, pregnant).*

Although all acknowledged the important role of the partner, some women felt that they would still go ahead and take PrEP even without the support of their spouses. The final decision as to whether or not to take PrEP during pregnancy and breastfeeding was entirely up to them.

> *"I think my husband can disapprove…. I can listen to him but that does not mean that I have to follow everything that he tells me to do. If at all I have decided to take the medication on my own, then he will have no right to stop me from taking it." (Married, pregnant).*

Daily dosing was also reported as a potential barrier to PrEP uptake. Women likened the idea of taking PrEP to taking oral contraceptives. They argued that there was no guarantee that they would remember to take PrEP on a daily basis when they were already having challenges taking oral contraceptives consistently during non-pregnant intervals. Some women were of the view that perhaps taking PrEP in form of injections would make it easier for them to use PrEP.

> *"I think the issue of taking it [PrEP] daily is a problem because I can forget. It would be better if at all the medication was in form of an injection for 3 or 5 months. Taking tablets on a daily basis is dangerous because a person can forget to take it sometimes. We sometimes forget to take family planning pills, what would make us not to forget to take PrEP?" (Married, breastfeeding).*

A few women made reference to structural factors when asked about barriers to PrEP use. Despite reporting that long distances and lack of transport money to the facility would make it difficult for them to take PrEP, most of the women felt that this would not stop them from using PrEP.

> *"The distance does not matter as long as you know the importance of taking this medication. I can give an example of the people who are on ARVs [HIV treatment], they move for long distances in order for them to access ARVs. They even keep transport money or look for transport money in order for them to collect their medication. (Married, pregnant).*

Preferences for PrEP delivery

Women were asked about health systems-related factors that could make it easy or difficult for them to use PrEP during pregnancy and breastfeeding. They described the attitude of health care providers as having the potential to either promote or hinder uptake of PrEP during pregnancy and breastfeeding. Women felt that health care providers needed to be polite, kind, patient, good-hearted and maintain confidentiality. They reported that a good attitude would encourage women to use PrEP. A bad attitude, on the other hand, could lead to discouragement for starting and maintaining PrEP.

> *"Some nurses are rude and when they are talking, you are able to tell that they are rude. They should be kind to us because sometimes, you can get upset and some of us are emotional. They should be good and polite to us, because if they continue being rude, people can be discouraged from taking PrEP because it is like we are forcing them to do what they do not want to do." (Married, breastfeeding).*

Women were asked whether the gender of the health care provider dispensing PrEP mattered when it came to influencing uptake of PrEP during pregnancy and breastfeeding. For most women, gender did not seem to be an issue with respect to PrEP uptake. However, among those who had a preference for a specific gender, choices were based on different factors, including attitude and ability to relate to their experiences; some felt that female health care providers were more understanding compared to males.

> *"They should be female because I am not comfortable with male health care providers…, I would feel shy when talking to a male health care provider. I can easily answer any question that a female nurse will ask me, but for a male nurse, I may not be free to answer accordingly." (Married, breastfeeding).*

We asked women whether waiting time at the health facility would be a source of concern when it came to using PrEP during pregnancy and breastfeeding. The majority of them reported that they would not want to be in the queue for a long time. The amount of time that women would be willing to wait at the facility in order to get PrEP ranged from 5 min to about 4 h. Most viewed waiting time as being dependent on how early one arrived at the facility and how many people they found already waiting in the queue. They also reported that waiting at the facility was something that they were used to doing and that it was normal practice to do so.

> *"Queues will always be there; it all depends on how fast the queue is moving. If one does not want to spend too much time in the queue, then they have to come [to the facility] early." (Married, pregnant).*

Women preferred a health facility close to where they lived as this would make it easier for them to get to the facility to access PrEP. The amount of time they were willing to spend en route to the facility dispensing PrEP ranged from 15 min to 2 h. Although women preferred a facility that was closer to their homes, they reported that even if the facility was far, they would still make an effort to overcome this barrier in order to get PrEP. All women reported that they wanted to get PrEP from a health facility, either a clinic or hospital. When asked whether they would want PrEP to be delivered to their homes, women had differing views. Home delivery of PrEP would address the challenges associated with transportation to and from the health facility. It would also provide a positive opportunity for other community members to learn about PrEP.

> *"I think it would be good if they delivered the medicine at my home. Home is actually better because other people can also get to learn about PrEP." (Married, breastfeeding).*

For other women, getting PrEP from the clinic was viewed negatively, as it would lead to discrimination and stigma. They expressed concern that queueing up for PrEP at the facility would make other people think that the women were actually on ART. For some women, getting PrEP from other facilities where people did not know them was seen as a better option.

> *"If we collect from the clinic, isn"t it that we are supposed to be in a queue and other people who see us may think that we are sick or that we are getting ARVs [ART]? It is even better to collect from a clinic where people do not know you. People have a tendency of concluding." (Married, breastfeeding).*

Summary of findings

In summary, we find that HIV-negative pregnant and breastfeeding women have positive attitudes towards PrEP use as a way of protecting themselves and their babies from HIV infection. Partners were cited as key referents when it comes to decision making on health-related matters and that their approval was critical if women were to use PrEP during pregnancy and breastfeeding. Women also believed that location for PrEP pick-up, attitude of health care providers, waiting time and distance to the facility may influence their decision to take PrEP during pregnancy and breastfeeding. These findings are mapped to the Theory of Planned Behavior conceptual model in **Figure 1**.

Discussion

Women's perceptions about PrEP, particularly as they relate to the health of their children, have the potential to promote or hinder uptake during pregnancy and breastfeeding (39). Several of our key findings, particularly on women's behavioural beliefs and knowledge about PrEP echo results from other qualitative studies (7, 40), including one conducted by team members in Zambia

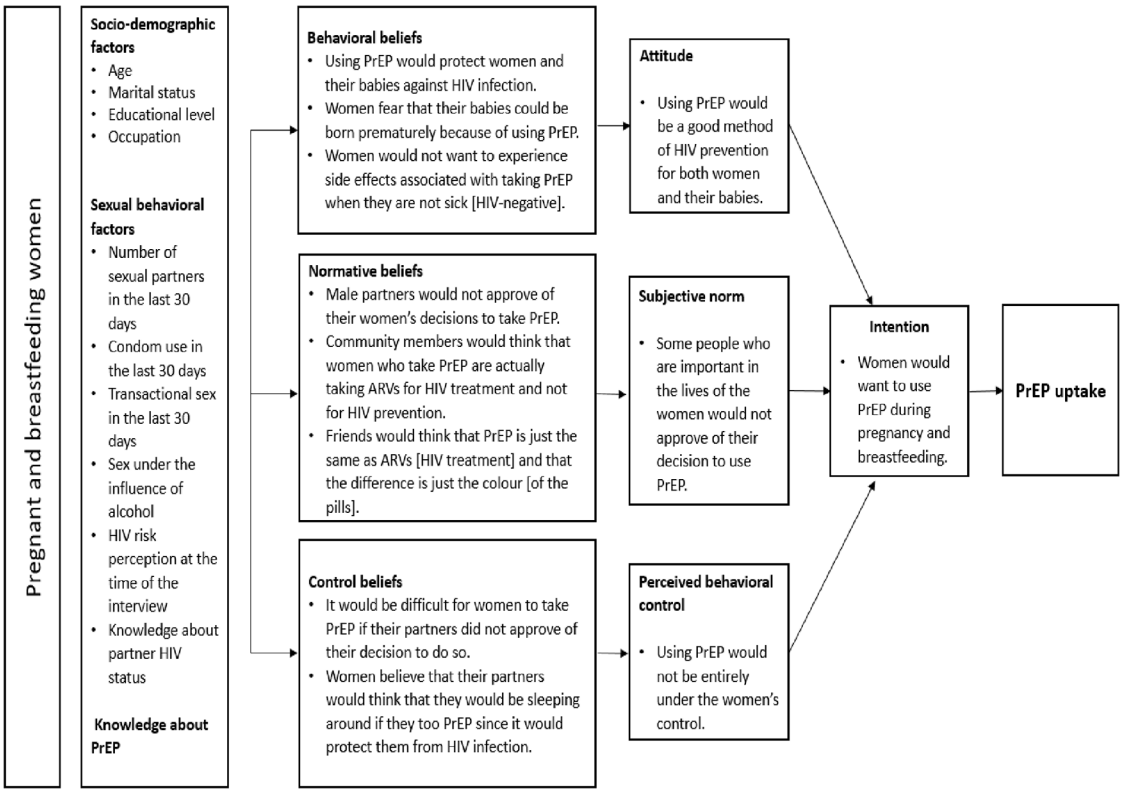

FIGURE 1
Mapping of findings onto the theory of planned behaviour conceptual framework.

and Malawi in 2017–2018 (41). Interestingly, despite the time that elapsed, many of the concerns remain the same, suggesting that more work is needed in outreach and education among prospective PrEP users.

Although women generally viewed PrEP as a good method to protect themselves and their infants from HIV infection, some participants expressed concerns that the availability of PrEP would encourage other women to engage in risky sexual behaviour. Health care providers in Kenya reported that PrEP users were sometimes confused, even frustrated, with their insistence on using condoms in addition to PrEP (40). Similar fears around the potential for PrEP to reduce condom use were reported in Eswatini (42). Davey et al. also noted that the perceptions that PrEP would lead to more risk or more condomless sex was a potential barrier to uptake and adherence (39).

Stigma and misinformation are often cited as barriers to PrEP use (43). From our results, women feared that, if they took PrEP, people would label them as being HIV-positive and not being truthful about their HIV status. They attributed this to inadequate knowledge about PrEP in their communities. In a similar study conducted in Uganda, South Africa and Zimbabwe, participants mentioned that they would refrain from taking PrEP because of its association with antiretroviral drugs and HIV-related stigma. This was a key barrier to uptake as participants linked taking daily tablets to people living with HIV (44). HIV-related stigma is common in Zambia (45, 46) and could negatively impact PrEP uptake, adherence, and retention in care at a time when women need it the most to ensure that their infants and themselves stay HIV-negative. Deliberate efforts aimed at developing community-based education programs with a focus on demystifying PrEP may have a significant impact on PrEP uptake among HIV-negative pregnant and breastfeeding women.

The level of male partner support may influence women's decision to take PrEP during pregnancy and breastfeeding. Evidence suggests that men are generally viewed as head of house and ultimate decision makers who are actively involved in health-related decision-making during pregnancy and breastfeeding (47, 48). Our study found that women had divergent views about who would approve of their decision to take PrEP during pregnancy and breastfeeding. The key referents, however, were mostly women's partners. Similar findings have been reported in similar settings. In a study that contextualized male roles and participation in PMTCT programs in Malawi and Zambia, for instance, both men and women reported that they had to consult and seek approval from their partners on decisions that related to their health (47). Other studies also reported that men were the primary advisors and key decision-makers on health-related decisions during pregnancy and breastfeeding (41, 49, 50).

From our findings, male partners may, to a greater extent, determine actual uptake of PrEP by women during pregnancy

and breastfeeding. Similar findings were reported elsewhere (50). Such gender-based power differentials, specifically the lack of autonomy among women to make decisions concerning their health may present a barrier to PrEP uptake during pregnancy and breastfeeding. Male involvement in promoting PrEP uptake among pregnant and breastfeeding women could increase the use of PrEP in this target population. In some circumstances, such engagement may be challenging and this should be recognized. Programs should offer these women additional support for HIV prevention, whether through PrEP or other proven modalities.

Participants in our study expressed concern about the gender of health care providers. Interestingly, however, gender was rarely discussed in isolation, but rather with reference to the attitude of health care providers. Women who preferred to be attended to by male health care providers viewed female health care providers negatively. This finding is supported by prior research where respondents complained about the poor attitude of health care providers, especially female nurses being disrespectful, rude and using abusive words (48). Participants in our study reported that health care providers who had a bad attitude would make it difficult for women to use PrEP during pregnancy and breastfeeding. Some women felt that they would not use PrEP if the health care providers dispensing PrEP were rude to them. Our findings on the impact of health care provider attitude on PrEP uptake are consistent with other studies (44).

Distance and waiting time are structural factors that may have a negative impact on PrEP uptake and retention in care. Women in our study reported that having a health facility nearer to where they lived would make it easier for them to take PrEP. A study in Uganda also found that walking time to the clinic of thirty minutes or greater was associated with decreased odds of uptake of PrEP (51). Although distance was cited as a barrier in our current study, it is possible that its effect on PrEP uptake could be indirect as women may have taken into consideration the transport-related costs of remaining in PrEP care if they decided to initiate PrEP in the future. Waiting time in the queue was also cited as a potential barrier to PrEP uptake. Women did not want to wait for a long time at the facility in order to collect PrEP. Similar to our findings, a study conducted in Botswana, Tanzania and Uganda reported that lost wages due to waiting time was a barrier to adherence among individuals on antiretroviral therapy (52). These findings are corroborated by those from a recent study conducted by our team (36).

Strengths and limitations

The main strength of this study is our use of an established theoretical framework to determine potential barriers and facilitators to PrEP use in pregnant and breastfeeding women. The perspectives shared are specific to this population, providing important insights during an important period in women's lives. At the same time, we also recognize some limitations. First, this study focused on individual-level cognitions and did not explore other unconscious influences that could potentially account for variances in PrEP uptake behavior. However, evidence suggests that interventions resulting in large changes in intention are likely to also change behavior (53). Second, our results are a mix of beliefs held by women who were and those who were not knowledgeable about PrEP prior to study participation. Responses of the latter could be prone to social desirability bias. Third, we enrolled only pregnant and breastfeeding women in our study. While this was viewed as a strength overall, we acknowledge our limited ability to compare these responses to those of other women outside of this window. Further, it is possible that some participants' responses may not have specifically focused on PrEP use during pregnancy and breastfeeding intervals, owing to their limited awareness about PrEP prior to the interviews and lack of experience using PrEP. Nevertheless, their perspectives still offer useful insights on beliefs likely to influence PrEP uptake in antenatal and postnatal settings. Exploring and documenting the lived experiences of women who have used PrEP during pregnancy and breastfeeding could enhance our understanding of facilitators and barriers to PrEP uptake and onward adherence and retention in care in this population. This represents a gap for further research. Fourth, the study was based at a single facility and, therefore, our results may not be generalized to the larger antenatal and postnatal populations in Zambia—or in the sub-Saharan African region. As with all qualitative studies, we instead focus on the depth of participant beliefs and preferences to inform future PrEP implementation in antenatal settings. Fifth, PrEP was not readily accessible at the study site at the time this study was implemented. The hypothetical nature of PrEP in the study only provided partial understanding of facilitators and barriers to PrEP uptake as the views of women interviewed may differ from those of women who have experience taking PrEP during pregnancy and breastfeeding. Nevertheless, the positive attitude towards PrEP use among participants was reassuring and provides an avenue to promote uptake of PrEP during pregnancy and breastfeeding.

Conclusion

Our study suggests that HIV-negative pregnant and breastfeeding women have positive attitudes towards PrEP but barriers to PrEP uptake are multifaceted. To ensure that PrEP implementation in antenatal settings is successful, there is need to address the inadequate knowledge about PrEP among pregnant and breastfeeding women—and the broader community as well. Interventions that promote male involvement in female-initiated methods for HIV prevention may result in improved knowledge and a more supportive attitude among men towards women who wish to use PrEP during pregnancy and breastfeeding. Addressing contextual barriers—including distance, waiting time at the facility, and health care provider attitude—could have a significant impact on PrEP uptake. Above all, exploring the lived experiences of pregnant and breastfeeding women who have used PrEP before would be critical to the design of effective PrEP implementation strategies in this population in need.

Data availability statement

The datasets presented in this article are not readily available because the qualitative nature of these data make it difficult for us to share them publicly, mainly owing to the potential for identification. However data will be made available through the University of Zambia, School of Public Health (deansoph@unza.zm) for researchers who meet the criteria for access to confidential data. Requests to access the datasets should be directed to Dean-School of Public Health, deansoph@unza.zm.

Ethics statement

The studies involving human participants were reviewed and approved by The University of Zambia Biomedical Research Ethics Committee (UNZABREC #: 934-2020) and the Human Research Ethics Committee at the University of the Witwatersrand (Wits HREC #: M200564 MED20-02-145. The patients/participants provided their written informed consent to participate in this study.

Author contributions

TEH, BHC, JI and WM conceptualized the study and TEH analysed the data. TEH wrote the first draft of the manuscript. All authors contributed to the interpretation of results, reviewed the manuscript and approved the final version.

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Conflict of interest

LMH reports receiving research funding from Gilead Sciences. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Integrating PrEP in maternal and child health clinics in Kenya: analysis of a service availability and readiness assessment (SARA) survey

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Background: Risk of HIV acquisition is high during pregnancy and postpartum, and pre-exposure prophylaxis (PrEP) is recommended for peripartum populations. Integrating PrEP into maternal and child health (MCH) clinics is feasible and acceptable. Understanding clinics' service availability and readiness is essential for effective scale up.

Methods: The PrEP in Pregnancy, Accelerating Reach and Efficiency study (PrEPARE; NCT04712994) engaged PrEP-experienced facilities previously linked to a programmatic or research study in Western Kenya to document available services and commodities via a modified service availability and readiness assessment (SARA) survey with 20 PrEP tracer items covering: staffing/guidelines, services/equipment, and medicines/commodities. Facilities' prior study engagement occurred between 2017 and 2019; SARA survey data was collected between April 2020 and June 2021. Descriptive statistics were stratified by prior study engagement. ANOVA tests assessed associations between facility characteristics and gaps. Fisher's tests assessed differences in commodity availability and stockouts.

Results: Of the 55 facilities surveyed, 60% had received PrEP training in the last two years, 95% offered PrEP integrated into MCH, and 64% and 78% had both auditory and visual privacy in PrEP and HIV testing service (HTS) delivery spaces, respectively. Supervision frequency was heterogeneous, but 82% had received a supervision visit within 3 months. Availability of commodities was variable and the most commonly unavailable commodities were PrEP in MCH (71% available) and risk assessment screening tool (RAST) and PrEP cards (60% and 75% available, respectively). The number of service and commodity gaps per facility ranged from zero to eight (median: 3; IQR: 2, 5). The most frequent gaps were: PrEP training and risk assessment cards (40% each), lack of privacy in PrEP (36%) and HIV testing services (31%) spaces, PrEP pills in MCH (29%), and PrEP cards (25%). There were no differences in mean number of gaps by county, previous study engagement, or public vs. private status. Level 4 facilities had fewer gaps (mean 2.2) than level 2, 3, and 5 facilities (mean 5.7, 4.5, and 5.3 respectively; $p < 0.001$).

Conclusions: PrEP service availability and readiness was generally high across MCH facilities. However, there is a need for increased frequency of provider training and supportive supervision focused on fidelity. To address key commodity stockouts such as PrEP pills, implementation of electronic logistics management information systems may be needed. Targeting these gaps is essential to effectively scale up integrated PrEP delivery, especially among facilities with limited infrastructure.

KEYWORDS

pre-exposure prophylaxis (PrEP), service readiness and availability, commodities, supervision, pregnancy, postpartum, health facilities (MeSH)

Introduction

HIV incidence among women is high during pregnancy and the postpartum period (1, 2). Women who acquire HIV infections during these periods of elevated risk contribute disproportionately and increasingly to vertical HIV transmission (3–5). Pre-exposure prophylaxis (PrEP) is recommended by both WHO and Kenyan guidelines during pregnancy and postpartum (6–9). Several studies have found that PrEP is safe and effective during pregnancy (10–13). In order to assess effective PrEP delivery for high-risk populations, the PrEP care cascade is used to identify gaps in intervention and program delivery as well as behavioral factors such as HIV risk perception (14, 15). Previous evaluations of PrEP delivery interventions and programs in sub-Saharan Africa have not incorporated data on service and commodity availability (16, 17). Assessing readiness of facilities for high quality PrEP delivery is useful in scale up planning, and previous work has called for the integration of demand, supply, and adherence analysis in HIV prevention program planning with specific interventions such as PrEP (15, 18–20).

PrEP delivery within maternal and child health (MCH) services is feasible and preferable to PrEP provision in HIV care clinics in Kenya (21–24). However, there is suboptimal implementation and integration of PrEP in MCH and family planning (FP) clinics, and MCH/FP clinic-delivered PrEP programming has not yet been systematically scaled up. In order to reduce siloed PrEP delivery for at-risk pregnant and postpartum women, there is a need for enhanced focus on the gaps in service availability and readiness in non-HIV dedicated clinics within the Kenyan health sector (25).

Service availability and readiness assessment (SARA) surveys are useful to track essential commodities and practices by systematically documenting availability of tracer items across facilities to identify strengths and gaps in service provision (26). These surveys may aid in meeting Kenya's strategic health sector goals because many reported barriers to community health services access are at the health facility level (27). The Kenya Harmonized Health Facility Assessment and previous qualitative work with HCWs experienced in PrEP delivery showed that healthcare worker (HCW) shortages, commodity shortages, and a lack of essential amenities impede access to community health services (27, 28). While barriers are understood, the lack of tracking and documenting these barriers at the individual facility level impedes the ability to integrate PrEP in MCH services.

The first component of programs aiming to prevent vertical HIV transmission is preventing HIV acquisition among pregnant women, yet this vital first prong receives little attention in Kenyan policies on vertical transmission (29). In addition to the limited scope of prevention efforts, the monitoring of PrEP service availability and readiness has been incomplete. The most recent national SARA survey was conducted in 2013, prior to the national launch of PrEP in 2017, and this survey found that 60% of facilities in Kenya were providing vertical transmission prevention services (30). However, ART drugs were the sole focus of the HIV commodity assessment, highlighting the need for an updated look at commodity availability following national PrEP scaleup. Integrating PrEP into MCH clinics and reducing vertical HIV transmission will remain a substantial challenge without understanding service and commodity availability in more granular detail.

This analysis comprises the largest sample of facilities with experience delivering PrEP in MCH. As each of these facilities have previously engaged in studies and programs related to HIV prevention for pregnant and postpartum women, we would expect a higher degree of service availability and readiness compared to all facilities across the counties. Identifying gaps in services and readiness after the conclusion of these prior research activities can inform strategic efforts to address these gaps and scale up intervention efforts. This descriptive and exploratory analysis provides a detailed assessment of the items necessary for delivering comprehensive HIV prevention for women at risk of HIV acquisition in the context of MCH services.

Methods

Study design

The *PrEP in Pregnancy, Accelerating Reach and Efficiency* (PrEPARE; NCT04712994) study develops, pilots, and evaluates four implementation strategy bundles to optimize PrEP integration and delivery in MCH and FP clinics. This analysis is a cross-sectional evaluation of facility Service Availability and Readiness Assessment (SARA) surveys (26). Data was collected between April 2020 and June 2021, prior to the implementation of strategy bundles.

Study facilities and prior study engagement

The SARA surveys were completed at facilities from three counties in Kenya: Kisumu, Homa Bay, and Siaya Counties. Each facility had previously participated in a component of the suite of PrEP in pregnancy studies: *PrEP Implementation for Young Women and Adolescents* program (PrIYA) (31), PrIYA Mentorship program (31), and *PrEP Implementation for Mothers in Antenatal Care* study (PrIMA; NCT03070600). A timeline of data collection across these studies is available in **Supplementary Figure S1**. *PrIYA description*: PrIYA sites integrated PrEP delivery for at-risk adolescent girls and young women attending family planning and pregnant and postpartum women and other women attending maternal and child health clinics in Kenya (31). Women seeking care at these facilities who had tested HIV negative at that visit or within a month, and were willing to receive PrEP counselling were offered PrEP. PrIYA activities were conducted between June 2017 and December 2018; in this programmatically-focused project, there was no specific intervention tested in a comparative design; instead, facilities focused on navigating how to deliver integrated PrEP in MCH and FP clinics in diverse settings. Study staff assisted with program implementation and service delivery during the study period; these additional staff were phased out after the first year (31). *PrIYA Mentorship description:* PrIYA Mentorship site activities were conducted between January and July 2018. There were no study procedures used, but former PrIYA nurses provided in-clinic guidance to existing HCWs at PrIYA Mentorship sites to assist with implementation; study staff were not involved in service delivery for PrIYA mentorship. *PrIMA description*: Finally, PrIMA was a research study that provided additional staff to assist in study activities. The 20 public clinic sites involved in PrIMA were assigned to one of two arms in a cluster randomized trial; pregnant women seeking routine MCH care at these clinics either (a) self-selected into PrEP after receipt of PrEP counseling (Universal arm), or (b) were evaluated for HIV risk via an objective risk-scoring tool and offered HIV self-tests for at-home partner testing (Targeted arm) (32, 33). In the Targeted arm, only individuals determined to be high risk for HIV acquisition were offered PrEP. PrIMA was conducted with study staff between January 2018 and July 2019.

Ethical approval

All participants provided oral informed consent to participate. This study was approved by the ethical review committees at the University of Washington and Kenyatta National Hospital.

Data collection

At each facility, a healthcare worker with experience delivering PrEP to pregnant and postpartum populations was asked to complete the SARA survey; the healthcare workers were purposively selected for higher levels of experience by the study staff who were familiar with the healthcare workers' level of experience at their facility. The SARA survey is a health facility assessment tool developed by the World Health Organization (WHO) and United States Agency for International Development (USAID) (26). A set of tracer items (commodities, clinical practices, and behaviors) is generated for the survey that allows for a systematic measure of facility service availability and readiness in a particular field of healthcare (see **Supplementary Table S1** for list of tracer items used in this survey). We adapted standard tracer items from HIV care to be applicable to PrEP delivery, including HIV testing services (HTS). Participants were asked to provide information on facility characteristics (e.g., facility level, urbanicity) and a set of 20 PrEP-delivery-specific tracer items which were categorized as pertaining to staffing and guidelines (e.g., training, supervisory visits), services and equipment (e.g., MCH services, private spaces for PrEP delivery), and medicines and commodities (e.g., HIV rapid test kits, PrEP pills, stockouts in the last month). All data on facility characteristics and the 20 tracer items were self-reported by the healthcare worker who completed the SARA survey for that facility. The surveys were administered online, over the phone, or in-person through REDCap, a secure, online data collection and management software (34).

Data analysis

Descriptive statistics – including counts and proportions – were calculated to summarize the facility readiness based on the presence of tracer items. In sensitivity analyses, descriptive statistics were stratified by facilities' prior engagement in PrIYA, PrIYA Mentorship, and PrIMA.

A heatmap was generated to identify common gaps across service availability and readiness tracer items for all facilities. Descriptive statistics, including average number of gaps, for each facility are provided. All gaps were coded as binary variables (1 = Yes, 0 = No), unless otherwise specified. Gaps in HTS and PrEP delivery spaces were defined as having no privacy, auditory privacy only, or visual privacy only. Gaps in supervision frequency were defined as not having received a supervisory visit within the last three months, in alignment with the recommendations from the Kenyan Ministry of Health (35). ANOVA tests were used to compare the average total number of gaps between the categories of facilities' county, level (categorization of facilities based on services provided and geographic region served; categorized as levels 1–6) (36), previous study enrollment, and managing authority using an α-level of 0.05.

To assess the relationship between current commodity availability and commodity stockouts, Fisher's exact tests were used with an α-level of 0.05. Commodities were coded as binary variables (1 = currently available vs. 0 = previously available or no); stockouts within the last month were similarly coded as a binary variable (yes, no).

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TABLE 1 Characteristics of the health facilities assessed. Kenya, 2020–2021.

	Overall (*N*=55)
County	
Homa Bay	9 (16%)
Siaya	10 (18%)
Kisumu	36 (66%)
Facility level	
2 – Dispensary or clinic	3 (6%)
3 – Health center	15 (27%)
4 – Sub-county hospital or private medium hospital	34 (62%)
5 – County referral hospital or large private hospital	3 (6%)
Managing authority	
Government/public	50 (91%)
Mission/faith-based	4 (7%)
Private-for-profit	1 (2%)
Implementing partner	
Yes	52 (95%)
Urbanicity	
Urban	8 (15%)
Semi-urban	22 (40%)
Rural	25 (45%)

Results

Facility characteristics

A total of 55 health facilities were included in this analysis; descriptive characteristics are included in Table 1 and Supplementary Table S2. The facilities included three dispensaries or clinics (level 2), 15 health centers (level 3), 34 sub-county hospitals or medium private hospitals (level 4), and three county referral hospitals or large private hospitals (level 5). There were no SARA surveys completed at community service centers (level 1) or national referral hospitals (level 6). There were 16 PrIYA facilities, 20 PrIYA Mentorship facilities, and 19 PrIMA facilities; 100% of PrIYA and PrIYA Mentorship facilities were in Kisumu County, while PrIMA facilities were located in Siaya and Homa Bay Counties (53% and 47% respectively). The majority of facilities (91%) were government or public facilities, and nearly all facilities worked with an implementing partner to deliver PrEP (95%). The plurality of facilities were located in rural areas (45%), followed by semi-urban (40%) and urban (15%) areas.

SARA survey tracer items

Twenty items were assessed in the SARA surveys to determine the current availability of staff and guidelines, services and equipment, and medicines and commodities (Figure 1). Sixty percent of facilities had received PrEP training within the past 2 years; 84% had national guidelines available at the site, and 80% had PrEP checklists and job aids at the site. PrEP training included trainings conducted by study staff, Ministry of Health officials, or other implementing partners. The majority (82%) of facilities had received a supervisory visit within the last three months, which included assessments of staffing, data, and pharmacy supplies. However, fewer (26%) had received a supervision visit within the last month.

All facilities offered MCH services and provided PrEP in HIV care clinics, and nearly all facilities still provided PrEP in MCH (95%). However, there were gaps identified in the amount of privacy provided in PrEP and HTS delivery spaces. Approximately 64% and 78% of facilities had both auditory and visual privacy for

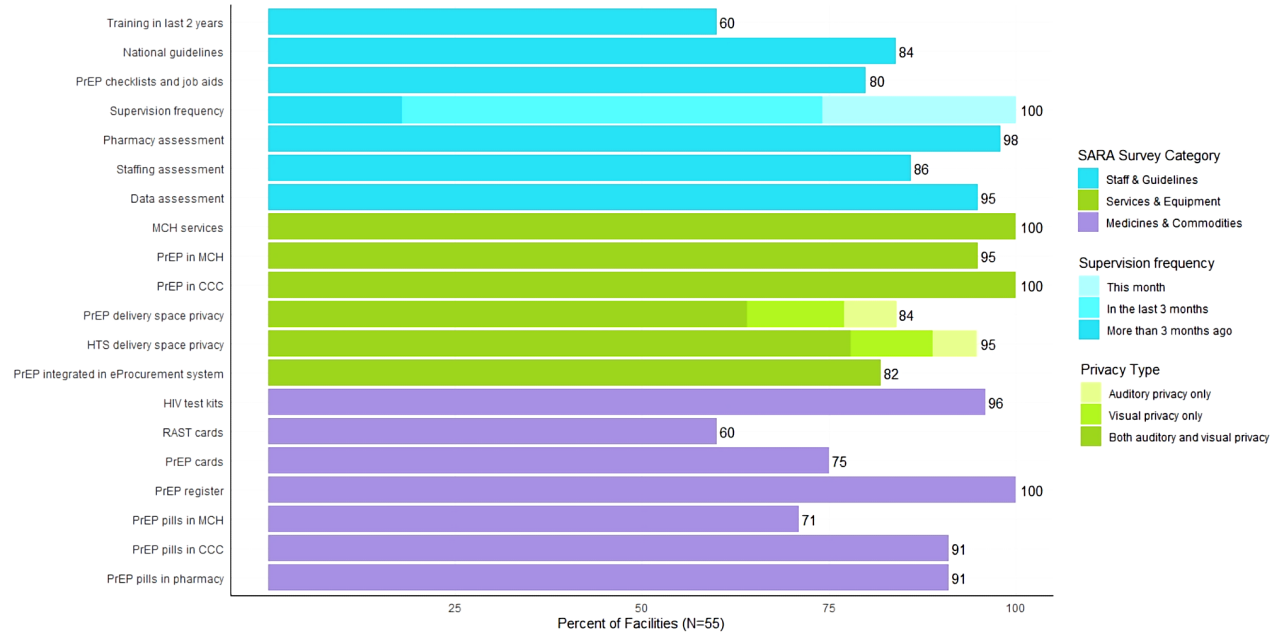

FIGURE 1
Percentage of facilities that have tracer items for PrEP delivery. Kenya, 2020–2021.

these delivery spaces, respectively. Integration of PrEP ordering into the eProcurement system was reasonably high at 82%.

Medicine and commodity availability was more varied across facilities. Most facilities reported availability of HIV test kits (96%), PrEP registers (100%), and PrEP pills in HIV care clinics (91%) and pharmacies (91%). However, availability of risk assessment screening tool (RAST) cards, PrEP cards, and PrEP pills in MCH clinics was lower (60%, 75%, and 71%, respectively).

Sensitivity analysis stratified by prior study engagement

In order to characterize the differences in infrastructure that might distinguish facilities chosen for research studies vs. more typical facilities, we conducted sensitivity analyses stratified by prior study engagement (**Supplementary Figure S2**). Of note, facilities selected as trial sites (PrIMA) had greater visual and auditory privacy than facilities selected as demonstration project sites (PrIYA) or expanded capacity-building sites (PrIYA mentorship). Similarly, facilities selected as trial and demonstration project sites were more likely to have eProcurement systems for PrEP than capacity-building sites (PrIYA mentorship). There were no meaningful differences between facilities selected as trial, demonstration project, or capacity-building sites in terms of availability of HIV test kits, PrEP registers, PrEP pills in HIV care clinic and pharmacy.

Frequency and heatmap of gaps

Across the 20 tracer items assessed, the number of facilities reporting a gap ranged from 22 facilities having not received a PrEP training in the last two years to zero facilities having a gap for having a PrEP register, offering PrEP in HIV care clinics, and offering MCH services (**Supplementary Table S1**).

Across the 55 facilities surveyed, the number of gaps ranged from zero to eight (median: 3; IQR: 2, 5). In an exploratory analysis, there was a significant difference in the total number of gaps based on facility level. The level 4 facilities (sub-county hospitals or private medium hospitals) had an average of 2.9 gaps compared to an average of 5.3, 3.7, and 5.3 gaps among level 2, 3, and 5 facilities respectively (dispensaries or clinics, health centers, and county referral hospital or large private hospitals respectively) ($p < 0.001$). There were no significant differences in the average number of gaps between facilities in different counties, by previous study enrollment, or by managing authority.

Concordance between current commodity availability and stockouts in the last month

Within the SARA survey, six commodities were measured in terms of current availability and history of stockout; we compared the two measures to determine the level of agreement between them by assessing two categories of concordance (stockout in the last month & commodity not available currently; no stockout in the last month & commodity available currently) and discordance (expected: stockout in the last month & commodity available currently; unexpected: no stockout in the last month & commodity not available currently). Across the six tracer items assessed, there was generally high concordance between reporting no stockout in the last month and current availability of the commodity, ranging from 45.5% for RAST cards to 88.9% for PrEP registers (**Supplementary Table S3**). Approximately 10%–15% of facilities reported a stockout in the last month and that the commodity was currently available, although this discordance between measures was expected due to the potential for restocking supplies over a month-long period. However, substantial discordance was observed in reports of availability for RAST cards and PrEP pills in MCH; for these commodities, 18.2% and 16.4% of facilities respectively reported no stockouts in the last month but that these commodities were currently unavailable. The Fisher's exact test could not be performed for the PrEP register (commodity was available at all facilities) or PrEP pills in HIV care clinics (no facilities reported stockouts in the last month and commodity currently unavailable). The four remaining commodities did have statistically significant associations, demonstrating non-random classification of commodity availability by the two measures.

Discussion

In the present study, we observed generally high service availability and readiness across facilities in three Kenyan counties. Lack of PrEP training and RAST cards were the most common gaps across facilities, followed by PrEP and HTS delivery space privacy, PrEP pills in MCH, and PrEP cards. Differences in infrastructure, but not commodities, between facilities selected for trial, demonstration project, and capacity-building activities reveal insights for PrEP scale-up in MCH clinics.

We observed that HCW training on PrEP delivery was one of the most common gaps. There were fewer gaps in supervision frequency in the last three months, but substantially fewer facilities whose last supervisory visit occurred in the past month. This survey question did not differentiate between trainings conducted by study staff, Ministry of Health officials, or other implementing partners, limiting inference for future scale-up efforts. Provider knowledge of PrEP is necessary for PrEP service scale-up (37–39). Qualitative work among HCWs delivering PrEP in Tanzania highlighted the need for repeat trainings on PrEP, and previous work in Kenya found that repeated encounters with standardized patient actors improved provider counseling and adherence to national PrEP guidelines (38, 40). One study showed that, following in-service trainings among HCWs in a variety of fields, there was a reduction in outcome-associated effectiveness each month after training, highlighting the waning impact of training over time (41). In light of this finding, measuring receipt of provider training within the last two years may overestimate the readiness of facilities to provide PrEP services in MCH with high fidelity. A shift to providing

refresher trainings and providing supportive supervision at the intended frequency of 3-monthly for PrEP delivery teams in MCH may be needed to sustain quality care.

While MCH and PrEP services were offered across most facilities, privacy was lacking for both PrEP and HTS delivery spaces. Stigma remains a major concern during pregnancy and postpartum and contributes to avoidance of HIV prevention health services (21, 22, 42, 43). For individuals not living with HIV, there is an aversion to being seen receiving services at clinics associated with HIV for fear of being stigmatized. Additionally, privacy is essential in PrEP counseling sessions, which include inherently sensitive questions regarding sexual history (44, 45). Without providing adequate privacy for HTS and PrEP delivery, it will be challenging to scale-up integration of PrEP in MCH in order to reach women with greatest need (46, 47). In the literature, the majority of stigma-reduction interventions focus on reducing stigma among HCWs or reducing internalized stigma among people living with HIV; these methods include trainings for HCWs and popular opinion leaders, group education and trainings including people living with HIV, restructuring facility anti-discrimination policies, and rarely, social media campaigns (48–51). There is a need for stigma-reduction interventions that target people not living with HIV that will enable them to take full advantage of HIV prevention services.

Additionally, a relatively large proportion of facilities selected for capacity-building activities (PrIYA mentorship facilities), which were commonly located in rural areas, did not have PrEP ordering integrated into the eProcurement system. Use of electronic record-keeping in logistics management information systems (LMIS) increases the accuracy of commodity supply records and reduces lead time for resupply (52, 53). Previous work showed that rural health facilities can reduce the likelihood of commodity stockouts up to 64% when using an electronic LMIS in conjunction with daily updating in the LMIS system (54). Increasing the use of electronic LMIS, particularly in rural health facilities, may be a useful intervention to reduce stockouts and effectively integrate PrEP in MCH.

We observed low availability of RAST and PrEP cards, as well as PrEP pills in MCH. Study staff noted that in Kenyan clinics delivering MCH-integrated PrEP dispensing, MCH clinics are given a certain supply of medication from the central PrEP pill supply manager (either in pharmacy or HIV care clinic); when there is risk of PrEP stockouts in the facility, the MCH commodities are reallocated to the HIV care clinic pharmacy. This could explain why we observed that more facilities did not have PrEP pills in MCH compared to the HIV care clinic. Study staff also noted that during the period of data collection, many facilities were transitioning from paper-based medical records to electronic medical records (EMR), eliminating the need for paper commodities. While paper commodities were less frequently available, this may not have as substantial an impact on readiness to provide PrEP in MCH as previously thought. Surveys conducted with HCWs at the facilities during the data collection period noted that paper commodity stockouts had little to no impact on their ability to implement PrEP in MCH (*Hicks et al, under review*). As there is currently no standard for the use of paper vs. EMR, future SARA assessments of PrEP delivery in MCH should include both paper and EMR tracer items.

We found that sub-county hospitals or private medium hospitals had fewer gaps compared to the other facility levels included in this analysis. The 2013 Kenya SARA mapping survey found that primary care facilities (Tier 2) had the highest HIV service readiness index score at 78% compared to community (Tier 1; 67%), county (Tier 3; 74%), and national level facilities (Tier 4; 52%) (30). However, dispensaries, clinics, health centers, and sub-county hospitals are included in the Tier 2 definitions from Kenya's Health Policy (30). The additional disaggregation of facility types in this analysis highlights disparities in facility level readiness that will be useful in targeting interventions to improve service readiness for PrEP scale-up and integration in MCH services.

While we observed differences between facilities selected for trial (PrIMA), demonstration project (PrIYA), and capacity-building (PrIYA mentorship) activities, we do not believe that facility engagement in research studies led to higher levels of availability and readiness. Facilities that are selected for research may be more likely to have higher baseline service availability and readiness, which are then supplemented by additional resources and staff provided by the studies. For example, the PrIYA and PrIMA studies selected facilities based on higher patient volumes and assessments of infrastructure readiness. As we look towards scale-up of PrEP integration approaches, we need to be cognizant of these differences and prepare for potentially greater resource gaps among facilities that have not been involved in previous research activities, due to either lower client volumes or organizational readiness.

Generally, we observed concordance between current commodity availability and stockouts within the last month. There was a relatively high proportion of facilities reporting expected concordance – the absence of stockouts across both measures and the presence of stockouts by both measures. However, a substantial proportion of facilities provided conflicting responses. While it is possible and expected that there might be a stockout in the past month but not at present, it is not possible for there to be a stockout at present but not in the last month. However, it is important to note that stockout questions may have been interpreted to mean the last full calendar month which could exclude the present day. While this question was intended to reflect stockouts over the past 30 days including today, misinterpretations may have led to data reporting inconsistencies. Literature on commodity availability across several health topics have included measures of stockouts over varying time periods; the WHO SARA reference manual also includes measures of both current availability and past stockouts for the same commodities (55–58). These findings suggest that both measures should be included in future SARA surveys to avoid underestimation of commodity stockouts.

This study emphasizes HIV prevention services among women not living with HIV in MCH, addressing a gap in academic literature and national vertical transmission prevention programming. We were able to take a facility-specific view of service availability and readiness, enabling the identification of gaps by facility characteristics and prior engagement in studies

focused on PrEP integration and delivery within MCH. The more comprehensive list of tracer items enhances our understanding of where service provision and readiness is lacking across facilities in order to target interventions that will assist in integrated PrEP delivery scale up. These study strengths shed light on how to target effective HIV prevention services for this unique population.

However, this study does have several limitations. First, we did not assess provider knowledge of PrEP initiation or continuation guidelines. Previous work from sub-Saharan Africa has shown that poor clinical knowledge has a greater impact on readiness to provide services than either commodity availability or HCW absenteeism (59). While the lack of training was identified in our analysis, we may be missing a key indicator for readiness by not measuring provider knowledge. Second, our sample primarily consisted of Level 3 and 4 facilities that are part of the government or public sector; there is limited generalizability to the private sector or other forms of managing authorities. Third, the survey was completed by a single HCW at each facility who may be subject to recall bias or lack of familiarity with certain components of the survey; we did not collect individual-level data about the healthcare workers, so we are unable to verify the representativeness of these participants and their facilities compared to other facilities in the region. However, this sample reflected all of the facilities in the region with experience delivering PrEP in MCH through the 3 mentioned projects. Additionally, there was no direct observation from study staff as is ideal in SARA surveys, especially for commodities, due to COVID-19 restrictions on facility access. The use of self-report data may be subject to recall bias. Finally, there was differential time since facilities were engaged in PrIYA, PrIYA mentorship, and PRIMA, so readiness may have waned due to staff rotations or other factors outside the control of study staff.

Conclusions

This study sought to identify strengths and gaps in service availability and readiness across Kenyan health facilities that are integrating PrEP delivery into MCH services. There are overarching gaps that need to be addressed for effective scale-up of PrEP integration in MCH, particularly among dispensaries, clinics, health centers, and county-level hospitals. PrEP training for HCWs needs to be more frequently implemented in addition to supportive supervision focused on fidelity. HTS and PrEP delivery spaces must provide adequate auditory and visual privacy to reduce stigmatization and facilitate PrEP uptake. Although paper commodities were lacking, utilization of EMRs may offset this need for effective PrEP integration. However, PrEP pill stockouts in MCH needs to be addressed, potentially through electronic LMIS and daily updating of stock supplies. As investigators typically select facilities with high client volumes and adequate infrastructure for study engagement, there is a need to consider and account for resource differences when scaling up PrEP delivery strategies, particularly in facilities with limited infrastructure and support.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the ethical review committees at the University of Washington and Kenyatta National Hospital. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JK, GJ-S and AW were study PIs. JK, GJ-S, AW and JD developed the study protocol. NN, LG, FA, BO, JD, JS, GJ-S, JK and AW developed the data collection materials. JS, FA and BO coordinated data collection, conducted by ES and GO. SH conducted data analysis, supervised by AW. SH wrote the first draft of the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1206150/full#supplementary-material

SUPPLEMENTARY FIGURE S1
Timeline and descriptions of previous study engagement. Kenya, 2020–2021.

SUPPLEMENTARY FIGURE S2
Percentage of facilities that have tracer items for PrEP delivery stratified by previous study engagement. Kenya, 2020–2021.

SUPPLEMENTARY TABLE S1
Heatmap of facility tracer items. Kenya, 2020–2021.

SUPPLEMENTARY TABLE S2
Characteristics of the health facilities assessed, overall and stratified by previous study engagement. Kenya, 2020–2021.

SUPPLEMENTARY TABLE S3
Fisher's exact tests of commodities available now vs stockouts in the last month. Kenya, 2020–2021.

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Oral HIV pre-exposure prophylaxis use among pregnant and postpartum women: results from real-world implementation in Lesotho

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Introduction: Lesotho has reached epidemic control, PrEP is an important component in maintaining that and in reaching the goal of eliminating mother-to-child transmission.
Methods: We conducted a retrospective review of existing, routine PrEP health records in 26 health facilities in Lesotho. PrEP visit data were collected for pregnant and postpartum women screened for PrEP and/or enrolled in PrEP programs from 1 January 2019 through 30 June 2021 with follow-up data collected up to the date of data abstraction per site between October 2021 and May 2022. Poisson regression with robust variance was used to evaluate the association between patient characteristics and continuation of PrEP.
Results: Indications for starting PrEP were significantly associated with continuation in PrEP use. Women starting PrEP due to having a partner known to be living with HIV were the most likely to return for follow-up. In all age groups, the most common reason for starting PrEP was being in a serodiscordant relationship, though the proportion varies by age.
Conclusion: As Lesotho is now in the process of optimizing PrEP use among pregnant and postpartum women, it is critical to revise data sources to capture information that will link PrEP records and ANC/PNC records and document pregnancy/postpartum status in order to better understand PrEP use and gaps in this population.

KEYWORDS

PrEP, HIV, pregnant women, breastfeeding, postpartum, sub-Saharan Africa, prevention, medical records

1. Introduction

Pregnancy and the postpartum period represent times of increased HIV acquisition risk (1). Driven by both biological and behavioral factors (2), this risk is further elevated in high-prevalence settings, such as sub-Saharan Africa (SSA) (3–5), which accounts for 70% of all new HIV infections globally (6). Compared to chronic infection, incident HIV during pregnancy and breastfeeding is associated with more than double the odds of vertical transmission in African cohorts (7). Breastfeeding is a particularly vulnerable period, with

a study from Zimbabwe demonstrating a fourfold transmission increase in infants born to mothers with acute infection during breastfeeding (8, 9). Transmission during breastfeeding accounts for an estimated 50% of MTCT, with the proportion of transmission during breastfeeding increasing over time relative to intrauterine or intrapartum transmission (10). Overall, new infections after first antenatal care (ANC) account for a disproportionate number of infant infections (11, 12). Effective prevention strategies are urgently needed to reduce maternal and infant HIV acquisition.

Oral pre-exposure prophylaxis (PrEP) with daily tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) is an efficacious HIV prevention option for the reduction of vertical and horizontal transmission among HIV-negative pregnant and breastfeeding women in sub-Saharan Africa (SSA). Modeling estimates from South Africa indicate that widespread use of oral PrEP among pregnant and postpartum women could reduce vertical transmission by 41% and overall transmission by 2.5% (13). However, oral PrEP effectiveness and population-level prevention impact depend on the uptake and use in real-world implementation. The WHO extended guidance for the provision of PrEP to pregnant and breastfeeding women at substantial risk of HIV in 2017 (14) and there has been an expansion of oral PrEP in SSA, representing approximately one-third of PrEP prescriptions worldwide (15, 16). However, PrEP use globally, and utilization of PrEP by key groups such as pregnant and postpartum women, has failed to reach levels required to achieve the anticipated prevention impact or reduce vertical transmission (15, 16). Prevention with PrEP is user-controlled and empowers pregnant and breastfeeding women to make decisions regarding the prevention of HIV and gives them control over their HIV risks (13, 17–22). Extant research demonstrates limited uptake and continuation of PrEP among general users and pregnant and postpartum women (3, 23, 24). Research has identified key implementation considerations for PrEP success among pregnant and postpartum women including individual, social, and facility-level concerns such as the need for integration with antenatal and postnatal care (ANC/PNC), patient and provider education, stigma reduction, and person-centered health systems and guidelines supportive of screening, access, and ongoing support (15, 25–27). However, few studies in SSA have evaluated PrEP use among pregnant and postpartum women through routine health service provision. Understanding oral PrEP use may also inform the successful use of new HIV prevention technologies, such as injectable, long-acting Cabotegravir.

As high HIV prevalence countries in sub-Saharan Africa, including Lesotho, scale up the use of PrEP among pregnant and postpartum women within routine ANC/PNC, evidence regarding PrEP uptake and continuation in this population is essential to guide successful implementation. Lesotho has reached epidemic control (28); PrEP is an important component of maintaining that and getting to the goal of eliminating mother-to-child transmission. PrEP was first included in Lesotho national guidelines in April 2016 (29); however, there were no specific provisions for either the inclusion or exclusion of pregnant/poatpartum women until July 2019, when revised guidelines recommended routine screening for PrEP eligibility at ANC and PNC clinics (30). Using retrospective data abstracted from routine PrEP clients' records at the health facilities in Lesotho, we sought to characterize the PrEP cascade and use patterns among pregnant and postpartum women to inform strategies to improve oral PrEP as an HIV prevention tool for women and their children.

2. Methods

2.1. Setting and study design

To understand real-world oral PrEP implementation and outcomes, we conducted a retrospective review of existing, routine PrEP health records in 26 health facilities run by the Government of Lesotho or the Christian Health Association of Lesotho. This included 6 hospitals and 20 health centers across four districts, all of which also received support from the Elizabeth Glaser Pediatric AIDS Foundation through the United States President's Emergency Plan for AIDS Relief (PEPFAR). These health facilities included all medium-to-high PrEP patient volume sites in the four study districts and offered a range of HIV prevention, treatment, and maternal-child health (MCH) services (including ANC and PNC). Data abstraction at these facilities took place between October 2021 and May 2022.

At the time of data abstraction, PrEP was offered to clients meeting the following eligibility criteria: negative HIV test on the day of PrEP initiation; sexually active and at substantial risk of acquiring HIV infection (as determined by clinician screening or client request for PrEP); no suspicion of acute HIV infection; minimal risk of renal impairment; weight ≥35 kg, and willingness to use PrEP as prescribed. Following national guidelines, clients were asked to return 4 weeks and 8 weeks after PrEP initiation and then every 3 months thereafter for refills and assessment of adverse drug reactions, PrEP adherence, HIV risk, and HIV testing. Counseling and psychosocial support were available to clients at each visit as needed. National guidelines also recommend that PrEP refill visits for pregnant and postpartum women should coincide with ANC, PNC, or childhood immunization visits. All pregnant women in Lesotho are recommended to have at least eight antenatal visits, the first occurring as early as possible within 12 weeks of gestation (31). Postpartum care for the new mother and infants includes recommended visits within 6 h, 1, 6, 10, and 14 weeks, and 6 months post-delivery (31). Mothers living without HIV are counseled to exclusively breastfeed for the first 6 months then introduce complementary foods while continuing to breastfeed for 24 months or beyond. HIV testing is conducted every 3 months during the breastfeeding period (31).

2.2. Study participants

The study population included pregnant and postpartum individuals screened for PrEP and/or enrolled in PrEP programs

from 1 January 2019 through 30 June 2021. Our data abstraction cohort included all individuals screened for or enrolled in PrEP. Because PrEP clinic records did not document pregnancy or postpartum status directly, we identified pregnant and postpartum as those with a documented PrEP entry point through ANC or PNC service points.

2.3. Data sources and data procedures

We abstracted individual-level screening, enrolment, and follow-up visit data from all PrEP-related routine forms at study sites, including PrEP risk and eligibility screening forms; PrEP-related registers; and individual client PrEP cards. For PrEP clients who seroconverted, we reviewed antiretroviral treatment (ART) registers and ART cards. PrEP follow-up visit data were collected up to the date of data abstraction per site between October 2021 and May 2022.

2.4. Statistical analysis

Our primary study outcome, continuation on PrEP, was measured dichotomously, defined as participants having any documented PrEP follow-up visit after PrEP initiation (yes/no). Patient age, marital status, and indications for starting PrEP were recorded directly from patient records. The study team classified each facility as urban or rural depending on the geographical location of each health facility and applied the Ministry of Health classification of sites as a hospital or health center. Documented screening for PrEP was measured as a dichotomous variable based on the presence or absence of a 'PrEP Screening for Substantial Risk and Eligibility' Form linked to a patient's name or medical record number. PrEP start indications were taken from the PrEP card and grouped for analysis as pertaining to a serodiscordant relationship, multiple concurrent sexual partnerships, self-request, or other. According to the guidelines, clients who request PrEP should be initiated and provided with all information about the purpose of PrEP (30). Documentation of stopping PrEP and reasons for stopping PrEP were abstracted from the PrEP register.

We assessed the distribution of variables descriptively and used Poisson regression with robust variance to evaluate the univariate and multivariable association between patient characteristics and continuation of PrEP. Variable inclusion in our multivariable model was guided by statistical significance ($p < 0.10$ in unadjusted analyses) and applied theory of relationships between the variables based on past research (32, 33). We used multiple imputations with chained equations and 15 imputed data sets to account for missing covariate data in the multivariable model (34).

2.5. Ethical review

This study was approved by the Lesotho National Health Research Ethics Committee and Advarra Institution Review Board (IRB) in the United States of America. The protocol is limited to retrospective secondary analysis of data that is routinely documented as part of standard medical or program services. No additional patient information was collected outside of what is routinely recorded in patient records during standard medical care of patients. A waiver of consent was obtained from the IRB to abstract data from medical records. All study team members were trained in the protection of human subjects.

3. Results

A total of 4,098 participants from different service points in the health facilities were enrolled into the retrospective cohort. Among the 4,098 individuals screened for or enrolled in PrEP during our study period, we identified 389 (9%) pregnant or postpartum women from antenatal (ANC) and postnatal (PNC) service points initiated on PrEP. There was variation by site, with pregnant and postpartum women ranging from 0.3% to 17% of the total number of clients engaging in PrEP at study facilities. The proportion of clients initiated through ANC/PNC service points increased over time (**Figure 1**). ANC/PNC services were the most common entry point for younger female PrEP enrolees: 48% ($n = 188$) of female clients under age 25 screened for or enrolled in PrEP came from ANC/PNC services.

Data for pregnant and postpartum women were largely complete, with 17% missing indications for starting PrEP and 6% missing marital status. **Table 1** details the demographic characteristics of the 389 pregnant and postpartum women. Women's ages at PrEP initiation ranged from 14 to 48 years (median: 26 years). Among those with documented marital status ($n = 364$), 87% ($n = 317$) were married. The majority (76%, $n = 295$) attended ANC or PNC services at urban facilities. Nearly half (49%, $n = 160$) with a documented PrEP start indication were initiated due to being in a discordant relationship [most commonly a partner living with HIV who was not on antiretroviral treatment (ART) or was newly starting ART]. The second most common reason listed for initiating PrEP was the client reporting that either she—or more commonly her partner—had multiple concurrent partners ($N = 82$, 25%).

Figure 2 shows the distribution of PrEP start indications by age among those with documented start indications. In all age groups, the most common reason for starting PrEP was being in a serodiscordant relationship, though the proportion varies by age. Serodiscordant relationships account for 63% of PrEP initiations among women aged 35 and older compared to 39% of initiations among women aged 14–20 years.

Data on PrEP screening were limited; only 245 (63%) of women initiating PrEP had documentation of screening. There were no records of pregnant or postpartum women being screened and not initiating PrEP. Having documented screening (i.e., a Screening Form linked to your name or medical record number) was more common among women in urban facilities compared to rural facilities (69% vs. 45%, $p < 0.001$) and in health centers compared to hospitals (71% vs. 40%, $p < 0.001$). Five sites had no completed screening forms for pregnant or

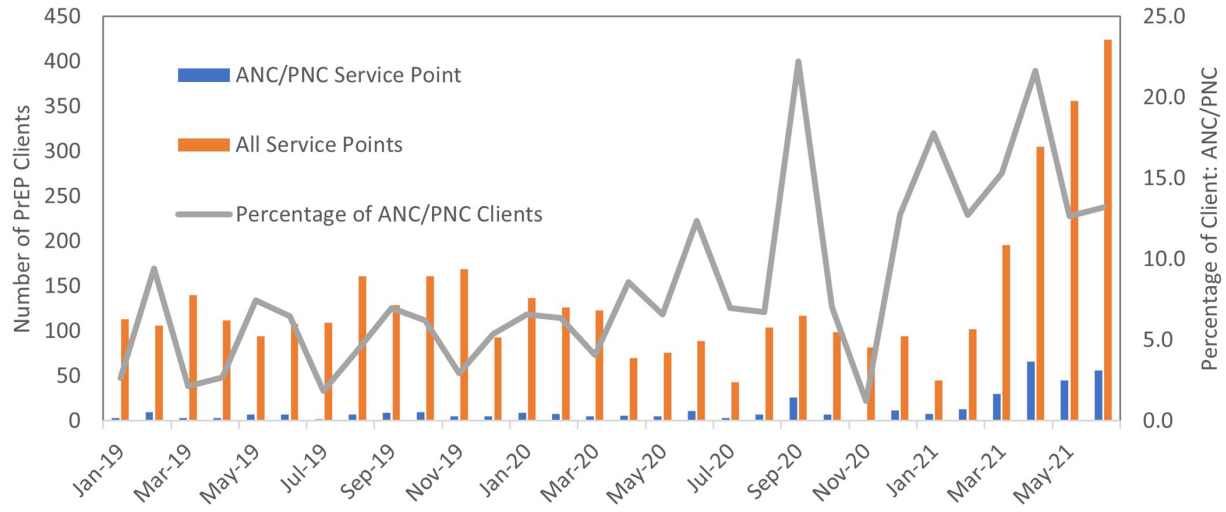

FIGURE 1
Distribution of PrEP clients by month of PrEP initiation.

postpartum women while three sites had screening forms available for all pregnant/postpartum women. Ninety-one percent of women with a screening form reported at least one behavioral risk factor for HIV acquisition: 17% ($n = 38$) reported unprotected sex in the last 3 days with someone living with HIV who was not on treatment and 39% ($n = 87$) had condom-less sex or other high-risk HIV exposure in the past 2–6 weeks.

Of the 389 pregnant and postpartum women initiated on PrEP, 40% ($n = 156$) had no recorded follow-up visits, 76 (20%) had only one recorded follow-up visit post-PrEP initiation, and the remaining 40% ($n = 157$) had at least two documented follow-up visits (the maximum number of documented follow-up visits was 14). Table 2 presents the univariate and multivariable analysis findings related to factors associated with the continuation of PrEP (i.e., having any documented follow-up visit after PrEP initiation). Having any recorded follow-up after PrEP initiation was significantly associated with initiating PrEP at an urban facility compared to a rural facility [adjusted prevalence ratio (aPR) = 1.34, 95% CI = (1.07; 1.67)]. Women who started PrEP due to serodiscordant relationships [aPR = 2.13; 95% CI = (1.38; 3.29)] or who started due to multiple concurrent partnerships [aPR = 1.78; 95% CI = (1.14; 2.77)] were more likely to continue using PrEP than women who self-requested PrEP ($p \leq 0.01$). Neither age nor marital status were significantly associated with continuation.

Only six women had documentation of stopping PrEP: four due to patient decision, and two due to HIV seroconversion. The two participants who had documented HIV seroconversion; were both initiated on ART.

4. Discussion

We assessed screening, initiation, and continuation of oral PrEP among pregnant and postpartum women accessing care through public health facilities in Lesotho to understand real-world PrEP outcomes and inform interventions to improve HIV prevention. Indications for starting PrEP were significantly associated with continuation in our study. Women starting PrEP due to having a partner known to be living with HIV were the most likely to return for any follow-up. While these women may be more likely to have continued elevated HIV risk over time, it is also possible that having a partner living with HIV may have reduced stigma or fears around taking PrEP in the home. Rural facilities had lower rates of PrEP continuation, underscoring the need for differentiated models of service delivery (including community-based distribution and multi-month PrEP dispensing) to ensure that difficulties in accessing sites in rural areas are not prohibitive to PrEP continuation.

Our findings underscore the need to promote and expand the uptake of PrEP among pregnant and postpartum women in Lesotho. Despite utilizing healthcare services at higher rates than the general adult population, pregnant and postpartum women represented a minority (9.5%) of PrEP initiations during this time period (though there was evidence of an increased trend over time in both the number of pregnant and postpartum women initiated and the proportion of PrEP initiations coming from ANC/PNC services). ANC/PNC services remain a critical means of reaching younger women, who are at increased risk of HIV. With guidelines revised in 2022 to include universal screening of pregnant and postpartum women living without HIV for PrEP eligibility, it will be important to evaluate whether there was a subsequent continued increase not just in the number of pregnant and postpartum women screened and enrolled in PrEP but also in the proportion of pregnant and postpartum women within the total cohort of PrEP clients. This evaluation will only be possible with improved routine documentation of screening and eligibility for PrEP within health facilities, which is a significant limitation of our study. This documentation is important not only to understand whether PrEP

TABLE 1 Demographic characteristics[a].

Characteristics	Total $N = 389$
Age (years)	
Median (IQR)	26 (21–31)
Range	14–48
Age categories	
14–20	114 (29.3)
21–34	222 (57.1)
35+	53 (13.6)
Marital Status	
Single/Divorced/Separated/Widowed	47 (12.9)
Married	317 (87.1)
Undocumented	25
Region	
Urban	295 (75.8)
Rural	94 (24.2)
Type of facility	
Hospitals	104 (26.7)
Health centers	285 (73.3)
Indications for starting PrEP (ungrouped)	
Participant self-requested PrEP	41 (12.7)
Serodiscordant relationship (not otherwise specified)	35 (10.8)
Serodiscordant relationship: partner not on ART or on ART < 12 months	76 (23.4)
Serodiscordant relationship: partner known to have elevated viral load (>1,000 copies/ml) and/or poor adherence	48 (14.8)
Serodiscordant relationship: partner not on ART or on ART < 12 months, AND partner known to have elevated viral load and/or poor adherence	1 (0.3)
Has multiple concurrent sexual partners	6 (1.9)
Client believes her partner has multiple concurrent sexual partners	76 (23.4)
Unknown partner HIV status	23 (7.1)
Patient being in antenatal or postnatal care only documented indication for PrEP start	9 (2.8)
Frequent exposure	3 (0.9)
Individual at high risk of being forced to have sex	6 (1.9)
Undocumented	65
Indications for starting PrEP (grouped)	
Self-requested PrEP	41 (12.7)
Serodiscordant relationship	160 (49.3)
Multiple concurrent partners	82 (25.3)
Other	41 (12.7)
Undocumented	65

[a]Percentages are among participants with data for that variable (Documented).

screening and initiation are being conducted in accordance with the guidelines but also to understand the true PrEP refusal rate.

A number of strategies have been documented to promote PrEP uptake among cisgender women (20, 22, 35). Differentiated models of PrEP delivery including client-centered approaches, offering multiple options for PrEP (including longer-acting drugs), provision of PrEP information through peer educators, and tailored PrEP education and messaging have been identified as facilitators to PrEP uptake and adherence (20, 22, 26, 35, 36). However, gaps still exist in the provision of PrEP to pregnant and postpartum women, including scale-up and integration of PrEP into routine antenatal and postnatal clinics (4, 25, 26).

Our findings are consistent with a number of other studies showing low levels of continuation of PrEP, including among pregnant and postpartum women (3, 24, 27, 37). Other studies with women living with HIV have also found sub-optimal adherence to ART refills during the post-partum period (38–41). However, these data are difficult to interpret without reliable data on the risk for HIV acquisition following PrEP initiation. For example, we cannot assess how many women may be discontinuing PrEP due to reduced risk (including women seeking event-driven PrEP around holidays when partners living with HIV return from remote work, which is common in Lesotho, or cultural practices around sexual activity during pregnancy or postpartum). Other women may have transferred their care to another facility; as there was no active tracking or outreach to women who did not return for PrEP refills, this would not have been captured. Understanding and documenting fluctuations in HIV risk, as well as a better understanding of the motivation to adhere to PrEP, will be even more critical as countries like Lesotho introduce long-acting cabotegravir (CAB-LA) as an option for HIV prevention. The high proportion of women in our study who did not return for any follow-up PrEP visits or refills (coupled with the low documented rate of PrEP refusal) may indicate that some women accepted PrEP at the recommendation of their providers despite low motivation to begin or continue taking PrEP. While CAB-LA offers a number of benefits compared to oral PrEP, low motivation to continue on PrEP would be very concerning given the increased risk of integrase inhibitor resistance associated with HIV acquisition while recently or currently on cabotegravir-PrEP. Motivation to continue PrEP among postpartum women may have also changed over time as concerns about mother-to-child transmission decreased after delivery and breastfeeding cessation.

There are other individual, social, and facility-related factors that could influence PrEP continuation that are not captured in available routine data. Pill fatigue, low awareness of optimal PrEP dosing, misalignment of HIV risk perception versus actual risk, concerns about side effects, forgetting to take PrEP daily, stigma associated with using antiretrovirals for prevention, gender norms, financial constraints, and accessibility of health facilities are some of the barriers that have been shown to undermine full utilization of PrEP among pregnant and postpartum women (19, 20, 22, 24, 35). Further studies with patients and healthcare workers are necessary to address this gap and consider which, if any, data points should be added to routine PrEP data collection.

Utilization of real-world program data is critical to understand real-world implementation. Our study identified key gaps in routine data that, if improved, may support improved service provision. While appropriate screening is considered critical to improving oral PrEP prevention impact (i.e., identifying women who can benefit and enrolling them), screening data were unavailable for 37% of our cohort. While lack of documented screening was not a barrier to initiation among these 37%, consistent documentation of screening is critical to ensuring appropriate PrEP use. Additionally, there were no records of women being screened but identified to be ineligible or choosing not to initiate. Improved documentation of all individuals

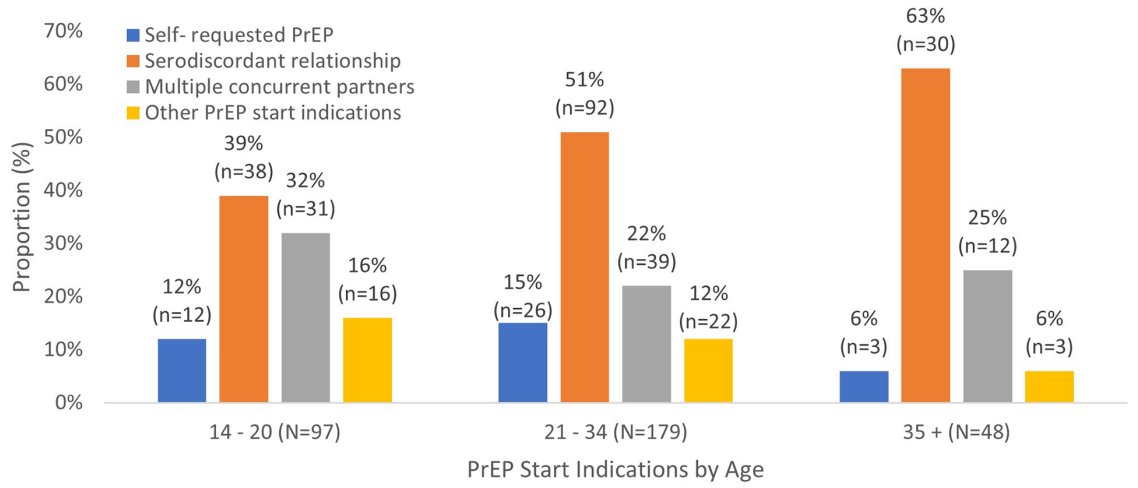

FIGURE 2
Distribution of PrEP start indications by Age.

TABLE 2 Factors associated with documentation of any follow-up visit after PrEP initiation.

			Analysis based on Multiple Imputation			
Characteristics	*n* (%)	Total	Unadjusted		Adjusted	
Continuation: Any follow-up after initiation	233 (59.9)	389	PR (95% CI)	*p*-value	PR (95% CI)	*p*-value
Age groups						
Less 21	63 (55.3)	114	1	0.379	1	0.942
21–34	135 (60.8)	222	1.10 (0.90; 1.34)		1.01 (0.83; 1.23)	
35+	35 (66.0)	53	1.19 (0.93; 1.54)		1.04 (0.81; 1.35)	
Marital Status						
Single/Divorced/Separated/Widowed	25 (53.2)	47	1	0.354	1	0.971
Married	193 (60.9)	317	1.14 (0.86; 1.52)		1.01 (0.75; 1.35)	
Region						
Rural	46 (48.9)	94	1	0.024	1	0.011
Urban	187 (63.4)	295	1.30 (1.04; 1.62)		1.34 (1.07; 1.67)	
Type of facility						
Hospitals	68 (65.4)	104	1	0.165		
Health Centers	165 (57.9)	285	0.89 (0.75; 1.05)			
Indications for starting PrEP						
Self-requested PrEP	14 (34.2)	41	1	0.001	1	0.002
Serodiscordant/discordant couples	112 (70.0)	160	2.04 (1.32; 3.14)		2.13 (1.38; 3.29)	
Multiple concurrent partners	46 (56.1)	82	1.64 (1.05; 2.57)		1.78 (1.14; 2.77)	
Other	20 (48.8)	41	1.40 (0.83; 2.37)		1.55 (0.91; 2.62)	

screened is necessary to understand: 1. who is being screened, 2. what proportion of pregnant and postpartum people are ineligible, and 3. what proportion of those eligible refuse PrEP. Programmatic assessment identified limited availability of and inconsistent knowledge about screening forms as a barrier to utilization. Support for improved documentation is recommended to ensure optimized PrEP service delivery. Further, while adherence was measured in routine records, inconsistent recording of adherence, mixing days adherence/7 days, and % of pills taken made assessment through routine record review infeasible. As understanding adherence within routine health settings is critical to assessing prevention-effective use, improving routine data collection will be important.

As with any study relying on routine data (an important source for implementation science and program improvement efforts), our study is limited by incomplete data. In addition, routine PrEP-related documentation did not directly capture whether a woman was currently pregnant or postpartum; as a result, we may have excluded a number of pregnant and postpartum women from analysis if they were screened or enrolled in PrEP outside of the ANC/PNC clinics.

5. Conclusion

As Lesotho is now in the process of optimizing PrEP use among pregnant and postpartum women, it is critical to revise data sources to capture information that will link PrEP records and ANC/PNC records and document pregnancy/postpartum status in order to better understand PrEP use and gaps in this population.

Data availability statement

The datasets presented in this article are not readily available as they are based on abstraction from routine health records owned by the Lesotho Ministry of Health, who must approve any additional use of the data. To request data access, contact corresponding author with details on the intended use of the data. Requests to access the datasets should be directed to lmasenyetse@pedaids.org.

Ethics statement

The study involving human participants was reviewed and approved by 1. Lesotho National Health Research Ethics Committee 2. Advarra IRB in the United States of America. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

VJT, FS, MM, and LKB supported conceptualization; FS, BS, MM, VJT, MJM, and LJM supported data collection; LJM, LG, LKB, and BS conducted formal analysis; all co-authors contributed to data interpretation; VJT and LG were study investigators; VJT and LKB, designed the methodology; MM and FS conducted project administration; LJM wrote the original manuscript draft, LG and LKB contributed to manuscript writing; All co-authors reviewed and edited the final draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Male partners' support and influence on pregnant women's oral PrEP use and adherence in Malawi

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Introduction: Daily oral pre-exposure prophylaxis (PrEP) is a safe and effective HIV prevention method for pregnant and postpartum women, but adherence barriers exist. Understanding the role of male partners in supporting PrEP use may inform strategies to support PrEP adherence among pregnant and breastfeeding women.

Methods: To understand male partners' involvement in women's use of PrEP, we conducted in-depth interviews with pregnant women in Lilongwe, Malawi who had recently decided to use PrEP ($n = 30$) and their male partners ($n = 20$) in the context of a PrEP adherence trial. Women were purposively recruited to ensure variation in their partners' HIV status. Interviews were conducted in Chichewa using a semistructured guide. We followed a thematic approach to analyze the interview data.

Results: Most male partners were receptive to women using PrEP during pregnancy because it eased their fears of the woman and baby acquiring HIV. Men often played a key role in women's PrEP adherence by providing daily reminders and encouragement to adhere to their medication. The majority of women appreciated this support from the men as it lessened the burden of remembering to take their medications daily on their own and aided their adherence. However, several women who lacked male partner support spoke of wanting their partners to be more involved. Many men living with HIV found the mutual support beneficial for their antiretroviral therapy adherence, while men without HIV or with status unknown appreciated knowing that the family was protected. While most men were open to women continuing PrEP beyond the current study, some would only support it if women were still at risk for acquiring HIV.

Conclusion: In this study, male partners were strongly motivated to support the PrEP adherence of their female partners as a way of ensuring that the pregnant women and unborn babies were protected against HIV. Promoting

disclosure and tangible support that arises organically among men may be helpful, but programs to enhance this support and identify ways to support women who do not receive support from their partners or do not wish to disclose their PrEP use to partners may be needed.

KEYWORDS

HIV, PrEP, pregnant and breastfeeding women, Malawi, male partners, social support

Introduction

Women in Eastern and Southern Africa face substantially elevated HIV risk during pregnancy and the postpartum period due to increased biological and behavioral risk factors (1–5). Acute maternal HIV infections are responsible for an estimated one-third to one-half of mother-to-child transmission (MTCT) (6, 7). Daily oral pre-exposure prophylaxis (PrEP) is a safe and effective method for preventing HIV acquisition when taken with high adherence (6–8).

To deliver on the promise of PrEP for MTCT, the World Health Organization guidelines recommend that oral PrEP be offered in standard Prevention of mother to child transmission practice (9). However, while many pregnant HIV-negative women are willing to initiate oral PrEP, early discontinuation and low adherence are common, especially in young pregnant women, and little is known about the potential facilitators of oral PrEP persistence in this population (10–13). Based on the broader medical literature, one potential factor—may be male partner support. Studies have suggested that direct engagement of male partners might play a role in women's adherence to HIV prevention technologies (14, 15). Women's disclosure of their HIV prevention products to their male partners and positive reactions from male partners have been reported to increase women's product adherence and facilitate partner adherence support (16, 17). In one clinical trial, women who had disclosed to social contacts (including male partners) had almost five times the odds of continuing oral PrEP at trial exit than women who had not done so (18).

Although studies have examined the use of oral PrEP during pregnancy from women's perspective, there is a gap in understanding the exact role male partners play in such decision-making from a dyadic perspective. A few studies have reported male partner support to be beneficial to women's PrEP use during pregnancy (10, 19); however, they did not explicitly describe how their support facilitated adherence or try to capture men's perspectives on how they provided support. Qualitative studies and the flexibility they provide are well suited to uncovering the types of support male partners provide and which types of support women find most helpful. Understanding the impact this support from male partners has on their adherence can inform strategies to help pregnant and breastfeeding women use PrEP at effective levels to help facilitate the development of better partner support programs. In this study, we used in-depth interviews to understand, from the perspective of both women and men, how male partners were involved in supporting women's oral PrEP use during pregnancy and postpartum and the impact this support had on their PrEP adherence. We further looked to understand the bidirectional impact of women's PrEP use on antiretroviral therapy (ART) use among male partners living with HIV.

Methods

Study context

The data presented here were collected as part of the Tonse Pamodzi 2 (TP2) pilot trial (20). The PrEP component of this study enrolled pregnant women, age 18 years or older, who were at risk of HIV acquisition and interested in initiating daily oral PrEP in Lilongwe, Malawi. Pregnant women living without HIV were eligible to participate if they met any of the following HIV risk indications for PrEP: having a known positive partner or an unknown partner HIV status, having multiple partners, having Sexually transmitted infections (STIs) diagnosis, using postexposure prophylaxis, or having an unspecified HIV risk concern; for full eligibility criteria, see (20). All women were counseled about their HIV risk and how PrEP could reduce it. Participants received basic HIV prevention education regarding the functions of daily oral PrEP, the importance of adherence, side effects, and safety. Women were prescribed PrEP at the enrollment visit and were given further details on PrEP dosage and efficacy, duration of use, and adherence strategies. Women were randomized 1:1 to either the standard support for PrEP or a combination adherence strategy that included Integrated Next Step Counseling and optional adherence supporter training. The intervention development process has been described in detail elsewhere (21).

Recruitment and data collection

We recruited a subsample of women ($n = 30$) to participate in individual in-depth interviews (IDIs) to explore their perspectives of men's involvement in their PrEP use experience. In addition, male partners of the women ($n = 20$) were recruited to investigate their involvement in women's PrEP use. We purposively recruited women from the TP2 trial for this substudy to ensure variation in their partners' HIV status. Male partner HIV status was reported by women during the baseline survey and was confirmed by the men during the IDI. Male partners ($n = 14$) were recruited through invitation by women participating in the substudy. When that recruitment approach was exhausted,

additional male partners ($n = 6$) were recruited via invitation by other women participating in the parent TP2 PrEP trial. All male partners were aware of the women's use of PrEP.

Women completed the IDI an average of 102 days after enrollment (range: 59–239 days), and interviews lasted approximately 25–40 min. All IDIs were conducted in a private room at the study site in Chichewa by a qualitative research officer fluent in Chichewa and English using a semistructured interview guide. A male qualitative research officer conducted IDIs with male partners who were uncomfortable being interviewed by a female officer. Both men and women interviewed were asked about partner involvement in women's PrEP use and adherence support that men provided their partners. In IDIs with the women, we also sought to understand the impact of partner support on their adherence. Male partners were also questioned about their feeling and attitudes toward the women's present and future PrEP use and, for partners living with HIV, the impact of the women's PrEP use on their ART use. All IDIs were audio-recorded, transcribed, and translated into English.

Analysis

A thematic approach was used to analyze the IDIs. The approach consisted of (1) reading transcripts in full and noting emerging themes; (2) creating a codebook including structural codes (corresponding to interview topics) and interpretive codes (corresponding to emerging ideas); (3) coding with 20% of transcripts double-coded by independent coders who reconciled discrepancies prior to further coding; (4) summarizing participant responses pertaining to each topic/code in matrices to facilitate summaries by topic and comparisons across participants (22); and (5) making dyadic comparisons (15 dyads and $n = 30$ total participants) of women's and male partner's narratives through combined matrices summarizing the different themes that emerged from the women and men, noting the differences in the narratives given by the women and male partners, and observing the variation within each theme by the HIV status of the male partner. Separate codebooks were used for men's and women's interviews with similar codes for similar interview questions and separate codes for interview questions unique to each participant group (e.g., questions for partners regarding the provision of adherence support). Coding was completed using the NVivo version 12 software tool (23).

Ethical considerations

Study procedures were approved by the Malawi National Health Science Research Committee and the University of North Carolina at Chapel Hill Institutional Review Board. The TP2 pilot trial was registered on www.clinicaltrials.gov (NCT04330989). All participants provided written informed consent prior to study procedures. A literate impartial witness was present during the consent process for illiterate participants.

Results

Sample description

A total of 50 participants (30 women and 20 men) completed IDIs (Table 1). The median age of women interviewed was 25 years. Of the women interviewed, six had a partner living with HIV, 14 had a partner without HIV, and 10 were unaware of their partner's status. The majority of the women ($n = 27$) were identified as PrEP candidates because of an STI diagnosis, while a good portion also had a partner with an unknown HIV status ($n = 8$) or an HIV-positive partner ($n = 7$). A few women ($n = 4$) reported having more than one sexual partner. Moreover, at the time of the interview, 13 women were pregnant and 17 were in the postpartum period. Among the male partners who agreed to have an IDI, six were living with HIV, 10 were without HIV, and four did not know their HIV status. Finally, of the 50 individuals interviewed, 30 of them were part of dyads ($n = 15$ dyadic couples).

Male partner feelings toward women's PrEP use

Overall, male partners reported being happy that women were using PrEP because it reduced their fears of women contracting HIV. They welcomed women's PrEP use, although some misconceptions about the benefits of PrEP were observed. The men rarely reported negative feelings regarding the time the women were using PrEP; however, some did express initial concerns that PrEP use could affect the unborn fetus. Only one partner mentioned concerns regarding his partner experiencing weakness in the morning; however, he was unsure whether it was

TABLE 1 Demographic description of participants ($N = 50$).

	N (%) or median (range)
Pregnant women ($n = 30$)	
Age	25 (18–40)
Reported partner's HIV status	
HIV-positive	6 (20)
HIV-negative	14 (46.7)
Unknown	10 (33.3)
PrEP eligibility reasons (past 12 months, not mutually exclusive)	
STI diagnosis	27 (90)
Partner of unknown HIV status	8 (26.7)
HIV-positive partner	7 (23.3)
Multiple sexual partners	4 (13.3)
Pregnancy status at the time of the interview	
Pregnant	13 (43.3)
Postpartum	17 (56.7)
Male partners ($n = 20$)	
HIV status	
HIV-positive	6 (30)
HIV-negative	10 (50)
Unknown	4 (20)
Dyadic couples	30 (60)

caused by PrEP or part of the pregnancy symptoms. These initial negative feelings or concerns were usually resolved as the women continued with PrEP use or through study staff support.

Reduced fears

Most men expressed happiness that women were using PrEP as their use alleviated some fears of the woman and child acquiring HIV. Many men feared that their partners were at risk for contracting HIV because of the STI diagnosis; thus, some saw women's use of PrEP as a way of protecting the health of the entire family.

> *"I liked it [PrEP] because it helps my wife's immunity, she is the one that is going to be bearing children for me so this will affect my unborn babies…When I understood that the PrEP is helping so that the mother should not be infected that meant that my baby would also not get infected that is why I said continue taking the medication." [Male partner, HIV-negative]*

This was especially salient among men living with HIV that were now comfortable having sex with their partners as they were no longer concerned about potential HIV transmission, as illustrated by one man:

> *"What I am loving is that when it's time for us to be intimate there are no problems because she would have already taken the medication so there are no fears," [Male partner, HIV-positive].*

Misconceptions of PrEP benefits

Among the men, there were misconceptions regarding the actual function of PrEP; however, in most cases, these misconceptions positively influenced men's feelings about women's PrEP use. Some men thought women's PrEP use had improved women's health by strengthening their general immunity as the women were no longer falling sick frequently or perceived the women's physical appearance to have improved while on PrEP. Two male partners illustrate this point below by contributing their partner's improved overall health to their PrEP use:

> *"…at the time that she had not started the PrEP she was one that was often sick but now I see that everything has changed meaning that its good…I never expected that there would be medication like this that would make the body better. She used to be complaining every day. [Male Partner, HIV-positive]*

> *"The way she takes the medication and her body looks good… She looks good and it shows that she is strong…from the time that she started taking the medication…Ok let me put it like this, before she used to have a malnourished body…Now her body is healthy…Meaning that what [PrEP] she is taking is helping add energy to her body." [Male Partner, HIV-unknown]*

A few of the men also thought PrEP simultaneously treated the STIs that some women had been found to have at the initiation of the study or that it would prevent future STIs. This misconception that PrEP was preventing more than just HIV or improved overall health was also shared among the women, who, like the men, thought they were now protected against other STIs. In the quote below, a woman explains her belief that PrEP use would treat her STI diagnosis and further protect her from future recurrences of STIs:

> *"From that time…the PrEP was supposed to help me from STIs that I was found with, so it helped to reduce the infection and to protect me." [Woman, Partner HIV-negative]*

While most men welcomed women's use of PrEP, it was challenging for one man to accept it as he did not understand the point of taking preventive medicine when not sick. To him, medication was reserved for when an individual was sick and wanted to improve their health condition. He did not understand the concept of "treating" something you did not have, as the effect of this medicine is not visible since the individual is already healthy:

> *"What I can say is that it is different from a person that is sick. It is like when a person is sick there are certain goals that you want to achieve which are for the person to recover. But for PrEP it's like the person just takes daily and you don't really see the goal that you want to achieve." [Male partner, HIV-negative]*

Male partner's involvement in women PrEP adherence

Male partners provided adherence support to the women in the form of reminders, motivation, strategy development, and instrumental support. This support was confirmed by most women who agreed that their male partners played a role in providing adherence support; however, some women spoke of their male partners not being involved in reminding them to take their medication. The ways in which partners supported women's PrEP use are discussed below.

Adherence support

Most men spoke of playing a key role in supporting women's PrEP use by providing daily reminders. On rare occasions, as characterized by the male partners, when women were struggling with adhering to their medication, some men went beyond just giving reminders and became motivators by encouraging the women to stick to the daily regimen, as illustrated by the quote below:

> *"So, you know maybe she is not in a good mood but you are still supposed to force her to take the medication, those are the major challenges but then I am thankful that the medication has been taken and she has completed them." [Male partner, HIV-negative].*

Some men also helped women come up with adherence strategies which included the men setting alarms to remind the women:

> *"I put an alarm on my phone so when that goes off I know that it's now time… It also happens that maybe I am still in town I just call her to remind her because it's not always that I get here at a good time sometimes I knock off late." [Male partner, HIV-negative]*

Other men provided instrumental support to their wives to take PrEP daily, such as bringing the pills and water to the women at their dosing time:

> *"My wife here is a cup of water and medicine for you to take. Don't bother moving out of where you are sitting. Just take the medicine." [Male Partner, HIV status unknown].*

In a unique case, one man spoke about reminding his wife to take her medication and even coming up with different signals (phrases) for the woman to give each other when in public or around other people to indicate when it was time for the woman to take her PrEP. He explained in the quote below how he reminds her and the different phrases he uses to signal it is time for her medication:

> *"I tell her to come and then remind her that it's time to take her medication, if she is in a group, I remind her. When we are in public there are signals that we give each other….I even tell her to go get me a cup of water or prepare my bath water and she knows that it's time to take the medication." [Male partner, HIV-positive]*

Men not only played the role of supporter or motivator when they were physically with the women (e.g., at home) but even when they were away from home either because of traveling or working late. A few still called the women to ensure they had taken their PrEP.

> *"I considered the time that she set to be taking the medicine and the time I knock off from work, sometimes I arrive home late so it because hard to be waking her up to take the medicine so I just call her to take the medicine." [Male partner, HIV-negative]*

While others, especially those who traveled often for work, reinforced the importance of adhering to the medication before leaving home. In the quote below, one woman talks about how her husband often travels part of the month for work and that while she was using PrEP, he always encouraged her to adhere to her medication while he was gone:

> *"He tells me to not forget to take the medication because his business involves him being away for around 2 weeks at the lake before coming home. He encourages me when he is going that I should not forget to take the medication when he is gone." [Woman, Partner HIV-positive]*

Reminders were not only for PrEP adherence but also included clinic reminders when it was time for the women's next visit. In a way, this ensured women received the essential PrEP refills needed to continue their adherence and protection. As previously stated, some men viewed women's decision to use PrEP as a family affair and not solely the PrEP user themselves, which meant everyone was involved in ensuring high adherence:

> *"We did this because we agreed in the home as a family that is why I chose to play a part by reminding her so that when her scheduled day [clinic appointment visit] is there she should be coming [to the clinic]." [Male partner, HIV-negative]*

The information above illustrates the key role that men played in assisting women with PrEP adherence. This narrative was reinforced by the women who agreed that the support from the men positively assisted with their PrEP use.

> *"…My husband tells me to be taking the medication… He says that I should be taking the medication so that it should be protecting me from the disease." [Woman, Partner HIV-positive].*

> *"… it is the person who reminds me to take my medicine, that's my husband, he is the one who encourages me to take my medicine with good adherence and on time." [Woman, Partner HIV-negative]*

Lack of support

Although most women received adherence support from the men, it was not the case for all. A few women spoke of not receiving any support from the men; however, these women motivated themselves to adhere to the medication regardless of the lack of support from the men because they wanted to protect themselves and their unborn children.

> *"There is nothing that they [my partner] do I just remember by myself." [woman, Partner HIV-positive]*

Indeed, in one dyadic relationship, one man spoke of being involved in the initial decision-making for the woman to use PrEP; however, he was not participating in her adherence because he felt she was handling the situation well and, therefore, did not feel compelled to provide encouragement.

> *"She adheres and even if I get home and she has finished taking the medication you see her checking her phone to check the time, she was apparently told the time that she should be taking the medication…I don't help her she just knows that it is now time for me to take PrEP." [Male partner, HIV-negative]*

Although the man in this case felt he was supportive of his partner's use of PrEP, the woman felt she was not supported because the support was not explicit, and she would have preferred encouragement and reminders.

> *"[I would like him] to be checking if I have taken the medication and if not be encouraging me to be taking." [Woman, Partner HIV-negative].*

In another dyadic relationship, one man living with HIV spoke of encouraging his partner by setting an alarm and often giving her transportation means for clinic visits; however, his account appeared to be contradicted by his partner's account, who said she was her own support. Other women who spoke of not receiving support from male partners were in non-dyadic relationships, and thus their partners' perspectives were not included as they did not participate in the study. Men did not express concerns about women struggling with PrEP adherence but rather felt it was important to provide moral support to show the women they supported their PrEP use. All women in the study, except for two women, disclosed their PrEP use to their male partners. For the two women who did not disclose, reasons for non-disclosure included the following: (1) male partner passing away right before she joined the study; and (2) no longer being in a relationship with the male partner.

Impact of male partner support on women's PrEP adherence

While the majority of women interviewed could not think of the ways in which men's support (e.g., reminders and encouragement) directly contributed to their adherence, a few of them spoke of the impact of the men's support on their PrEP use. These women felt the support provided by the men influenced their overall adherence as it ensured they took the medication on time and provided them a sense of comfort knowing that they were not on the PrEP journey alone.

> *"At times when I forget, such as if I just wake up and start working, you know one is just human and can forget, he reminds me to take my medication before I start working… I feel so good!…Yes, I feel that we are together in this journey." [Woman, Partner HIV negative].*

Some men provided additional support by addressing women's concerns about using PrEP, especially as it pertains to potential future adverse effects on the unborn child. In one case, one man spoke of encouraging the woman not to listen to rumors from friends that PrEP caused her miscarriage and was "satanic." He reached out to the study staff, who counseled the woman once he realized she was still discouraged and planned on dropping out of the study. The woman affirmed that her partner's involvement ensured that she continued with study participation and product use because had he not called the doctor, she would have discontinued PrEP. In the quote below, she explains the role her partner played in ensuring she continued with study participation:

> *"… So I told him [doctor] everything that happened and he encouraged me there. He [doctor] came because my husband called him on the phone telling him 'My wife has called me saying she is dropping out of the study for such and such reasons. So, I want to come there so you can explain to her because I have encouraged her but she doesn't look convinced.' That's when they called me to come here and the doctor talked to me and encouraged me so I understood." [Woman, Partner HIV-negative]*

Women were generally satisfied with the support they received from their partners, although some wanted men to be more involved in their PrEP journey, including escorting them to clinic visits. There were no discrepancies in the direction of women citing support and the men saying they did not really provide any support.

Impact of women's PrEP use on men's ART

The male partners who were living with HIV ($n = 6$) spoke of the domino effect of the women's PrEP use on their ART adherence as they were able to remind each other when it was time to take their medication. Most of these men gave the impression that women's use of PrEP improved their ART adherence through encouragement and mutual support. The quote below showcases a collaborative effort between the male partner and the woman to ensure they both take their respective medications at the appropriate times, highlighting the communication and support within their relationship regarding HIV prevention and treatment.

> *"I just tell her to take [her PrEP], or I just take other times [sometimes he just gives the woman her PrEP when he gets his own ART] I just tell her that it's time for us to taking the medication," [Male partner, HIV-positive].*

The woman affirmed this man's narrative and added:

> *"On the issue of medication, we did not discuss anything because it is him who encourages me when it is time to take my medication and he takes his too," [Woman, Partner HIV-positive].*

The concept of the women's PrEP use being a family affair also emerged when some men discussed how it impacted their ART adherence. One man spoke of his children getting involved with their PrEP and ART adherence.

> *"She also reminds me that you should be taking the medication as we have both been told to be adhering to the medication. We have now reached the point of getting used to the extent that we even send the children to get the medication for us," [Male Partner, HIV-positive].*

Men spoke of adhering to their medication because they understood it would improve their quality of life, prevent them from future health issues, and, most importantly, decrease the

likelihood of women and future children acquiring HIV. There was no indication of decreased motivation among the men on the basis of women's PrEP use as they understood that adhering to their ART the same way the women were adhering to their PrEP would ensure continued protection of the woman and baby and further recognized that PrEP and ART were two distinct medications.

> *"I am encouraged and she also frequently reminds me…You just feel that if you skip the medication, you can develop a problem in your body…That is why I try to be taking the medication daily." [Male Partner, HIV-positive]*

> *"Yes, I adhere [to my ART]… Because the medicine is different the ARTs and PrEP are different so I should not take advantage of that so I stop taking the medication, no… Its better I be taking the ARTs and she also be taking her medication." [Male Partner, HIV-positive]*

Men's thoughts on women's future PrEP use

The desire for women to stay protected even after the conclusion of their participation in the TP2 trial by continuing their PrEP use was supported by a majority of men, especially since there were no observed negative side effects on the women during use. Some men felt that women's discontinuation of PrEP use upon study conclusion would lead to a worsening of health issues (e.g., immunity, STIs). Men living with HIV, in particular, worried that women's discontinuation of PrEP could potentially lead to the men transmitting HIV to the women and thus believed, as illustrated in the quote below, that it was vital for women to continue using PrEP, while the men continued with ART. Furthermore, these men worried that with PrEP discontinuation, women would revert to their previous health status (e.g., weak immunity, stomach pains) before they initiated PrEP:

> *"Because it's possible that she could stop taking PrEP while am continuing to take the ARTs. I feel that it's important that she continues because it's possible she could stop which could lead to problems in the future like she used to complain of…The issues that she used to complain of like sometimes she would feel pain in the stomach, other times maybe just eat a little I feel that if she stops these issues could reoccur." [Male Partner, HIV-positive]*

Similarly, men without HIV or whose HIV status was unknown felt that women's continuation of PrEP beyond the study would safeguard the family as HIV could be acquired in various ways.

> *"I would encourage her because we can face different situations in life, so in order for us to protect each other she can still be taking the medication… I can say that people contract HIV in many ways so I would encourage her to be taking PrEP as a way of protecting her." [Male Partner, HIV-negative]*

Only a few men felt they would only agree to women's use if they or the woman felt it was appropriate and that the women were at risk for acquiring HIV (e.g., future STI diagnosis). This is not to say these men were not currently supporting the women with PrEP use; however, it came across as if they felt that since the women had already been treated for STIs, they would not necessarily need to continue PrEP due to low susceptibility to HIV. One male partner illustrates this opinion in the quote below, saying that he would not allow his partner to continue using PrEP because she would have finished her STI treatment and was no longer at high susceptibility for HIV:

> *"For her she cannot continue since I thought after she has taken all her medicine as per prescription then she doesn't have to keep on taking them." [Male Partner, HIV-negative].*

This further illustrates a misunderstanding that some men had in that they believed the treatment of STIs implied women were no longer at risk for HIV. Moreover, only one man mentioned the cost of PrEP potentially being a barrier to the woman's PrEP continuation and advocated for it to be given out freely.

Discussion

The study findings suggest that male partners can play an important role in supporting women's PrEP use and adherence to reduce the risk of HIV transmission to both mother and unborn child. Several women reported unsupportive male partners regarding PrEP use, despite desiring their involvement, emphasizing the need to engage disinterested partners. Involving male partners in identifying and implementing PrEP adherence strategies, such as providing motivation and reminders, may prove helpful in supporting pregnant women's adherence to PrEP as suggested by our findings. For male partners living with HIV, the study suggests that promoting women's oral PrEP use may positively affect their ART use through shared motivation and mutual support. Finally, while most male partners were supportive of women's PrEP continuation outside the study setting, a few were reluctant due to a perceived lack of HIV risk.

Most women interviewed received support from their male partners in the form of reminders and encouragement to take PrEP; however, only some were able to explicitly comment on how partner support was vital for their adherence to the medication. Receiving practical and emotional support, especially from male partners, in the form of reminders, encouragement, reassurance, and management of side effects has been reported in other studies as an important driver of consistent PrEP use (12, 24, 25). This suggests that interventions designed to increase women's PrEP uptake and adherence should consider the role of male partners and encourage their involvement in HIV prevention efforts, particularly when it comes to women's PrEP adherence. In addition to those reported in our study, other types of support from partners that women in other settings have deemed helpful include demonstrating interest in women's clinic visits (often asking what had transpired during visits), observing drug doses,

doing pill counts, assisting with housework, and providing financial support for transportation to clinics for visits or refills (11, 25, 26). Women in our study illustrated the myriad ways support from male partners was instrumental in assisting women with their PrEP adherence, though primarily in the form of instrumental support. Moreover, some women who reported a lack of support from their male partners expressed a desire for their partners to actively participate in their daily adherence to PrEP and accompany them to clinic visits. Conversely, male partners expressed a willingness to provide increased support in the future by being more involved in the women's decision-making phase regarding the use of PrEP. A recent study in South Africa emphasized women's desire for increased male partner support through participation in HIV testing and counseling, aiming to enhance engagement in antenatal care services (27). Future interventions should seek to leverage the natural ways in which partners provide support while promoting other types of social support from partners or other sources, such as emotional and informational support (21), which may confer additional benefits for PrEP adherence (15, 28). Furthermore, healthcare providers should encourage women to involve their partners in their PrEP use and provide education to both partners about PrEP and its importance for preventing HIV transmission.

Most women in our study had disclosed their PrEP use to their male partners, and the men interviewed displayed good knowledge of PrEP's function. Yet, some men had misconceptions about oral PrEP's benefits, and—despite the incorrect knowledge—this sometimes motivated their support for women's use of PrEP. Although men had some initial concerns that PrEP could negatively affect the unborn fetus, more information from the woman or study staff usually alleviated these concerns. Partner PrEP education and involvement in initial counseling before women's PrEP use is essential to address partner PrEP knowledge about PrEP to facilitate appropriate partner support. By involving male partners in PrEP education and counseling, healthcare providers can ensure that both partners have accurate information about PrEP and address any concerns they may have (15, 29, 30). Future research should explore the effectiveness of different approaches to involve both partners in PrEP education and counseling, such as group sessions, couples, or individual counseling. Additionally, it is necessary to research on why some men, who do not have HIV but support women's PrEP use, may be motivated to protect the baby rather than the woman herself. Furthermore, a better understanding of how this primary motivation may impact these men's attitudes toward women's use of PrEP postpartum and after weaning is crucial.

The male partners living with HIV who we interviewed appreciated knowing the women had added protection outside their ART use and reported a perceived benefit in the mutual support for ART use. Shared reproductive health goals among couples, such as protecting the unborn child from HIV acquisition through oral PrEP, can promote mutual adherence (19, 31, 32). Evidence from other studies suggests that having oral PrEP as an option for women may help male partners living with HIV by giving them time to accept their HIV status, initiate ART, and create a feeling of being on the journey together by taking their medication at the same time (31, 33). For the PrEP-using partner, evidence suggests that matching dosing schedules with the partner taking ART may help to support their adherence to PrEP (25). Partner support programs are needed to facilitate this mutual ART-taking and support among serodiscordant couples to realize these many apparent benefits. Such programs might entail coeducation and training on supporting each other's ART use and joint adherence counseling. These programs may be particularly suitable in cases where the partner living with HIV is newly diagnosed, has not achieved viral suppression, or if the woman is uncertain about their partner's viral suppression status.

Our results illuminate the role that male partners can play as key supporters of oral PrEP use to promote prevention-effective oral PrEP use among pregnant and breastfeeding women. These results should be interpreted with key limitations in mind. First, participants' reports of male partner involvement and support of women's PrEP use and representations of PrEP adherence may be susceptible to social desirability bias. Participants were reminded that there were no right or wrong answers and that their responses would not affect their participation in the TP2 PrEP study or their relationship with the study clinic to minimize this bias. Second, male partners were purposively recruited primarily through women's referral; thus, more supportive partners may have been recruited; their experiences may differ from those of male partners who were not invited to be interviewed or were invited but did not enroll. Third, participants were recruited from urban and periurban areas; thus, the results could not be generalized to the larger Malawian population because perspectives and experiences might differ among women and men in rural areas. Finally, nearly all women who agreed to be interviewed had disclosed their PrEP use to their partners and thus cannot offer insight into the experiences of women who did not disclose their partners or declined to be interviewed. Future studies are needed to better understand the experiences of women who cannot or do not wish to disclose their PrEP use to their partners to identify alternative support strategies for women lacking partner support or to support partner disclosure of PrEP use if deemed appropriate.

Conclusion

In our study, male partners generally supported women's use of oral PrEP during pregnancy, often motivated by the perceived desire to protect their unborn child from acquiring HIV. Men provided support in the form of reminders and encouragement for women's PrEP use and adherence. For male partners living with HIV, women's use of PrEP did not negatively impact their ART use; rather, the mutual support was viewed as enhancing by both parties. These findings emphasize the need for interventions to increase women's PrEP uptake and adherence to consider the role of male partners and encourage their involvement. This could lead to more successful HIV prevention outcomes for women and promote mutual support between partners to collaboratively address HIV prevention. Finally, policymakers and health practitioners could consider providing information on the importance of PrEP use for HIV prevention, regardless of perceived HIV risk, and involving male partners in promoting its use to reduce transmission rates.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

The studies involving humans were approved by the Malawi National Health Science Research Committee and the University of North Carolina at Chapel Hill Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AY led the qualitative analysis and wrote the manuscript. LH conceptualized and designed the study, contributed to the analysis, and mentored AY on the manuscript. CG, LP, and SM contributed to the study conceptualization and design. FS contributed to the study design and oversaw the study conducted at the research site. TP coordinated the study and contributed to qualitative analysis. JT collected qualitative data and contributed to qualitative analysis. BC and WM contributed to the study conceptualization and design and coled the parent study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

LH and CG report grant support from Gilead Sciences. This does not alter our adherence to journal policies on sharing data and materials. The authors otherwise have declared that no competing interests exist.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Evaluating the use of oral pre-exposure prophylaxis among pregnant and postpartum adolescent girls and young women in Cape Town, South Africa

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Background: Adolescent girls and young women (AGYW) in South Africa are at a higher risk of acquiring HIV. Despite the increasing availability of daily oral pre-exposure prophylaxis (PrEP) for HIV prevention, knowledge on PrEP use during pregnancy and postpartum periods at antenatal care (ANC) facilities remains inadequate.

Methods: Data from HIV-uninfected pregnant women in Cape Town, South Africa, were used in this study. These women aged 16–24 years were enrolled in the PrEP in pregnancy and postpartum (PrEP-PP) cohort study during their first ANC visit. Using the PrEP cascade framework, the outcomes of the study were PrEP initiation (prescribed tenofovir disoproxil fumarate and emtricitabine at baseline), continuation (returned for prescription), and persistence [quantifiable tenofovir diphosphate (TFV-DP) in dried blood samples]. The two primary exposures of this study were risk perception for HIV and baseline HIV risk score (0–5), which comprised condomless sex, more than one sexual partner, partner living with HIV or with unknown serostatus, laboratory-confirmed sexually transmitted infections (STIs), and hazardous alcohol use before pregnancy (Alcohol Use Disorders Identification Test for Consumption score ≥ 3). Logistic regression was used to examine the association between HIV risk and PrEP, adjusting for *a priori* confounders.

Results: A total of 486 pregnant women were included in the study, of which 16% were "adolescents" (aged 16–18 years) and 84% were "young women" (aged 19–24 years). The adolescents initiated ANC later than the young women [median = 28 weeks (20–34) vs. 23 weeks (16–34), $p = 0.04$]. Approximately 41% of the AGYW were diagnosed with sexually transmitted infection at baseline. Overall, 83% of the AGYW initiated PrEP use during their first ANC. The percentage of PrEP continuation was 63% at 1 month, 54% at 3 months, and 39% at 6 months. Approximately 27% consistently continued PrEP use through 6 months, while 6% stopped and restarted on PrEP use at 6 months. With a higher risk score of HIV

(≥2 vs. ≤1), the AGYW showed higher odds of PrEP continuation [adjusted odds ratio: 1.85 (95% CI: 1.12–3.03)] through 6 months, adjusting for potential confounders. Undergoing the postpartum period (vs. pregnant) and having lower sexual risk factors were found to be the barriers to PrEP continuation. TFV-DP concentration levels were detected among 49% of the AGYW, and 6% of these women had daily adherence to PrEP at 3 months.
Conclusions: AGYW were found to have high oral PrEP initiation, but just over one-third of these women continued PrEP use through 6 months. Pregnant AGYW who had a higher risk of acquiring HIV (due to condomless sex, frequent sex, and STIs) were more likely to continue on PrEP use through the postpartum period. Pregnant and postpartum AGYW require counseling and other types of support, such as community delivery and peer support to improve their effective PrEP use through the postpartum period.

Clinical Trial Number: ClinicalTrials.gov, NCT03826199.

KEYWORDS

South Africa, AGYW, adherence, breastfeeding, cohort studies, oral pre-exposure prophylaxis, pregnant

Introduction

Adolescent girls and young women (AGYW, aged 16–24 years) in South Africa have a higher risk of acquiring HIV. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that in 2021, approximately 250,000 AGYW were infected with HIV worldwide and six out of seven cases of HIV infections among adolescents (aged 15–19 years) in sub-Saharan Africa occurred among girls (1). Despite representing only 10% of the total population in sub-Saharan Africa, AGYW accounted for 25% of all acute HIV infections (2). AGYW are at a higher risk of acquiring HIV (3), and they may acquire HIV 5–7 years earlier than their male peers (3, 4). Thus, UNAIDS aims to reduce new cases of HIV infections among AGYW to less than 50,000 cases by 2025 (1).

Acquiring HIV is especially high during pregnancy and postpartum periods. AGYW have an immature cervix that has greater proportion of an exposed genital mucosa susceptible to HIV, and they also have higher levels of genital inflammation and hormonal effects compared with older women (5). The factors associated with higher risk of acquiring HIV among AGYW include age-disparate sexual partners, multiple partners, unknown serostatus of the partner, low marital or cohabitation prevalence rates, earlier sexual debut, gender-based violence, lack of sexual education, frequent condomless sex, and sexually transmitted infections (STIs) (6–8). In South Africa, the prevalence rate of pregnancy in adolescents (aged <19) is estimated at 20% (9), and 76% of these pregnancies are unintended (10). Young women without the intention of getting pregnant usually delay seeking antenatal care (ANC), and associated HIV testing and care, compared with those with planned pregnancies. Moreover, the risk of vertical transmission is much higher among those with HIV infections during pregnancy/postpartum than that of those who are already living with HIV (11). In 2021, 22,000 cases of HIV infections occurred during pregnancy or breastfeeding periods in Eastern and Southern Africa (1). The pooled HIV incidence rate during pregnancy and postpartum periods was found to be 3.6 per 100 person-years (95% CI: 1.2–11.1) in sub-Saharan Africa (12), which met the UNAIDS threshold for substantial risk of acquiring HIV (1). Therefore, the prevention of acquiring HIV throughout pregnancy and postpartum periods is particularly not only important for maternal health but also pivotal in eliminating vertical HIV transmission (11).

The South African National Department of Health supports the provision of oral pre-exposure prophylaxis (PrEP) and HIV prevention counseling as part of a comprehensive combination prevention strategy for AGYW and pregnant and breastfeeding women who are at substantial risk of acquiring HIV (1, 13). Oral PrEP with tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) is an antiretroviral medication that can be taken daily by HIV-negative individuals before HIV exposure to prevent acquiring the infection; however, high adherence to this medication during periods of high HIV risk is required for PrEP to be effective (11). The PrEP cascade, an analogous extension of the HIV care cascade (14), provides a quantifiable framework for measuring the progress of HIV prevention methods and PrEP delivery. It illustrates the following stages of PrEP delivery: PrEP eligibility, initiation, persistence on PrEP during periods of high HIV risk, and adherence to PrEP for sufficient protection from HIV (15). 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 (16, 17). Studies on pregnant and postpartum women have also identified delivery patterns that were unique to pregnancy, such as the high attrition rates during postpartum periods (18–22). However, there is a gap in knowledge for PrEP cascade and adherence studies among AGYW during pregnancy and postpartum periods.

We utilized the PrEP cascade among pregnant AGYW to examine PrEP initiation, continuation through 6 months, and persistence at a busy ANC facility in Cape Town, South Africa. We also evaluated the association between baseline HIV risk and PrEP delivery outcomes to inform the national and regional

PrEP programs that are scaled up for pregnant/postpartum women 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 initiation, continuation, and persistence among a subset of pregnant and postpartum AGYW. The study's methodology has been described in detail in another study (21). In summary, PrEP-PP study participants (aged ≥16 years) were recruited into the study during their ANC visit at a public health clinic from August 2019 to October 2021 and were followed up through 12 months postpartum. Interested study participants provided written informed consent in English or their local language (isiXhosa). The participants were eligible for the study if they were confirmed to be pregnant, not living with HIV (confirmed by a fourth-generation rapid HIV antigen/antibody test from Abbott Laboratories), and negative for hepatitis B surface antigen (confirmed by a rapid hepatitis B surface antigen test from Abbott Laboratories).

Enrollment and measurements

Upon enrollment, the 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. The participants underwent a point-of-care testing for STIs, and those participants diagnosed with sexually transmitted infection (STI) were provided with treatment according to the South African national guidelines for STI (23). Pregnant AGYW underwent HIV testing and counseling, with an offer to start using PrEP as part of a comprehensive combination prevention strategy along with promoting condom use and HIV prevention counseling, regardless of the responses to behavioral HIV risk factors and STI status. The study participants interested to start using PrEP had their blood tested to confirm whether their baseline creatinine levels (i.e., glomerular filtration rate of >60) met the clinical eligibility for PrEP or not. The participants who started using PrEP were provided with a 1-month supply of Truvada (TDF-FTC or "PrEP").

Follow-up visits were conducted at 1, 3, and 6 months and were scheduled with the participants' regular ANC visits until delivery. At the 1-month visit, the participants were provided with a PrEP refill. At the 3- and 6-month visits, the participants completed brief follow-up surveys regardless of PrEP use through interviews conducted by trained study staff in a private clinic room. Furthermore, the participants were supplied with additional PrEP prescriptions (for those interested); dried blood spot (DBS) samples were also collected from 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 Institutional Review Board of the University of California, Los Angeles (IRB#18-001622). This study followed the reporting guidelines based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

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 accepting and receiving a PrEP prescription at the baseline visit, which was also their first ANC visit. PrEP continuation was defined as receiving a PrEP prescription at each study visit after the baseline visit among those who initiated PrEP at baseline. PrEP continuation through 6 months was defined as attending the study visits and receiving a PrEP prescription at all study visits (1, 3, and 6 months) among those who initiated PrEP at baseline compared with those who did not attend the study visits or those who reported discontinued PrEP use.

Objective PrEP persistence was measured using erythrocyte intracellular tenofovir diphosphate (TFV-DP) concentration levels detected by liquid chromatography and mass spectroscopy, which is a measure of cumulative PrEP adherence over several weeks (24). We defined objective PrEP persistence as any TFV-DP or "PrEP" concentration levels detected in the collected DBS samples at the follow-up study visit (3 and 6 months) from those who initiated PrEP at baseline and those with DBS samples that were collected and analyzed. The DBS samples were analyzed for a non-random sample of TFV-DP measures of the first 900 participants of the full cohort ($n = 1{,}195$) among those who reported using PrEP in the last 30 days of the study visit.

As recommended by the pharmacokinetic study by Stranix-Chibanda et al. (24), we used separate thresholds for adherence using TFV-DP in DBS in pregnant vs. postpartum women. High adherence or daily intake oral PrEP (~7 doses/week) was defined by DBS with a TFV-DP value of ≥600 fmol/punch for pregnant women and ≥1,000 fmol/punch for postpartum women; moderate adherence (2–6 doses/week) was defined as DBS with a TFV-DP value of 200–599 fmol/punch for pregnant women and 400–999 fmol/punch for postpartum women; and low adherence (<2 doses/week) was defined as quantifiable with a TFV-DP value of <200 fmol/punch for pregnant women 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 women with quantifiable TFV-DP concentrations with those with unquantifiable TFV-DP concentrations. We also included those

who did not report taking PrEP in the last 30 days as part of the denominator and classified them as non-adherent. However, those who reported recent adherence, but did not have DBS analyzed, were marked as missing from the analysis because their adherence levels were unknown.

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), which was adapted from another study examining HIV risk among AGYW (17). The HIV risk score is a sum of five factors that are scored at 1 point each: condomless sex, having more than one sexual partner, having a primary partner living with HIV or with unknown serostatus, laboratory-confirmed STI diagnosis at baseline, and hazardous alcohol use [Alcohol Use Disorders Identification Test for Consumption (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 and ≥ 2) to examine the differences between lower and higher risk scores. We defined risk perception as answering either "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 were collected by a study interviewer at each study visit using a survey on REDCap. Clinical characteristic measures were gestational age in weeks at the first ANC visit. 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, the participants were asked with regard to the number of sexual activity, condom use during the last sex, number of sexual partners in the past 12 months, HIV status of the partner in the past 12 months, intimate partner violence (IPV) in the past 12 months (WHO IPV scale) (25), and alcohol use in the past 12 months and before finding out about their pregnancy using the AUDIT-C (26). Alcohol use was defined as reporting any alcohol use or by a cutoff of AUDIT-C score of ≥ 3, which was used in our previous study to identify hazardous alcohol use among pregnant women in South Africa (20). 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

We restricted the analytical sample of this study to participants aged 16–24 years at baseline ($n = 486$). First, the baseline characteristics were described overall and stratified by age categories of adolescent girls (aged 16–18 years) and young women (aged 19–24 years). We reported the median [interquartile range (IQR)] for the continuous variables and frequency/percentage for the categorical variables. We then compared the baseline characteristics by age using Student's *t*-test, chi-squared test, or Fisher's exact test. We used Fisher's exact test, which uses the data directly, when we had cell counts of <10 as a conservative measure instead of the chi-squared test, which only relies on an approximation (27).

We evaluated the PrEP cascade by estimating the proportion of AGYW who were eligible for, initiated, and continued PrEP use (1, 3, and 6 months). We censored those who experienced pregnancy loss and infant loss or those whose HIV status changed to positive during the study follow-up; these participants were removed from the denominators during follow-up. The cascade was shown as overall, by their HIV risk scores, and by sub-age categories. Finally, we ran the 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 the associated 95% CI for each model. In the adjusted analyses, we controlled for maternal age and gestational age at baseline and whether the baseline data were collected before or during/after the national COVID-19 lockdowns in South Africa (before/after 28 March 2020) (28). All analyses were performed using SAS version 9.4 (SAS Institute).

Results

Patient characteristics

Out of the 1,195 women enrolled in the PrEP-PP study, 486 were AGYW. Specifically, 16% ($n = 77$) were "adolescents" aged 16–18 years, and 84% ($n = 409$) were "young women" aged 19–24 years (**Table 1**). In total, 67% ($n = 327$) were pregnant with their first child, and 70% ($n = 340$) were neither married nor cohabitating with their partner. Compared with young women, more adolescent girls were neither married nor cohabiting with their partners (78% vs. 68%, $p = 0.01$).

Clinical characteristics

The overall median gestational age during the first ANC visit was 24 weeks (IQR = 17–34) (**Table 1**). The median gestation age at baseline for adolescent girls was later [28 (20–34) weeks] when compared with that for young women [23 (16–34) weeks, $p = 0.04$]. Thus, more adolescents attended ANC visits for the first time at over the recommended 14 weeks of gestation compared with young women (88% vs. 79%, $p = 0.06$). Moreover, almost all the adolescent girls were primigravida compared with the proportion of young women (91% vs. 63%, $p < 0.01$). Over half (54%, $n = 41$) of the adolescent girls were diagnosed with STI at baseline compared with the 39% ($n = 159$) of the young women. Adolescent girls also presented with multiple sexually transmitted co-infections compared with young women (19% vs. 9% with multiple STIs, respectively).

TABLE 1 Baseline characteristics of pregnant adolescent girls and young women (aged 16–24 years at enrollment) from the PrEP-PP study in Cape Town, South Africa ($N = 486$).

	Overall	Age (16–18 years)	Age (19–24 years)	*p*-value
	n (%)	*n* (%)	*n* (%)	
Total	486 (100)	77 (16)	409 (84)	
Demographics				
Highest level of education				
<Grade 12	209 (43)	54 (70)	155 (38)	**<0.001**
≥Grade 12	277 (57)	23 (30)	254 (62)	
Socioeconomic status				
Low SES	160 (33)	33 (43)	127 (31)	**0.04**
Moderate to high SES	326 (67)	44 (57)	282 (69)	
Gravidity				
Primigravida	327 (67)	70 (91)	257 (63)	**<0.001**
Multigravida	159 (33)	7 (9)	152 (37)	
Relationship status				
Neither married nor cohabiting	340 (70)	60 (78)	280 (68)	**0.01**
Married or cohabitating	90 (19)	5 (6)	85 (21)	
Not in a relationship	56 (12)	12 (16)	44 (11)	
Clinical characteristics				
Gestational age at first ANC visit, weeks (median, IQR)	24 (17–34)	28 (20–34)	23 (16–34)	**0.04**
Gestational age at first ANC visit, weeks				
≤14	95 (20)	9 (12)	86 (21)	0.06
>14	391 (80)	68 (88)	323 (79)	
Any STI diagnosed (CT, NG, and/or TV)				
No STI	283 (59)	35 (46)	248 (61)	**0.01**
STI diagnosed	200 (41)	41 (54)	159 (39)	
Type of STI diagnosed (CT, NG, and/or TV)				
CT only	120 (60)	22 (54)	98 (62)	NE
NG only	13 (7)	0 (0)	13 (8)	
TV only	16 (8)	4 (10)	12 (8)	
CT and NG	29 (15)	11 (27)	18 (11)	
CT and TV	16 (8)	2 (5)	14 (9)	
TV and NG	5 (3)	1 (2)	4 (3)	
CT, NG, and TV	1 (1)	1 (2)	0 (0)	
Behavioral risk factors				
Sexually active in pregnancy (at baseline)				
Not sexually active	17 (4)	4 (5)	13 (3)	**0.04**
Yes, 1–4 times per month	303 (62)	56 (73)	247 (60)	
Yes, 5+ times per month	166 (34)	17 (22)	149 (36)	
Condom use during last sex (at baseline)[a]				
Condomless sex	291 (62)	42 (58)	249 (63)	0.39
Condom used	178 (38)	31 (42)	147 (37)	
Number of sexual partners in the past 12 months				
One sexual partner	392 (81)	63 (82)	329 (80)	0.78
>1 sexual partners	94 (19)	14 (18)	80 (20)	
Partner's HIV status in the past 12 months (at baseline)[a]				
HIV-negative	319 (66)	47 (61)	272 (67)	0.40
HIV-positive	4 (1)	0 (0)	4 (1)	
Do not know	163 (34)	30 (39)	133 (33)	
IPV in the past 12 months[b]				
No IPV	430 (88)	68 (88)	362 (89)	0.96
Reported IPV	56 (12)	9 (12)	47 (11)	
Alcohol use in the past 12 months before pregnancy				
No alcohol use	217 (45)	40 (52)	177 (43)	0.16
Any alcohol use	269 (55)	37 (48)	232 (57)	
Hazardous Alcohol use (AUDIT-C ≥ 3)	167 (34)	23 (30)	144 (35)	0.37
Baseline HIV risk[c] (dichotomized)				
No/low HIV risk (score ≤ 1)	179 (37)	29 (38)	150 (37)	0.87
Moderate/high HIV risk (score > 1)	307 (63)	48 (62)	259 (63)	
Baseline HIV risk score[c]				
0	44 (9)	9 (12)	35 (9)	0.52
1	135 (28)	20 (26)	115 (28)	
2	172 (35)	23 (30)	149 (36)	
3	105 (22)	18 (23)	87 (21)	
4	25 (5)	5 (6)	20 (5)	
5	5 (1)	2 (3)	3 (1)	

Bold values represent *p*-values <0.05.
NE, not estimated; Data are *n* (%) or median (IQR).
[a]In women who reported sexual partners.
[b]The participants were considered to have experienced any IPV if they endorsed at least one of four items asking about their recent physical, emotional, or sexual violence from a sexual partner.
[c]HIV risk score is the sum of points for reporting each of the following risk factors at baseline: condomless sex, >1 sexual partner, partner living with HIV or unknown partner HIV status, laboratory-confirmed STI diagnosis at baseline, and hazardous alcohol use.

Behavioral risk factors

Of the 96% ($n = 469$) of AGYW who were sexually active at baseline, the majority (62%, $n = 291$) practiced condomless sex at baseline, and most (81%, $n = 392$) reported having only one sexual partner (Table 1). Overall, 66% ($n = 319$) reported having partners who were not living with HIV, 34% ($n = 163$) reported that they did not know their partner's HIV status, and 1% ($n = 4$) reported that their partner is living with HIV at baseline. Approximately 12% of AGYW reported experiencing intimate partner violence in the past 12 months, and over half (55%, $n = 269$) reported alcohol use in the last 12 months before pregnancy. Prior to their pregnancy, 34% ($n = 167$) reported hazardous alcohol use (AUDIT-C ≥ 3).

Most behavioral risk factors, such as condom use during sex (42% vs. 37%, $p = 0.39$), multiple sexual partners (18% vs. 20%, $p = 0.78$), knowledge regarding their partner's HIV status in the past 12 months (61% vs. 67%, $p = 0.40$), and composite HIV risk score (62% vs. 63% scoring 2+, $p = 0.83$), were similar among AGYW.

PrEP cascade in pregnant and postpartum AGYW

Figure 1 displays the HIV PrEP cascade indicators among pregnant and postpartum AGYW at baseline and at 1-, 3-, and 6-month follow-up visits. Of the 83% (403/486) who initiated PrEP, the percentage of continuation during follow-up was 63% (253/

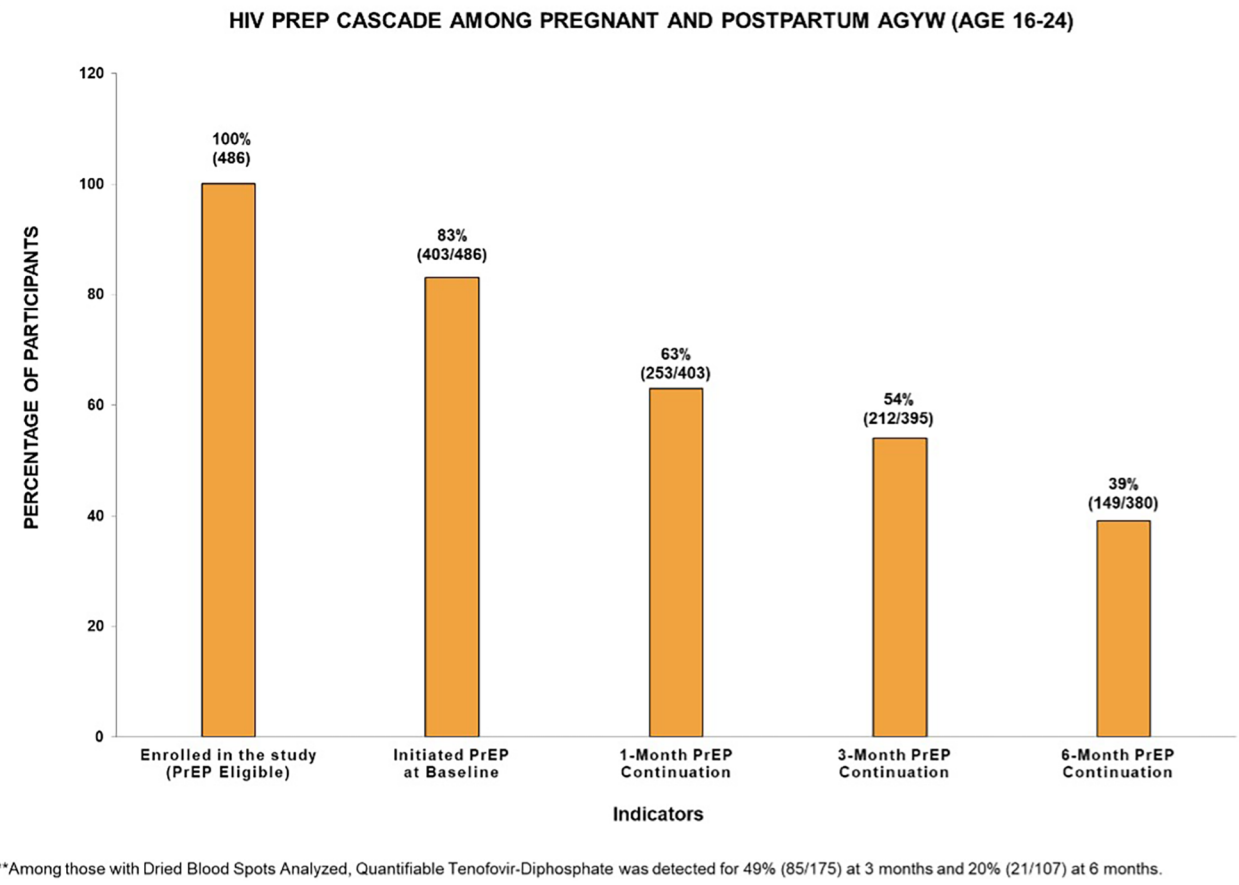

FIGURE 1
HIV PrEP cascade among pregnant and postpartum adolescent girls and young women (aged 16–24 years) in the PrEP-PP study ($n = 486$).

403) at 1 month, 54% (212/395) at 3 months, and 39% (149/380) at 6 months. These AGYW had similar PrEP uptake and continuation prevalence across the cascade (Supplementary Figure S1). Approximately 27% (110/403) consistently attended all visits through 6 months after initiating PrEP, and 6% (25/408) missed either the 1- or 3-month visit but restarted on PrEP at 6 months (Table 2). Among those who restarted on PrEP, most were postpartum women at 6 months (80%, $n = 20$). Of those with DBS samples collected and analyzed, a quantifiable TFV-DP concentration was detected among 49% (85/175) at 3 months and 20% (21/107) at 6 months. Disaggregating adherence data further, 6% ($n = 10$) were found to have high adherence (~7 doses/week), 20% ($n = 35$) had medium adherence (~2–5 doses/week), 23% ($n = 40$) had low adherence (<2 doses/week), and 51% ($n = 90$) had unquantifiable TFV-DP concentration levels or did not report using PrEP in the last 30 days at the 3-month visit. Meanwhile, 1% ($n = 1$) were found to have high adherence (~7 doses/week), 5% ($n = 5$) had medium adherence (~2–5 doses/week), 14% ($n = 15$) had low adherence (<2 doses/week), and 80% ($n = 80$) had unquantifiable TFV-DP concentration levels or did not report using PrEP in the last 30 days of the 6-month visit.

Most pregnant AGYW (96%) were sexually active at baseline. Of those who continued participating in the study, 68% were sexually active at the 3-month follow-up, and 71% were sexually active at the 6-month follow-up (Table 2). At the 3-month visit, 51% ($n = 238$) were pregnant, and 49% ($n = 226$) were postpartum women. A higher proportion of adolescent girls reported being sexually abstinent during the postpartum period compared with young women (75% vs. 52%, $p = 0.04$). However, at 6 months, the frequency of sexual activity during the postpartum period was similar among AGYW (31% vs. 32%, $p = 0.89$). At 3 months, most AGYW had sex while pregnant (84%, $n = 135$), whereas fewer AGYW had sex during the postpartum period (45%, $n = 53$). However, the young women reported being more sexually active during the postpartum period than the adolescent girls (51% vs. 25%, $p = 0.04$). At 3 months, the adolescent girls who reported no perceived HIV risk also reported sexual abstinence (55%, $n = 12$); meanwhile, approximately 55% ($n = 131$) of the young girls reported no perceived HIV risk, and only 28% ($n = 37$) reported sexual abstinence.

Supplementary Figure S2 displays the PrEP cascade indicators among pregnant and postpartum AGYW at baseline and at 1-, 3-, and 6-month follow-up visits stratified by their baseline HIV risk scores (≤1 and ≥2). Although the proportions of AGYW who initiated PrEP at baseline were similar (82% vs. 83%, $p = 0.72$), the percentage of continuation at 1 month (56% vs. 66%, $p = 0.05$), 3 months (45% vs. 59%, $p = 0.01$), and 6 months (34% vs. 42%, $p = 0.09$) was higher among those with greater HIV baseline risk

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TABLE 2 The PrEP cascade indicators among pregnant and postpartum adolescent girls and young women (aged 16–24 years) from the PrEP-PP study in Cape Town, South Africa (*N* = 486).

	Overall	Age (16–18 years)	Age (19–24 years)	*p*-value
	n (%)	*n* (%)	*n* (%)	
Baseline				
Total at baseline	486 (100)	77 (16)	409 (84)	
HIV risk perception at baseline				
No chance	283 (58)	48 (62)	235 (57)	**0.04**
Low chance	161 (33)	18 (23)	143 (35)	
High chance	42 (9)	11 (14)	31 (8)	
Sexually active at baseline				
Not sexually active	17 (4)	4 (5)	13 (3)	**0.04**
Yes, 1–4 times per month	303 (62)	56 (73)	247 (60)	
Yes, 5+ times per month	166 (34)	17 (22)	149 (36)	
PrEP initiation at baseline				
Did not initiate PrEP	83 (17)	13 (17)	70 (17)	0.96
Initiated PrEP at baseline	403 (83)	64 (83)	339 (83)	
1-month follow-up				
Total at the 1-month follow-up				
Attended and continued PrEP	253 (63)	38 (59)	215 (63)	NE
Attended and discontinued PrEP	23 (6)	3 (5)	20 (6)	
Missed visit and discontinued PrEP	119 (24)	22 (29)	97 (24)	
Initiated PrEP at 1-month visit	1 (0.2)	0 (0)	1 (0.2)	
Never on PrEP	81 (17)	13 (17)	68 (17)	
Censored	9 (2)	1 (2)	8 (2)	
Pregnancy status at 1 month				
Pregnant	314 (78)	47 (75)	267 (79)	0.49
Postpartum	89 (22)	16 (25)	73 (21)	
3-month follow-up				
Total at the 3-month follow-up				
Attended and continued PrEP	176 (40)	28 (37)	148 (41)	NE
Attended and discontinued PrEP	21 (5)	0 (0)	21 (6)	
Missed visit and discontinued PrEP	21 (4)	21 (28)	126 (31)	
Restarted PrEP	37 (8)	11 (15)	26 (7)	
Initiated PrEP at 3-month visit	16 (3)	0 (0)	16 (4)	
Never on PrEP	62 (13)	13 (17)	49 (12)	
Censored	18 (4)	3 (4)	15 (4)	
Pregnancy status at 3 months				
Pregnant	238 (51)	25 (34)	213 (54)	**<0.01**
Postpartum	226 (49)	48 (66)	178 (46)	
HIV risk perception at 3 months				
No chance	153 (55)	22 (55)	131 (55)	0.41
Low chance	103 (37)	13 (33)	90 (38)	
High chance	21 (8)	5 (13)	16 (7)	
Sexually active at 3 months				
Not sexually active	89 (32)	22 (55)	67 (28)	**<0.01**
Yes, 1–4 times per month	143 (52)	14 (35)	129 (54)	
Yes, 5+ times per month	45 (16)	4 (10)	41 (17)	
Sexually active while pregnant	135 (84)	12 (75)	123 (85)	0.28
Sexually active while postpartum	53 (45)	6 (25)	47 (51)	**0.04**
PrEP persistence at 3 months (30-day self-report)				
High adherence (~7 days)	134 (57)	20 (51)	114 (51)	0.81
Medium adherence (2–6 days)	53 (23)	9 (23)	44 (20)	
Low adherence (<2 doses/week)	4 (2)	1 (3)	3 (2)	
Did not adhere to PrEP	44 (19)	9 (23)	35 (18)	
PrEP persistence at 3 months (TFV-DP)				
High adherence (~7 days)	10 (6)	1 (3)	9 (6)	0.52

(*Continued*)

TABLE 2 Continued

	Overall	Age (16–18 years)	Age (19–24 years)	*p*-value
	n (%)	*n* (%)	*n* (%)	
Medium adherence (2–6 days)	35 (20)	9 (29)	26 (18)	
Low adherence (>BLQ)	40 (23)	7 (23)	33 (23)	
BLQ or reported not using PrEP	90 (51)	14 (45)	76 (53)	
PrEP persistence at 3 months (TFV-DP)				
Any TFV-DP concentration levels detected	85 (49)	17 (55)	68 (47)	0.44
BLQ or reported not using PrEP	90 (51)	14 (45)	76 (53)	
6-month follow-up				
Total at the 6-month follow-up				
Attended and continued PrEP	132 (30)	26 (37)	106 (29)	NE
Attended and discontinued PrEP	35 (8)	2 (3)	33 (9)	
Missed visit and discontinued PrEP	181 (39)	28 (38)	153 (40)	
Restarted PrEP	25 (6)	3 (4)	22 (6)	
Initiated PrEP at 6-month visit	4 (0.9)	0 (0)	4 (1)	
Never on PrEP	51 (11)	11 (15)	40 (10)	
Censored	31 (7)	3 (4)	28 (8)	
Pregnancy status at 6 months				
Pregnant	83 (19)	4 (6)	79 (21)	**0.001**
Postpartum	357 (81)	66 (94)	291 (79)	
HIV risk perception at 6 months				
No chance	125 (57)	17 (52)	108 (58)	0.74
Low chance	86 (39)	15 (45)	71 (38)	
High chance	7 (3)	1 (3)	6 (3)	
Sexually active at 6 months				
Not sexually active	62 (28)	9 (27)	53 (29)	0.62
Yes, 1–4 times per month	118 (54)	20 (61)	98 (53)	
Yes, 5+ times per month	38 (17)	4 (12)	34 (18)	
Sexually active while pregnant	51 (94)	2 (100)	49 (94)	NE
Sexually active while postpartum	105 (64)	22 (71)	83 (62)	0.41
PrEP persistence at 6 months (30-day self-report)				
High adherence (~7 days)	87 (48)	17 (55)	70 (47)	0.53
Medium adherence (2–6 days)	44 (24)	7 (23)	37 (25)	
Low adherence (<2 doses/week)	3 (2)	1 (3)	2 (1)	
Did not adhere to PrEP	47 (26)	6 (19)	41 (27)	
PrEP persistence at 6 months (TFV-DP)				
High adherence (~7 days)	1 (1)	0 (0)	1 (1)	NE
Medium adherence (2–6 days)	5 (5)	2 (11)	3 (3)	
Low adherence (>BLQ)	15 (14)	2 (11)	13 (15)	
BLQ or reported not using PrEP	86 (80)	15 (79)	71 (81)	
PrEP persistence at 6 months (TFV-DP)				
Any TFV-DP concentration levels detected	21 (20)	4 (21)	17 (19)	1.00
BLQ or reported not using PrEP	86 (80)	15 (79)	71 (81)	
Continued PrEP through the 6-month visit[a]	110 (27)	22 (34)	88 (26)	0.17

Bold values represent *p*-values <0.05.
BLQ, below the limit of quantification; NE, not estimated.
[a]Continued consistently through the 6-month visit are those who attended all study visits (1-, 3-, and 6-month follow-up) among those who initiated PrEP at baseline.

scores compared with the percentage among those with lower risk scores. However, the proportion of those with any TFV-DP concentration levels detected in the blood was similar at 3 months (48% vs. 49%, $p = 0.84$) and 6 months (14% vs. 22%, $p = 0.43$).

Table 3 summarizes the associations between HIV risk score, risk perception, and outcomes from the PrEP cascade. Frequencies for these associations can be found in Supplementary Table S1. AGYW with a higher risk score (≥2) showed higher odds of PrEP continuation at 3 months [adjusted odds ratio (aOR): 1.60 (95% CI: 1.05–2.43)] and consistent PrEP continuation through 6 months [aOR: 1.85 (95% CI: 1.12–3.03)], after adjusting for maternal age and gestational age at baseline and whether the baseline data was collected before/after 28 March 2020 (national COVID-19 early pandemic lockdowns). Compared with AGYW who perceived no HIV risk at baseline, those with high HIV risk perception showed higher adjusted odds of PrEP continuation at 3 months [aOR: 1.90 (95% CI: 0.88–4.13)] and consistent PrEP continuation through 6 months

Table 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.

	PrEP status, Odds Ratio (95% CI)						
	Initiation (Baseline)	Continuation (1-month)	Continuation (3-month)	Continuation (6-month)	Continued through 6 months	Any TFV-DP at 3-month	Any TFV-DP at 6-month
Crude							
Baseline HIV Risk Score (continuous)	1.03 (0.82, 1.28)	1.26 (1.04, 1.53)	1.21 (1.01, 1.46)	1.11 (0.91, 1.34)	1.31 (1.06, 1.61)	1.24 (0.94, 1.62)	1.58 (0.98, 2.57)
Baseline HIV Risk Score No/Low HIV risk (score .1) Moderate/High HIV risk (score .2)	Reference 1.09 (0.67, 1.78)	1.52 (1.01,2.31)	1.72 (1.14, 2.59)	1.44 (0.93, 2.22)	2.00 (1.23, 3.26)	1.07 (0.57, 1.99)	1.71 (0.57, 5.14)
HIV Risk Perception at baseline							
No Chance	Reference						
Low Chance	0.85 (0.51, 1.41)	1.32 (0.85, 2.07)	1.29 (0.83, 1.98)	1.16 (0.74, 1.83)	1.14 (0.71, 1.85)	1.30 (0.68, 2.49)	NE
High Chance	0.97 (0.41, 2.32)	1.46 (0.68, 3.12)	2.18 (1.02, 4.66)	1.71 (0.83, 3.53)	2.26 (1.09, 4.7)	0.82 (0.30, 2.22)	NE
Adjusted*							
Baseline HIV Risk Score (continuous)	1.05 (0.84, 1.31)	1.25 (1.03, 1.51)	1.19 (0.98, 1.43)	1.09 (0.89, 1.32)	1.29 (1.04, 1.59)	1.21 (0.91, 1.59)	1.62 (0.98, 2.66)
Baseline HIV Risk Score***							
No/Low HIV risk (score .1)	Reference						
Moderate/High HIV risk (score .2)	1.18 (0.72, 1.93)	1.47 (0.96, 2.23)	1.60 (1.05, 2.43)	1.32 (0.85, 2.06)	1.85 (1.12, 3.03)	1.03 (0.54 1.93)	1.73 (0.56, 5.40)
HIV Risk Perception at baseline							
No Chance	Reference						
Low Chance	0.89 (0.53, 1.50)	1.31 (0.84, 2.06)	1.29 (0.83, 2.02)	1.15 (0.72, 1.83)	1.11 (0.68, 1.82)	1.41 (0.73, 2.75)	NE
High Chance	1.24 (0.51, 3.00)	1.35 (0.63, 2.91)	1.90 (0.88, 4.13)	1.42 (0.67, 3.00)	1.89 (0.89, 4.00)	0.93 (0.34, 2.57)	NE

Abbreviations: PrEP, pre-exposure prophylaxis; aOR, adjusted Odds Ratio; TFV-DP = tenofovir disoproxil fumarate/emtricitabine; CT = Chlamydia trachomatis, 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) N(%) for this table can be found in Supplemental Table 1 NE = Not estimated due to insufficient sample size for a logistic regression.

*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)

***HIV risk score is a sum of points for reporting each of the following risk factors 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 = 486); b) continuation at 1 are those who attended and requested a PrEP prescription among those who initiated PrEP at baseline (n = 403); c) continuation at 3, 6 months are those who attended and requested a PrEP prescription among those who initiated PrEP at baseline and removed those who were censored for pregnancy/infant loss or HIV seroconversion (n = 395 for 3-month and n = 380 for 6-month); 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 = 403); d) persisted on PrEP is any TFV-DP detected among those who reported PrEP use in the last 30 days and had dried blood spots analyzed. Those who reported not using PrEP in the last 30 days were marked as "did not adhere" (n = 175 at 3 months and n = 107 at 6 months).

[aOR: 1.89 (95% CI: 0.89–4.00)], although the confidence intervals crossed the null.

Compared with those with no STI at baseline, pregnant AGYW diagnosed with STI at baseline had 1.5 times the adjusted odds of PrEP continuation at 1 month [STI: aOR: 1.46 (95% CI: 0.96–2.24)], and a similar association was observed for those with consistent PrEP continuation through 6 months [STI diagnosed: aOR: 1.28 (95% CI: 0.81–2.03)] (**Supplementary Table S4**). Frequencies for these associations can be found in **Supplementary Table S2**. Compared with those with no alcohol use at baseline, AGYW who reported alcohol use had slightly higher odds of PrEP continuation at 3 months [alcohol use: aOR: 1.65 (95% CI: 1.10–2.49)] and 6 months [alcohol use: aOR: 1.41 (95% CI: 0.92–2.17)] and consistent PrEP continuation through 6 months [alcohol use: aOR: 1.51 (95% CI: 0.96–2.40)]. AGYW with a partner living with HIV or with unknown serostatus also had slightly higher adjusted odds of consistently continuing PrEP through 6 months compared with those with a partner not living with HIV [partner living with HIV or with unknown serostatus: aOR: 1.40 (95% CI: 0.88–2.21)].

Discussion

In this cohort study of 486 pregnant and postpartum AGYW, we observed high overall PrEP initiation (>80%). However, at 6 months, only just over one-third of those who initiated PrEP continued. Meanwhile, among those who discontinued, 6% of AGYW restarted on PrEP use at 6 months. PrEP continuation was higher among those with greater baseline HIV risk scores

and higher perceived HIV risk. Moreover, we identified important age-specific clinical characteristics between pregnant and postpartum AGYW in our study. This study also contributed to the paucity of literature on the PrEP cascades among the pregnant/postpartum AGYW from health facilities in South Africa.

Clinical characteristics of AGYW at baseline

Most adolescent girls (aged <19 years) attended their first ANC visit much later at 28 weeks of gestation, which is in the third trimester of the pregnancy. This differs from our previous study among the overall PrEP-PP samples with older women, where the median gestation at ANC initiation was 21 weeks (second trimester). Although this timing is still later than what is recommended in the WHO guideline for women to initiate ANC, which is approximately 12 weeks (first trimester) (29), and in the national South African guidelines, which is 14 weeks, it supports the findings of previous studies that reported that AGYW access ANC much later than older women in sub-Saharan Africa (30). The early timing of initiating ANC is particularly important in HIV prevention methods as this could impact access to early PrEP initiation for those at risk, HIV diagnosis, and early HIV treatment.

Moreover, over half (54%) of the adolescent girls in our sample were diagnosed with STI at the baseline visit, often presented with multiple sexually transmitted co-infections (19%). STI case management is typically performed at a primary care setting, and for AGYW, the 2022 guidelines by the Southern African HIV Clinicians Society recommended that STI screening should be conducted at least once a year based on the assessment of risk factors (e.g., multiple sex partners, engagement in transactional sex, sex under the influence of drugs, or STI diagnosis in the past year) (31). Given the late ANC initiation and high STI burden among adolescent girls in our study, HIV prevention methods should promote early ANC visits and strengthen interventions to actively test, manage, and treat STIs beyond a primary care setting (32, 33).

PrEP initiation and continuation

The prevalence of PrEP initiation in our study was comparable with that of other studies on AGYW in sub-Saharan Africa (34). Unlike other studies that reported lower PrEP uptake for AGYW (34, 35), PrEP uptake in our study (83%) was similar to the finding of the overall PrEP-PP study with older women (84%) (21), and we also did not observe any differences between the age groups of AGYW. Although the percentage of PrEP continuation in our sample was low (63% at 1 month, 54% at 3 months, and 39% at 6 months), it was higher compared with that of similar studies on AGYW (32% at 1 month and 6% at 3 months) in Kenya (34). Both studies had oral PrEP-focused projects among AGYW; however, our study was comprised of only pregnant AGYW who were regularly coming in for their prenatal care, because non-pregnant AGYW had no reason 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. The risk scores had previously been used to identify those at high risk of acquiring HIV (36, 37). We used a modified risk score to fit the data available in our study and to reflect the relevant clinical and behavioral factors (e.g., condomless sex, more than one sexual partner, primary partner living with HIV or unknown serostatus, STI diagnosis at baseline, and hazardous alcohol use). Despite the low overall percentage of continuation, we found that those with greater HIV risk had higher odds of consistent PrEP continuation through 6 months. We also found that having a high-risk perception at baseline was correlated with higher odds of consistent PrEP continuation PrEP. Although the risk scores are objectively calculated on a series of sexual behaviors and risk perception is seemingly subjective, studies have found the concepts overlapping (38). Hensen et al. reported that AGYW made decisions on PrEP use based on their HIV risk perception, including condom use, number of sexual partners, and being married/cohabitating with a partner (38), all of which were used to develop our risk score. Prior studies also reported that AGYW who initiated PrEP were motivated by a high perceived HIV risk (34). The risk score at baseline may be used to objectively identify those that would benefit the most from HIV prevention methods, such as PrEP.

PrEP persistence (tenofovir levels in DBS)

PrEP persistence, measured using DBS to detect the presence of TFV-DP, was only examined among a systematic subset of women who reported PrEP use in the last 30 days. The proportion of those with quantifiable TFV-DP concentration levels was low (49% at 3 months and 20% at 6 months). Due to this finding, a limitation of our study was that this may be under- or overreporting the true proportion of women taking oral PrEP. However, similar to prior studies, we measured the quantifiable vs. unquantifiable TFV-DP concentration levels in our analysis since the number of AGYW with high TFV-DP concentration levels, consistent with ~7 doses per week, was small (6% at 3 months and 1% at 6 months) (17). We remain concerned that the tenofovir concentration levels in our sample were low and inadequate for ample HIV protection even among those reporting recent PrEP use. A strength of our analysis was using a biomarker (i.e., TFV-DP levels in the blood) to measure persistence over self-reported adherence, which correlated poorly with each other in our previous study (22).

Adherence challenges among pregnant/postpartum AGYW

Qualitative assessments among AGYW have described that PrEP persistence is difficult with dwindling motivations for taking a preventative pill while being healthy, citing the daily pill

burden (size and frequency) (21, 39, 40) and stigma with taking the pill (19, 39, 40). Meanwhile, others indicated the benefits of PrEP, citing that they feel safer while on the pill especially with changing risks (39). 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 (21). Prior literature has indicated that PrEP adherence may be less among pregnant women due to pregnancy itself and waning could occur during the postpartum periods (22), which was also observed among the AGYW in our study.

We also recognized that evaluating prevention-effective adherence, which aligns changing HIV risk with PrEP adherence levels, is important in PrEP studies (17, 41, 42). Studies have reported that women, including AGYW, may already be starting and stopping PrEP with changing risks (16). Approximately 6% of the AGYW in our study stopped and restarted PrEP at 6 months, and most (80%) of them were postpartum women. However, we were unable to examine changing sexual risks because those who discontinued PrEP use also missed attending follow-up study visits. Therefore, we were unable to obtain the changing HIV risk information among those who discontinued participating in the study. 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 (vs. abstinence) by gestational weeks and examine prevention-effective adherence to PrEP by gestational timing. Future interventions could include concepts such as community PrEP delivery in pharmacies or community pick-up points for postpartum women, biofeedback using accurate reflections of PrEP use to align with changing sexual risks (using urine or other tenofovir testing), and peer support models for PrEP. Moreover, implementing the long-acting injectable PrEP (cabotegravir) may improve HIV protection for pregnant/postpartum AGYW. Studies have reported that pregnant and postpartum women who have used oral PrEP showed a theoretical preference for long-acting injectable PrEP (43), and this finding may help address notable barriers to sufficient HIV protection due to adherence challenges (44). Future trials on long-acting injectable PrEP should include pregnant/postpartum populations and AGYW so that cabotegravir can be widely implemented among those at high risk of acquiring HIV.

Limitations

Our study has a few limitations. First, we analyzed a non-random sample of TFV-DP measures among the first 900 participants (when the study budget was available) of the cohort who reported using PrEP in the last 30 days. Thus, for those who reported using PrEP, but did not have their DBS analyzed later in the study, we marked their adherence levels as unknown/missing. Second, the low adherence to PrEP among AGYW could be due to the changing HIV risks. Since many of the AGYW are visiting the clinic closer to their delivery date, they may not be sexually active during their late pregnancy or early postpartum period. We were unable to examine the changing HIV risks due to the collinearity between those who discontinued PrEP use and missed attending the study visits. Third, the PrEP-PP study data were collected from one urban ANC clinic in Cape Town, South Africa, which may not be generalizable to other geographical regions or populations. Fourth, given that the surveys were administered by study staff at a health clinic on sensitive information such as sexual behaviors, intimate partner violence, and alcohol use among AGYW, errors might be reported due to social desirability bias. However, we used the biomarkers when feasible, such as STI diagnosis at baseline and DBS, to measure the TFV-DP concentration levels.

Conclusion

Using the PrEP cascade for pregnant and postpartum AGYW accessing ANC in South Africa, we found a high percentage of PrEP initiation but retained just over 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 20%–49% had detectable TFV-DP concentration levels, which means that PrEP coverage remained inadequate for ample HIV protection. Moreover, pregnant AGYW initiated ANC visits much later, with a high burden of untreated STIs. These findings suggest the existence of key barriers in HIV prevention methods for AGYW during pregnancy and postpartum periods. Based on our findings, we recommend integrating HIV and PrEP counseling, including longer-acting treatments when they become available, into ante- and postpartum care and community delivery to de-medicalize and simplify PrEP delivery among pregnant and breastfeeding women.

Data availability statement

The data sets presented in this article are not readily available. Requests to access the data sets should be directed to DJosephDavey@mednet.ucla.edu.

Ethics statement

The studies involving humans were approved by The Human Research Ethics Committee at the University of Cape Town (#297/2018) and by the Institutional Review Board at the University of California, Los Angeles (IRB#18-001622). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the study is no more than minimal risk; and the nature of the research is acceptable to the Committee, parents or legal guardians, or the community at large. Our study was approved by the HREC, and AGYW PrEP is actively being rolled out in South Africa. In particular, we note that HREC has approved

projects to use PrEP in adolescent girls aged 16–17 years without parental consent in this area (see HREC REF: 567/2016).

Author contributions

NK and DJ contributed to the conception and design of the study. NK, RM, NM, and DJ contributed to the data collection and cleaning. NK and RM performed the statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1224474/full#supplementary-material

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Implementation determinants and strategies in integration of PrEP into maternal and child health and family planning services: experiences of frontline healthcare workers in Kenya

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Background: Delivery of PrEP to adolescent girls and young women (AGYW) and to pregnant women through maternal and child health (MCH) and family planning (FP) clinics is scaling up in Kenya. Evaluation of implementation challenges and strategies is critical to optimize delivery.

Methods: We conducted focus group discussions (FGDs) with healthcare workers (HCWs) in MCH and FP clinics offering PrEP in a large implementation project in Kisumu, Kenya. Discussion guides were based on the Consolidated Framework for Implementation Research (CFIR). FGDs were audio recorded and transcribed. Directed content analysis was used to identify implementation challenges and strategies to overcome them.

Results: Fifty HCWs from 26 facilities participated in 8 FGDs. HCWs believed PrEP integration was appropriate because it met the needs of AGYW and pregnant women by providing a female-controlled prevention strategy and aligned with policy priorities of elimination of vertical HIV transmission. They were universally accepting of PrEP provision, especially through MCH clinics, noting the relative advantage of this approach because it: (1) enabled high coverage, (2) harmonized PrEP and MCH visits, and (3) minimized stigma compared to PrEP offered through HIV care clinics. However, HCWs noted implementation challenges affecting feasibility and adoption including: (1) increased workload and documentation burden amid workforce shortages, (2) insufficient health care worker knowledge (3) multiple implementing partners with competing priorities (4) drug and documentation form stockouts. HCWs employed various implementation strategies to overcome challenges, including task shifting from nurses to HIV testing providers, patient flow modifications (e.g., fast-tracking PrEP clients to reduce wait times), PrEP demand generation and myth clarification during health talks, provider education, dedicated PrEP delivery rooms, and coordination with adolescent-friendly services. Additional suggested strategies to improve PrEP integration included community education to increase broader PrEP awareness and enable shorter counseling sessions, and task-shifting data entry and client risk assessments.

Conclusions: HCWs were enthusiastic about the appropriateness and acceptability of integrating PrEP services into MCH and FP clinics but noted challenges to adoption and feasibility. Strategies to address challenges focused on improving provider time and space constraints, and increasing provider and client knowledge.

KEYWORDS

pre-exposure prophylaxis (PrEP), pregnancy, postpartum, adolescent girls and young women (AGYW), implementation science, consolidated framework for implementation research (CFIR), implementation strategies

Introduction

There has been continued progress in decreasing HIV incidence in sub-Saharan Africa over the past decade as a result of expanded treatment and increased use of pre-exposure prophylaxis (PrEP) (1–3). Despite these successes, there is still room for improvement, particularly in preventing HIV acquisition among adolescent girls and young women (AGYW) and eliminating vertical transmission. A disproportionate number of HIV infections in sub-Saharan Africa are occurring among AGYW—with an estimated 4,200 AGYW acquiring HIV each week in 2020 (4). An increasing proportion of vertical transmissions occur as a result of acute maternal HIV acquisition during pregnancy or lactation (5, 6).

PrEP is highly effective as a woman-controlled HIV prevention option (7), and is safe for use during pregnancy and breastfeeding (8–10). PrEP is recommended for populations with substantial risk of HIV acquisition, including AGYW and pregnant and postpartum people, by the Kenyan Ministry of Health and the World Health Organization (2, 11). Despite the benefits of PrEP and guidelines supporting PrEP use in these populations, major challenges remain at the individual, provider, and systems-level for ensuring PrEP is accessed, taken up, and appropriately continued by AGYW and pregnant/postpartum people most at risk of acquiring HIV (12, 13).

Utilizing existing clinical structures to reach pregnant people and AGYW may substantially expand PrEP uptake and adherence and reduce HIV acquisition in these populations. Delivering PrEP through integration with existing services such as Maternal Child Health (MCH) clinics and Family Planning (FP) clinics is promising (14–16). However, challenges to implementation and integration at the facility level exist (13, 17) and evaluation of implementation challenges and strategies within health systems are critical to inform future scale-up (17, 18). Specifically, understanding how best to approach integrating PrEP into busy clinics while ensuring appropriate HIV testing, adequate pre-initiation and adherence counseling, and minimizing impact on other critical clinic functions is essential to the success of PrEP programs in MCH and FP clinics (17).

We completed a large demonstration project, the PrEP Implementation for Young Women and Adolescents (PrIYA) project, which provided real-world programmatic delivery of PrEP via 37 MCH and FP clinics in Kisumu County, Kenya (15, 16). The PrIYA project screened >20,000 girls and women ≥15 years of age for HIV risk and offered PrEP counseling to all women, regardless of HIV risk. As part of a broad evaluation of this project, numerous barriers to PrEP uptake and continuation were identified. Community advisory board members noted community-level misconceptions that PrEP will make AGYW promiscuous, conflating PrEP with HIV treatment, and stigma and fear felt by AGYW accessing PrEP outside of a youth-friendly space (19). AGYW described misinformation related to cost, dosing, and focus populations for PrEP, misconceptions that were more pronounced among those receiving information from community outreach campaigns (20). AGYW also described fearing partner reactions and fearing that PrEP interfered with either contraception or fertility as barriers to using PrEP, even when at higher risk of HIV acquisition (21). In this specific study, we explored HCW perspectives on barriers to PrEP delivery and strategies for overcoming those barriers that can be empirically tested in future studies as programs seek to integrate PrEP into existing clinical services.

Methods

Study design

We conducted focus group discussions (FGD) with healthcare workers (HCWs) from MCH and FP clinics who offered PrEP as part of the PrIYA project. Within the PrIYA project, integrated delivery of PrEP included: integrated PrEP screening and counseling and integrated PrEP medication dispensing within the MCH or FP clinic. Between October and December 2018, eight FGDs were conducted with 50 purposively recruited HCWs experienced with PrEP delivery through the PrIYA project. Participants were recruited through study staff and in collaboration with facility leadership and were informed that their decision to participate in the FGDs would not impact their job. Half of the FGDs (27 HCWs) were conducted with PrIYA staff. PrIYA staff were full-time PrIYA employees who were tasked with working with diverse clinics to build sustainable systems for PrEP delivery within clinics and were responsible for PrEP delivery and implementation at 16 PrIYA project sites. The other FGDs (23 HCWs) were conducted with routine clinic staff working at the 21 newly expanded PrIYA-mentorship sites. These HCWs were full-time employees of the clinic who were trained by PrIYA team members to add PrEP delivery to their existing clinic activities. PrIYA project sites and PrIYA-mentorship sites were selected in collaboration with the Kisumu County Department of Health to maximize patient volumes and geographic locations.

Ethical review

This study was reviewed and approved by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee and the University of Washington Institutional Review Board. Participants provided written informed consent for participation in focus group discussions.

Data collection

Semi-structured topic guides were developed based on the Consolidated Framework for Implementation Research (CFIR), a flexible, meta-theoretical framework used to describe heterogeneity in implementation across settings, as well as the relative effect of key determinants in influencing implementation outcomes (22). FGDs explored determinants of early implementation acceptability, appropriateness feasibility, and adoption, and strategies that facilitated improved implementation. FGDs were conducted in English by two female Kenyan social scientists (MA, WO) who did not have prior relationships with the participants. One of five note takers (4 female, 1 male) was also present at all FGDs. FGD facilitators and note takers were trained on the goals of the study, the clinical effectiveness of PrEP, and the importance of maintaining participant confidentiality and neutrality. Participants were apprised of the purpose of the research through the consent form. FGDs were conducted, and audio recorded, in a quiet, confidential setting and lasted an average of 104 min. Facilitators wrote detailed FGD debrief memos (23), and transcription was ongoing throughout data collection.

Data analysis

Directed content analysis (24) was used to identify the main CFIR constructs influencing HCW beliefs about PrEP delivery through MCH/FP clinics. All transcripts were coded using an iteratively developed codebook. The codebook was developed using a deductive approach, based on CFIR domains and constructs, and an inductive approach to identify implementation strategies. The coding team (KBS, ADW, GO) included qualitative and implementation science researchers with >10 years of experience working in HIV prevention in Kenya. Discussion by the coding team helped operationalize the CFIR constructs into codes and focused primarily on constructs within the CFIR inner setting, intervention characteristics, and process domains. Using open coding, an additional set of codes were developed to capture specific strategies used or identified to improve PrEP delivery, including strategies related to integration, logistics, education, counseling, uptake, adherence, and task shifting.

Dedoose was used to support data management and analysis (Dedoose version 7.0.23, Los Angeles, CA, USA: Sociocultural Research Consultants, LLC). Members of the coding team (KBS, ADW, GO) independently coded one-third of the transcripts using the final version of the codebook. Code application and text segmentation was then reviewed by a second member of the team and any disagreements were noted and resolved through group discussion. The team synthesized the coded data to identify key themes related to factors impacting PrEP implementation in MCH/FP clinics, as well as recommended strategies for improving PrEP implementation in these settings. The FGD facilitators were involved in the development of this manuscript to ensure findings reflect participant experiences shared during FGDs.

Results

Fifty HCWs from 26 facilities participated in 8 FGDs. Demographics have been previously reported (25). The majority (72%) were female, and the median age was 28 (IQR: 26–32). HCWs were primarily nurses (56%), clinical officers (16%), and nurse counselors (12%). HCWs had a median of 13 months' experience providing PrEP (IQR: 10–18) and 92% had received additional training on providing PrEP specifically to AGYW. PrIYA staff reported an average of 3 months more experience providing PrEP to AGYW when compared to HCWs from PrIYA mentorship sites. Overall, participants were enthusiastic about PrEP provision for AGYW and pregnant women via FP and MCH clinics, finding this integration strategy to be acceptable and appropriate. Despite high enthusiasm, HCWs described specific challenges to integration that limited feasibility and adoption. HCWs were able to overcome many barriers to PrEP integration through adapting delivery strategies to optimize implementation in their respective clinics. Grounded in the CFIR, we identified key determinants influencing HCW perceptions of acceptability, adoption, appropriateness, and feasibility, and potential implementation strategies for future integration (**Figure 1**).

PrEP delivery through MCH/FP clinics addresses policy priorities, is easily adaptable, meets patient needs, and provides a relative advantage over existing delivery strategies (outer setting and intervention characteristics)

HCWs felt PrEP delivery through MCH/FP clinics aligned with policy priorities of elimination of mother-to-child HIV transmission, policy priorities to reduce HIV acquisition among young women, and their larger overarching mission (as HCWs) of providing high quality services to patients, relating to the outer setting domain.

> *"One thing we have agreed is that introduction of PrEP at the MCH/FP has had more advantages than disadvantages, so it is upon us as the health workers who are at those various stations to carry on because the reason as to why we are here*

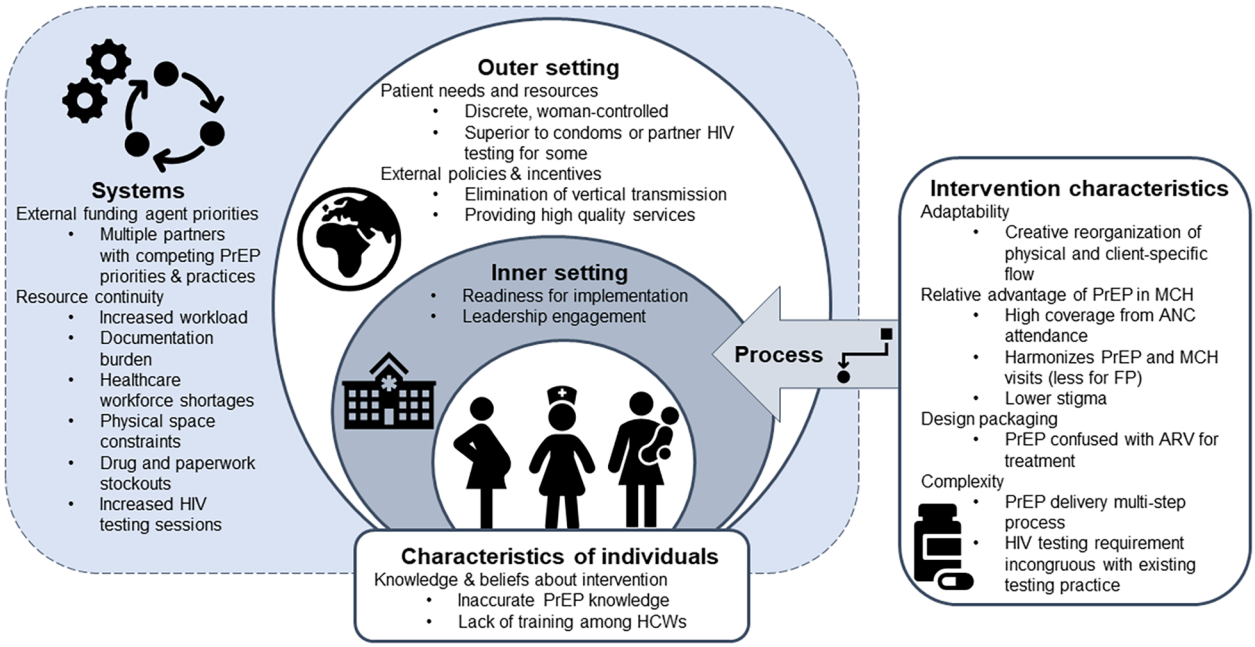

FIGURE 1
Overview of CFIR determinants affecting HCW perceptions of the acceptability, adoption, appropriateness and feasibility of delivering PrEP within MCH and FP services.

> *is to give quality service to our clients and all of us want to help in reduction of HIV prevalence in our country, so it is upon us to change our attitude and maybe not to wait for support supervision (laughter).....it is upon us to embrace the new intervention that has come and give good services to our clients"*—29 year-old male, Mentorship clinic

HCWs found PrEP delivery to be acceptable because it could be easily adapted and optimized within their clinic setting, relating to the intervention characteristics domain. Facility-specific adaptations identified by HCWs included determining the best way to integrate PrEP into the physical- and client-specific flows in that facility.

> *"We had the plan… but when we reached the facility we had to deliver PrEP according to the flow of how the facility works because not all facilities are the same, so we had to work with what we found in the facility…"*—45 year-old female, PrIYA nurse

Finally, HCWs universally believed that oral PrEP was appropriate because it met the needs of AGYW by providing a discrete, female-controlled prevention strategy, relating to the outer setting domain. HCWs were enthusiastic about PrEP provision to AGYW and pregnant women through MCH and FP clinics as it allowed them to accommodate the complex reproductive health counseling needs of AGYW patients. They frequently referenced MCH delivery as advantageous because it enabled high coverage, harmonized PrEP and MCH visits, and lowered stigma compared to PrEP offered through HIV care clinics. FP clinic provision was viewed as slightly less advantageous, because FP visits did not sync as well as with PrEP delivery visits, but still provided an access point with lowered stigma when compared to HIV care clinics.

> *"These are women, adolescents and women of reproductive age. MCH will offer all those services that they need– family planning, child immunization, ANC (antenatal care) and all those things so they just come and they do all those things at one go."*—24 year-old female, Mentorship clinic

> *"(O)ne of the advantages I see myself through delivery of PREP through MCH is that there is no stigma associated with clients. When (they) go to the MCH they are very comfortable going there, they do not have any issues."*—27 year-old female, PrIYA nurse

Importantly, although PrEP integration into MCH and FP clinics addressed many patient needs and had lower stigma than HIV care clinics, HIV stigma surrounding PrEP remained for some PrEP clients and confusion around PrEP as being an antiretroviral created challenges to PrEP retention and adherence, relating to the intervention characteristics domain. For example, HCWs noted one of the biggest challenges to initial uptake by women was related to the design quality and packaging. At the time of the study, PrEP was in an identical bottle to Truvada medication for HIV treatment, which led to confusion about why someone not living with HIV would take an antiretroviral (ARV), and fear of reactions by others who would assume the woman was living with HIV if she was seen with PrEP pills.

These fears also affected retention and adherence among those who initially accepted.

> *"…there are people who started PrEP but because they (heard), 'hey! That drug is ARVs, used by people who are HIV positive,' now they will stop at some point and now they will not come to the facility and probably they are not even at the facility that we serve."—25 year-old female, PrIYA nurse*

The biggest challenges to PrEP integration centered on readiness for implementation, especially available resources and intervention complexity

Despite noted advantages, integrating PrEP into MCH/FP clinics was not without challenges, particularly around integrating the requirements of PrEP delivery within already busy clinical settings. HCWs noted early phase implementation challenges affecting adoption, that mirror implementation of many new programs, including: (1) increased workload (including time for documentation, counseling, running lab tests) relating to the systems domain (2) lack of HCW knowledge and training, relating to the characteristics of individuals domain (3) multiple implementing partners with different PrEP priorities at the same site, relating to the systems domain and (4) drug and paperwork (e.g., paper registries and PrEP clinical monitoring tools) stockouts, relating to the systems domain.

Although enthusiastic, HCWs acknowledged that PrEP is a more complex intervention than most other HIV prevention options. As noted above, PrEP initiation requires clinical assessments, counseling, laboratory testing, side effect monitoring, and regular HIV testing, which results in increased time with clients, HCW workload, and training requirements for staff compared to other combination prevention strategies.

> *"Providing PrEP is actually more technical than those other HIV preventing measures, because you need a lot of time… unlike other preventive measures, (like) condoms, you could only give (it) out to those who do not know (have experience) and being that it is something new, it takes a lot of time for a client to understand what you are talking about."*—24 year-old female, PrIYA nurse

Understanding documentation and staffing requirements to implement PrEP in MCH and FP presented substantial barriers to early adoption and perceptions of feasibility of integrated PrEP delivery. HCWs struggled with staffing shortages, reporting that they were often "*only two nurses within the MCH/FP, and you are not there to offer PrEP only, you also offer other services so the workload sometimes becomes much" (28-year old male, PrIYA nurse),* or they were required to rotate through other departments while trying to keep up with their PrEP delivery responsibilities. Similarly, documentation presented a large burden in the beginning, and participants described challenges figuring out how to navigate the multiple PrEP-specific tracking documents.

> *"There was a challenge because people were like, now we have been added more work and then the daily activity register was introduced… then there is PrEP register at the end of the month, nearly three reporting tools…"*—28 year-old female, Mentorship site

Sometimes this required harmonization across PrEP documentation in multiple locations or going to another clinic to complete their PrEP documentation. However, with time, experience, and improved efficiency with PrEP implementation, despite these initial challenges, HCWs reported "*later on we came to realize that the work actually is very minimal* (28 year-old female, Mentorship site)".

The requirements for additional HIV testing caused confusion among facility staff who had not been sensitized on PrEP delivery. HCWs reported challenges with facility HIV testing services (HTS) counselors who were not aware of the repeat HIV testing requirements and would "*send her back (saying) that no, the client is not yet due for retest" (32-year old female, PrIYA nurse).* HCWs also noted the challenges of delivering PrEP in MCH clinics when there were competing priorities from implementing partners, NGOs, and the Ministry of Health. They described added responsibilities without added staffing to provide services.

> *"…we have so many NGOs bringing in a lot of activities in the MCH, so we would find (partner 1), brought (project 1) they have something they are bringing, (partner 2) want(s) to bring their own (project 2), so we had like very…very many things to do at a time and we were just here nursing. They bring the activities but they don't bring their nurses, we are the ones to incorporate everything and we still had our things to do, so I think that was also a challenge."*—26 year-old female, PrIYA nurse

In addition to available workforce, competing priorities and time, HCWs reported other challenges that limited feasibility, including procuring physical supplies, which was noted as being critical to ensuring facility buy-in and early support of PrEP delivery. National HIV guidelines for PrEP delivery recommend, but do not require, laboratory testing including creatinine clearance and Hepatitis B surface antigen tests when available. Ensuring facilities had adequate supply resources—including lab testing supplies, PrEP commodities, and PrEP documentation—was important for ensuring facility support of PrEP integration.

> *"…I know that currently there are issues with PrEP drugs (stockouts), like we were instructed not to initiate new clients and just to maintain those who are already on PrEP…, this client is still at risk (and) has come for PrEP as a new client, will you give or will you not give and if you fail to give and it happens that this client seroconverts… PrEP stock is a big thing that they need to do, yes."*—28 year-old male, Mentorship clinic

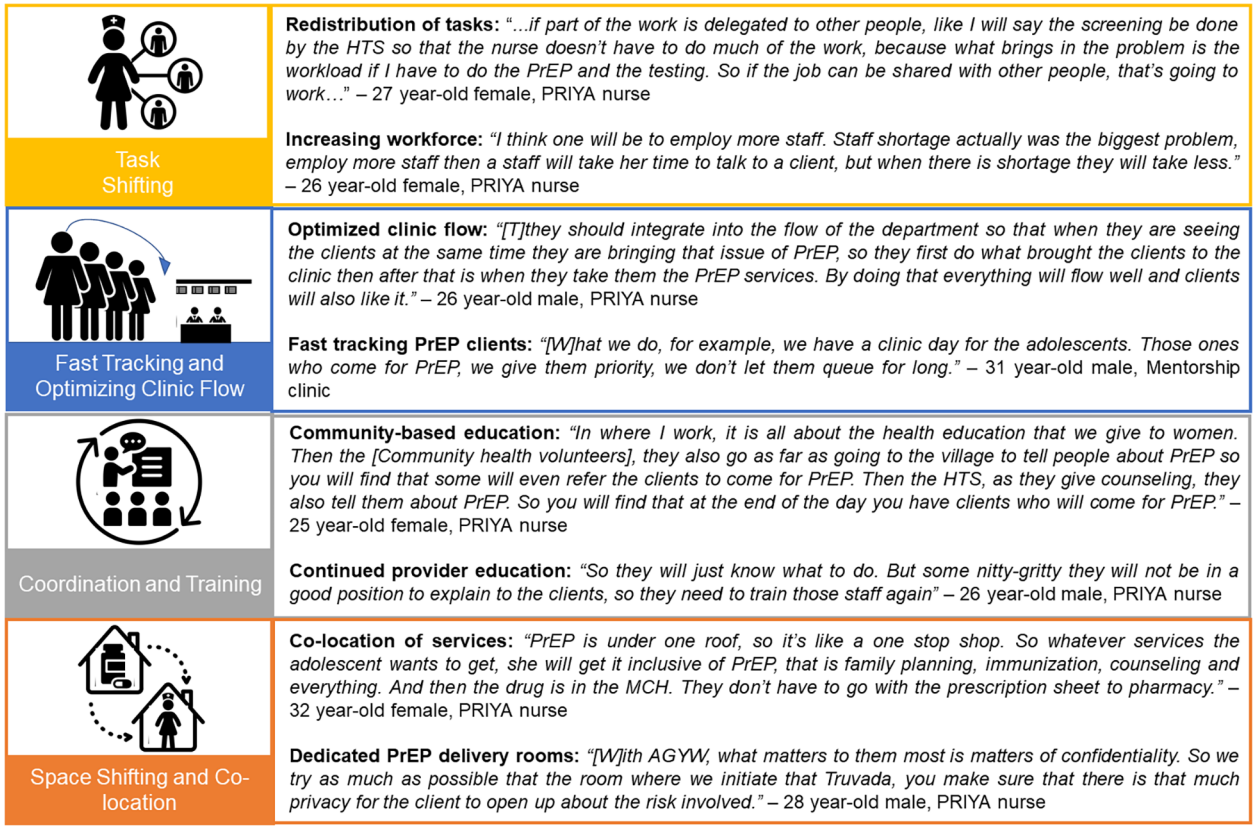

FIGURE 2
HCW identified strategies to integrated PrEP delivery.

Implementation facilitators and strategies that supported successful integration and high PrEP uptake included leadership engagement, open communication, and clinic flow optimization

Engagement with facility leadership was essential for overcoming challenges to PrEP adoption and feasibility, relating to the inner setting domain. In particular, the facility in-charge was critical in addressing and overcoming many of the early challenges to early adoption of PrEP including, space requirements for PrEP delivery, navigating conflicts between Ministry of Health staff, other partner organizations, and the PrIYA nurses, supporting PrIYA nurses in the case of supply challenges, and leading the integration of PrEP into facility activities as more than an external program.

> *"In my facility we have worked as a team, and the team include (d) the MOH, (implementing partner) and us… we get our supplies from (implementing partner) pharmacy and we have never run out of stock, the matron in-charge at that time made work very easy for us."*- 26 year-old male, PrIYA nurse

In addition to facility leadership, engagement and buy in from all cadres of facility staff was critical to ensuring smooth PrEP delivery in the facilities. Facility staff supported PrEP delivery through sharing responsibilities, educating clients on HIV prevention and PrEP, and sharing physical spaces as needed.

> *"Our lead was really consulting with the HTS lead in our facility and I remember there was this one particular day we lacked the questionnaire and he said just give me one I go and do the photocopy. So he was really in the forefront just to make sure we are doing the screening…"*—43 year-old female, Mentorship clinic

In addition to engaging leadership, HCWs employed multiple implementation strategies, including: (1) task shifting, (2) fast-tracking and optimizing visit flow, (3) coordination and training of providers and clients in facilities and communities, and (4) space shifting and co-location (Figure 2). HCWs identified and organically tested a wide range of strategies, motivated to find context-specific solutions to deliver quality services.

> *"(W)e, from different facilities, had to find something that would work in wherever we were working, because at the end of the day what will work for this facility might not work for the other, and*

> *we had to come up with ways to make PrEP delivery better for the future generation."*—24 year-old female, PrIYA nurse

Strategy category 1: task shifting

Given the added time burden and complexity of PrEP delivery, some facilities identified ways to redistribute the added tasks of PrEP delivery across multiple HCW cadres. Through the flexible approach for PrEP delivery taken through the PrIYA project, each facility identified an optimal flow for clients in their clinic. Many facilities realized that HCWs working in HTS, in particular HIV testing counselors, were well equipped to conduct the HIV testing and HIV risk reduction counseling required for PrEP delivery.

> "*(S)ome of the work was delegated to other departments like the HIV testing, and the (risk assessment) was relocated to the HTS to make the work of the nurse easier*"—27 year-old female, PrIYA nurse

Some providers described how increased patient volumes and amount of service time needed by PrEP clients could decrease the quality of information delivered, suggesting that task shifting could preserve quality of care. Specific suggested shifts included shifting screening, risk assessment, and counseling from nurses to HTS providers.

Strategy category 2: fast tracking and optimizing clinic flow

With multiple steps involved in PrEP delivery, some facilities described ways in which they modified clinic visit flow, integrating PrEP delivery into the cadence of visits both physically and conversationally. For example, since PrEP clients need to receive multiple sequential services within an already long MCH visit, providers recommended fast tracking or prioritization of PrEP clients within queues to save time, including at the laboratory or pharmacy.

> *"At some point we give these clients first priority in terms of services and queue because they have extra services which is PrEP that they came for so if a client come for ANC then we'll first prioritize on those who take PrEP."*—26 year-old male, PrIYA nurse

HCWs also discussed optimizing PrEP visits by offering differentiated services to individuals with good PrEP adherence, including longer intervals between appointments and multi-month drug dispensing to better align with mother and infant services. In order to address documentation challenges, HCWs suggested assessing data sources for overlap, removing individual cards for HIV risk assessment or PrEP provision and instead relying on large multi-patient registers. Finally, some HCWs highlighted multiple competing copies of the same register housed at different clinics within the same facility, suggesting having either one master copy per facility or revised record numbering systems.

Strategy category 3: coordination and training

The complexity, for example the HIV testing requirements, and novelty of the PrEP intervention required initial education and sensitization of all facility staff in order to ensure their buy-in and support.

> *"…as a facility we hold a meeting where all the health care providers at the facility, including everybody. We disseminated the same message to them. Then now we decided when to start with everybody having the knowledge of PrEP."*—48 year-old female, Mentorship clinic

Developing strategies to train and retrain facility staff about PrEP was critical for ensuring clients were receiving accurate PrEP information and willing to come to the facility to access PrEP. For HCWs in the facility, ensuring they had information about PrEP in pregnancy, including "*adequate information, adequate (understanding of biology) of PrEP in relationship to pregnancy and the rest" (28 year-old female, PrIYA nurse)* was essential. Some pointed to the need to retrain providers to maintain a high level of technical competence. In addition to increasing technical knowledge, providers described broadly inclusive trainings as a way to increase provider buy-in for PrEP implementation.

> *"Yes, most of the staff they accepted it because before it was rolled out the CME (continuing medical education meeting) that was conducted and the sensitization, almost all staff were involved so no one was left behind… they were aware about it, so we didn't force some resistance."*—28 year-old male, Mentorship clinic

HCWs also highlighted their important role of providing facility-based education for clients, often focused on myth-busting or providing factual information related to PrEP.

> *"The myths on providing PrEP initially was too much, so you had to deal with the myths, you had to deal with the facts and then clients were so curious to know even if I myself was using PrEP, like why are you giving us PrEP, are you using it?"*—27 year-old female, PrIYA nurse

Beyond facility-based client education, HCWs pointed to the importance of multiple educational touch points from community to the facility; the purpose ranged from generating demand to introducing PrEP to providing specific details to facilitate decision-making. HCWs also noted the importance of peer education and peer leads to facilitate PrEP-related communication with adolescents.

Strategy category 4: space shifting and co-location

HCWs highlighted the importance of a dedicated PrEP delivery room within the MCH and FP clinics, which provided privacy, confidentiality, and minimized disruptions to other

service areas. In addition, nearly all HCWs were in favor of co-locating PrEP delivery and dispensing activities within the MCH and FP clinics, rather than referring clients to HIV care clinics or sending them to fill prescriptions at a separate pharmacy building. One HCW described the ease that co-location provided for all.

> *"…it is very easy to give PrEP at MCH because everything is integrated, so it will give the client and even the clinicians and the patient an easier time."*—28 year-old female, Mentorship clinic

While some HCWs noted that there were logistical and coordination challenges in implementing co-location, especially dispensing medication outside of a pharmacy, co-location was generally felt to be worthwhile.

Discussion

HCWs with experience delivering PrEP in MCH and FP clinics to AGYW and pregnant populations were enthusiastic about the acceptability and appropriateness of PrEP service integration but noted challenges to adoption and feasibility. Integration offered the benefits of leveraging high attendance at antenatal care services, a harmonized visit schedule between PrEP provision and antenatal care, less stigma from receiving care outside HIV care clinics, and alignment with policy priorities. Affecting perceived feasibility and adoption, HCWs felt integration increased workload and was affected by healthcare workforce shortages, physical space constraints, stockouts, multiple implementing partners with different priorities, complexity of PrEP-specific steps, and inaccurate PrEP knowledge or lack of training among HCWs. HCWs suggested strategies to improve PrEP integration within MCH/FP clinics, including task-shifting client risk assessments and other elements of visits including documentation, fast tracking at different areas, shifting the use of spaces for PrEP specific service delivery, and alternative communication tools and approaches for facility- and community-based education.

A 2020 systematic review of completed, ongoing, and planned implementation science studies, focused on PrEP delivery to pregnant and postpartum populations, noted several barriers at the levels of inner and outer setting, in addition to workload challenges (17). Noted determinants of adoption included whether guidelines specifically endorsed PrEP for pregnant populations, related to the outer setting. Determinants of implementation or fidelity included stockouts and provider knowledge, related to the inner setting. These results are similar to determinants identified in the present qualitative study. While there are numerous studies in the systematic review that assessed determinants of individual-level maintenance (e.g., demographic characteristics), or PrEP persistence, there were none that assessed determinants of sustained delivery at a clinic or provider level. A recent Kenyan study highlighted presence and gaps in availability of commodities and resources, identifying infrequent gaps in HIV and PrEP commodities (26). In the Kenyan context where the present study took place, the costs of PrEP drugs and lab tests are covered for patients in public health clinics.

Concerns have been raised by HCW in Zambian, Malawian, and Kenyan studies about the time constraints and workload associated with integrating PrEP services into MCH and FP (25, 27, 28). Indeed, PrEP related activities in PrIYA added 13 min (among PrEP non-initiators) and 18 min (among PrEP initiators) to their MCH/FP visits (13), representing additional service time that would be challenging to deliver by existing already overstretched HCW. However, integrating PrEP services into MCH and FP clinics has been successful in demonstration projects and in implementation studies, particularly those with additional staff provided. For example, in PrIYA uptake was 22% among pregnant and postpartum women and other AGYW (15, 16). In the PrIMA trial, which also involved additional staff support, PrEP acceptance was 18.6% among pregnant and postpartum women (29). In contrast, PrEP uptake was substantially lower in the PrEPARE implementation science study focused on MCH, which did not provide additional staff, at 3.9% among those offered PrEP (30) (*Sila & Wagner, under revision*). Similarly, after PrIYA staff departed, uptake of PrEP in FP clinics decreased to 4% (31). These four studies took place in Kenya; a systematic review noted that Kenya has been a leader in implementation research related to PrEP for pregnant and postpartum populations (17), with fewer studies planned or ongoing that measure uptake of PrEP outside of a trial setting. A study in South Africa observed substantially higher uptake of PrEP at 84% within a trial setting with additional staff; however, it was not possible to assess pre-trial enrollment attrition to determine whether the trial enrolled a population of women more likely to accept PrEP (32). A Ugandan cohort assessing pre-conception PrEP use among predominantly sero-different couples with fertility intention observed high PrEP uptake at 90%, but did not assess uptake during pregnancy (33). Future studies should consider how staffing ratios impact not only PrEP uptake, but also upstream steps of PrEP screening, counseling, and offer within busy MCH/FP clinics and test strategies to improve service provision reach broadly without adding new HCW. While time burden is one barrier to integrated PrEP delivery, provider training and knowledge, as well as retention, may be additional drivers of differential delivery.

Other studies have tested additional strategies to address a range of barriers similar to those we observed among HCWs in our study. One study utilized standardized patient actors to address lack of effective provider training and found that the training was associated with significantly improved counseling quality (34). The PrIMA study tested risk-guided versus universal offer of PrEP to assess whether a simplified PrEP offer was sufficient within routine practice to alleviate the time burden of PrEP-specific risk screening; this trial concluded that universal offer is superior to risk-guided offer due to its simplicity and comparable performance (29). Point-of-care sexually transmitted infection testing was assessed to address

the barrier of low risk perception; this pilot found that PrEP uptake was significantly higher among women who accepted point-of-care sexually transmitted infection testing (35) and point-of-care testing was highly acceptable (36). Flow reorganization, task shifting, and provider training were tested to enhance the efficiency of integrated PrEP delivery within the PrIYA study (13). Within an ongoing South African stepped care trial, enhanced counseling and biofeedback plus rapid PrEP collection using HIV self-testing to expedite visits are being tested to decrease time and enhance continuation (37). Outside the context of pregnancy and postpartum, other studies have assessed the impact of an efficiency-focused "one stop shop" for PrEP delivery in a similar context, finding decreased waiting time, increase acceptability, and no changes in PrEP initiation and continuation (38).

Within the present qualitative study, numerous potential strategies were suggested to address barriers to PrEP delivery within MCH/FP clinics. In the context of limited resources, it is critical to prioritize which implementation strategies to adopt, ideally based on empiric testing. Prioritization methods within implementation science are evolving and being assessed for pragmatic utility (39, 40). Within the PrEPARE implementation science study, which is piloting implementation strategies to improve integrated PrEP delivery in MCH, the strategies identified in the present qualitative study were prioritized by HCWs and other key stakeholders using a series of quantitative surveys and ranking approaches (41). Prioritized strategies that were feasible to implement in the absence of additional staffing were then packaged for testing within MCH clinics in Kenya. Recent results for one implementation strategy package offering video education, HIV self-testing, and co-located PrEP dispensing, demonstrated significant improvements in PrEP screening, PrEP offer, PrEP knowledge, and client satisfaction. However, as mentioned above, PrEP acceptance among women offered PrEP was substantially lower than in the PrIYA study, suggesting that insufficient staffing is a major barrier to offering integrated PrEP (30) (*Sila & Wagner, under revision*). PrEPARE is currently testing two additional bundles of strategies to assess their impact on implementation outcomes for integrated PrEP delivery in MCH clinics in Kenya.

This study has several limitations. Most notably, half of the participants were staff members of a study focused on delivering integrated PrEP. Their roles focused on being ambassadors and implementers of PrEP; they may be more optimistic about the acceptability and feasibility of PrEP delivery and may not typify the usual staffing in public clinics. During the study period, there were substantial changes in the implementing partners who supported service provision, which impacted contracts for non-study staff; it is possible that the reflections from non-study staff reflect recent challenges with donor-imposed priority setting and lack of autonomy. Finally, these data were collected several years ago and the outer setting contextual factors captured during early implementation may differ from modern outer setting contextual factors.

Conclusion

Overall, HCWs with experience delivering integrated PrEP in MCH and FP clinics to pregnant women and AGYW populations found this integration acceptable and appropriate. They highlighted that—for pregnant women—integration takes advantage of high attendance at antenatal care services and can align with visit schedules. For women in MCH and FP, delivery outside of an HIV care clinic was important to reduce stigma. Co-delivery of PrEP and MCH or FP services aligned with policy priorities of eliminating vertical transmission of HIV and providing comprehensive HIV prevention services. HCWs identified a range of barriers related to adoption and feasibility, including HIV testing and human resource shortages, documentation, stockouts, physical space constraints, complexity of PrEP delivery, and gaps in knowledge for providers and clients. Suggested implementation strategies, that improved adoption and perceived feasibility, included task shifting, fast tracking, communication aids and approaches, and shifting physical spaces should be further explored in future studies to better understand when and how to best employ these approaches.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Washington IRB and Kenyatta National Hospital ERC. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

GJ-S, PK, JK, and AW are the principal investigators, they obtained grant funding and supervised protocol development and implementation. KB-S is the project director and led protocol development, implementation, and analysis. KB-S, GOM, and AW designed the qualitative collection tools. MA and WO facilitated the FGDs. KB-S, AW, JD, JN, and GOM were responsible for qualitative coding and analysis. KB-S, AW, JN, and JD wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Clinical trial simulation to evaluate tenofovir disoproxil fumarate/emtricitabine HIV pre-exposure prophylaxis dosing during pregnancy

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Objective: To evaluate upward-adjustment of tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) pre-exposure prophylaxis (PrEP) dosing during pregnancy in order to maintain target plasma concentrations associated with HIV protection.
Design: Population pharmacokinetic (PK) modeling and clinical trial simulation (CTS).
Material and methods: We developed population pharmacokinetic models for TFV and FTC using data from the Partners Demonstration Project and a PK study of TDF/FTC among cisgender women by Coleman et al., and performed an in-silico simulation. Pregnancy-trimester was identified as a significant covariate on apparent clearance in the optimized final model. We simulated 1,000 pregnant individuals starting standard daily oral TDF/FTC (300 mg/200 mg) prior to pregnancy. Upon becoming pregnant, simulated patients were split into two study arms: one continuing standard-dose and the other receiving double standard-dose throughout pregnancy.
Results: Standard-dose trough TFV concentrations were significantly lower in pregnancy compared to pre-pregnancy, with 34.0%, 43.8%, and 65.1% of trough plasma concentrations below the lower bound of expected trough concentrations presumed to be the protective threshold in the 1st, 2nd, and 3rd trimesters, respectively. By comparison, in the simulated double-dose group, 10.7%, 14.4%, and 27.8% of trough concentrations fell below the estimated protective thresholds in the 1st, 2nd, and 3rd trimesters, respectively. The FTC trough plasma concentration during pregnancy was also lower than pre-pregnancy, with 45.2% of the steady-state trough concentrations below the estimated protective trough concentrations of FTC. In the pregnancy-adjusted double-dose group, 24.1% of trough plasma concentrations were lower than protective levels.
Conclusions: Our simulation shows >50% of research participants on standard dosing would have 3rd trimester trough plasma TFV concentrations below levels associated with protection. This simulation provides the quantitative basis for the design of prospective TDF/FTC studies during pregnancy to evaluate the safety and appropriateness of pregnancy-adjusted dosing.

KEYWORDS

pregnancy, pre-exposure prophylaxis, HIV infection, tenofovir, emtricitabine, clinical trial simulation, population pharmacokinetic modeling

Introduction

Pre-exposure prophylaxis (PrEP) is critically important for the prevention of Human Immunodeficiency Virus (HIV) during pregnancy, both for prevention of maternal HIV and secondary perinatal transmission. Oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) is the most commonly used PrEP medication for people with receptive vaginal exposure to HIV and has extensive safety data in pregnancy; however, dosing and efficacy have not been prospectively evaluated in pregnancy. Multiple studies of TDF/FTC during pregnancy both for treatment and prevention of HIV report lower tenofovir (TFV) exposures in the 2nd and 3rd trimesters attributed to pregnancy-related increased volume of distribution and renal clearance (1–16). Similar declines in FTC concentrations are also reported (7–9, 11). The Partners Demonstration Project showed the largest decline during pregnancy compared to non-pregnant women, with 45%–58% reductions in plasma TFV and intraerythrocytic TFV diphosphate (TFV-DP) concentrations from dried blood spots, respectively, compared to non-pregnant women (1). Decreases in peripheral blood mononuclear cell (PBMC) TFV-DP concentrations of up to 49% were also reported (1). Additionally, although plasma TFV concentrations are 20%–25% higher during the first 6 weeks postpartum than in the 3rd trimester, they remain lower than non-pregnant concentrations (4, 5). Lower TFV exposure during pregnancy is of particular concern, as meta-analyses, pooled study analyses, and pharmacometric modeling studies indicate that non-pregnant women already require higher drug concentrations required to achieve high levels of HIV protection in women compared to men (17–21). While plasma and PBMC concentrations of parent drugs (TFV, FTC) and active anabolites (TFV-DP, FTC-TP), respectively, are the same in men and women, drug deposition and TFV-DP concentrations are lower in cervicovaginal tissue as compared to colorectal tissue, which may contribute to the differences in TDF/FTC efficacy between men who have sex with men (MSM) vs. women (22–28).

We hypothesized that without doubling the TDF/FTC dose in pregnancy, substantial losses in HIV protection of 20%–40% would be expected due to moving down the concentration-response curve (17, 18, 29). The objective of the current analysis is to evaluate the effect of pregnancy on the pharmacokinetics (PK) of TDF and FTC in a population pharmacokinetics (popPK) modeling framework using a nonlinear mixed effects approach and to perform a clinical trial simulation to evaluate the appropriateness of a pregnancy-adjusted double TDF/FTC dose. Since the majority of TDF is rapidly converted to TFV after oral absorption, TFV is the primary circulating form of the drug in the plasma (30); thus the modeling and simulation were based on TFV plasma concentrations.

Materials and methods

Study design and study data

This analysis utilized popPK models of TFV and FTC and clinical trial simulation to compare the adequacy of standard TDF/FTC dosing to a pregnancy-adjusted, double TDF/FTC dose to maintain target plasma concentrations associated with HIV protection in the 1st, 2nd and 3rd trimesters of pregnancy. The pregnancy-adjusted double-dose TDF/FTC regimen was selected based on the demonstrated pregnancy-related concentration decreases in both TFV and FTC reported in the PK literature (1–9, 11–13, 15, 16).

We included data from two studies in the popPK modeling: the Partners Demonstration Project and data from the TDF/FTC arm of a phase I, prospective, open-label study conducted in Baltimore, Maryland by Coleman and colleagues (31, 32). The Partners Demonstration Project was a multi-site, randomized, double-blind, placebo-controlled clinical trial conducted in Kenya and Uganda, which included PK data from 116 female participants, including 33 pregnant and postpartum participants who became pregnant while taking TDF/FTC and elected to continue on TDF/FTC. TDF/FTC was provided in a MEMS® container, which records a time-and-date stamp for each container opening as a proxy for medication ingestion. The Coleman study included intensively sampled, steady-state PK data from 12 non-pregnant, pre-menopausal, HIV negative, cisgender women taking TDF/FTC under directly observed therapy (DOT). We chose the Partners Demonstration Project as it sampled the largest published cohort of pregnant and postpartum individuals on TDF/FTC PrEP. We included the Coleman, et al., PK study to supplement the Partners Demonstration Project PK data with intensive PK data under DOT. For both studies, plasma TFV and FTC concentrations were measured using a previously described, validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) assay (27). Lower limits of quantification (LLOQ) for plasma TFV and FTC were 0.31 ng/ml. All plasma drug concentrations were measured by the Clinical Pharmacology Analytical Laboratory at the Johns Hopkins University School of Medicine.

Dataset preparation

We prepared the datasets for modeling by integrating MEMS data on adherence and TFV/FTC concentration data from the Partners Demonstration Project and dosing records from the Coleman et al. study. We used “M3” method articulated by Beal to handle drug concentrations below the limit of quantification (BLQ) in the Partner Demonstration Project. The M3 method accounts for measurements BLQ explicitly without censoring them. Thus, these observations are included in the PK model analysis using an appropriate statistical approach (33).

Modeling and simulation

We conducted the population analysis using NONMEM (version 7.3. ICON Development Solution, USA) with the gfortran compiler interfaced with Perl-speaks-NONMEM (PsN). Dataset preparation and diagnostic plot plotting were carried out using R (4.1.1). The clinical simulation was carried out using mrgsolve package (1.0.8) in R.

Model development

We developed the base model for TFV and FTC using the data from the Coleman et al. study. Based on the published models, we tested one-compartment and two-compartment models with first-order absorption and with or without lag time. After the development of the base model, we simultaneously used data from both the Coleman et al. study and the Partners Demonstration Project study for parameter estimation. For TFV, the exponential between subject variability was supported on first order absorption rate constant (Ka), apparent clearance (CL/F), apparent central (Vc/F) and peripheral volumes (Vp/F), and apparent inter-compartmental clearance (Q/F); For FTC, the exponential between subject variability was supported on Ka, CL/F, Vp/F, and Q/F:

$$P = \mathrm{TVP} \cdot \exp(\eta_p) \quad \eta_p \sim N(0, \omega_P^2)$$

Where the P represents the individual value of the parameter P, the TVP represent the typical value of the parameter P, the η_p denotes the inter-individual variability (IIV) which is assumed to have a normal distribution with mean equals to 0 and variance equals to ω_P^2.

For both TFV and FTC, we used a proportional residual model for the Coleman et al. study and a combined residual model for the Partners Demonstration Project to account for the heterogeneity of two clinical trials:

$$\begin{aligned} C_{ij} = \widehat{C_{ij}} \cdot (1 + \varepsilon_{1ij} \cdot (2 - \mathrm{STUDY}) + \varepsilon_{2ij} \cdot (\mathrm{STUDY} - 1)) \\ + \varepsilon_{3ij} \cdot (\mathrm{STUDY} - 1) \\ \varepsilon_{1ij} \sim N(0, \sigma_1^2), \varepsilon_{2ij} \sim N(0, \sigma_2^2), \text{ and } \varepsilon_{3ij} \sim N(0, \sigma_3^2) \end{aligned}$$

Where the C_{ij} represents the observed concentration of subject i at time j, the $\widehat{C_{ij}}$ represents the predicted concentration, STUDY represents the study number (i.e., 1—Coleman et al. study, 2—Partners Demonstration Project). ε_{1ij} and ε_{2ij} represent the proportional error of data from the Coleman, et al. and the Partners Demonstration Project studies. ε_{3ij} represents the additive error of data from the Partner Demonstration Project.

Covariate evaluation

We tested potential covariates for TFV and FTC parameters, independently, using study number (i.e., 1 or 2 as above), baseline creatinine clearance, and pregnancy status. We treated pregnancy status as a categorical variable using 4 categories (0—non-pregnant, 1—1st trimester, 2—2nd trimester, and 3—3rd trimester). We evaluated different grouping methods on pregnancy data to test if the influence of each trimester could be identified separately. The pregnancy data were grouped as 1st trimester vs. 2nd trimester vs. 3rd trimester, 1st trimester and 2nd trimester vs. 3rd trimester, 1st trimester vs. 2nd trimester and 3rd trimester. Aggregation of all trimesters as a single factor was also tested. To assess covariate relationships, we first visualized the empirical Bayes estimates versus the potential covariates, and then employed stepwise selection method. For the forward selection, a decrease of the OFV more than 3.84 was considered significant for one degree of freedom ($p < 0.05$). For the backward elimination, an increase of OFV more than 6.63 was considered significant for one degree of freedom ($p < 0.01$).

Model evaluation

We evaluated the performance of the final model by the diagnostic plots. This included evaluating the conditional weighted residuals and review of visual predictive checks. Concentrations associated with extreme deviations from the model prediction were assessed individually for physiologic plausibility. If an appropriate explanation of the outlier was not identified, the outlier was removed. A prediction corrected visual predictive check (pcVPC) of the final model showed the 5th, 50th, and 95th predicted percentiles from 1,000 simulated datasets with 128 individuals (12 from the Coleman et al. study and 116 from the Partners Demonstration Project), and generated the observed concentrations of TFV and FTC. The simulated concentrations that were BLQ were truncated to the LLOQ (0.31 ng/ml). We stratified the VPC by study.

Clinical trial simulation

Based on the selected final population pharmacokinetic model, we conducted a clinical trial simulation to evaluate trough concentrations (C_{trough}) of TFV and FTC during pregnancy. We simulated PK profiles of 1,000 cisgender female participants taking standard daily oral 300 mg TDF/200 mg FTC prior to pregnancy. Upon becoming pregnant, simulated participants were split into two arms: arm 1 ($n = 500$) continuing the standard dose regimen and arm 2 ($n = 500$) receiving a pregnancy-adjusted, double-dose of both TFV and FTC. We assumed an increase in renal clearance due to pregnancy beginning in the 1st trimester. Simulated trough plasma concentrations of TFV and FTC were compared with the lower bound of expected trough concentration benchmarks, estimated to be the protective thresholds associated with daily dosing estimated from HPTN 066, 35.5 ng/ml for TFV and 49.1 ng/ml for FTC (28).

Results

The final dataset included data from 128 women (12 from the Coleman, et al., study and 116 from the Partners Demonstration Project; see Table 1). Data included 33 pregnant women, of whom, 29, 24, and 23 women contributed data from their 1st, 2nd, and 3rd trimesters, respectively. For TFV, there are 39 (6 BLQ) samples in the 1st trimester, 59 (14 BLQ) samples in the 2nd trimester, and 62 (20 BLQ) samples in the 3rd trimester. For FTC, there are 37 (9 BLQ) samples in the 1st trimester, 55 (15 BLQ) samples in the 2nd trimester, and 55 (22 BLQ) samples in the 3rd trimester. Total concentrations available for modeling included 487 TFV and 465 FTC measurements. Upon visual exploration of the final model, outliers were noted in the pcVPC. Further examination revealed four TFV measurements (0.82% of the total measures) and twelve

TABLE 1 Participant demographics from the partners demonstration project and the coleman et al. study.

Parameter	Partners demonstration		Coleman et al.
	Non-pregnant	Pregnant	Non-pregnant
Number of participants	97 (83 with plasma samples)	37 (33 with plasma samples)	12
Race[a]	–	–	9B, 2W, 1A
Ethnicity[a]	–	–	1H
	mean (SD)		median (IQR)
Age	30.6 (7.4)	25.1 (4.8)	34 (28–37)
Weight (kg)	–	–	90 (78–101)
BMI	24.5 (4.3)	24.6 (4.7)	–
CrCl (ml/min)	101.8 (18.4)	111.7 (27.5)	139 (115–172)
iGFR (ml/min/1.73 m^2)			102 (88–114)

[a]Black (B), White (W), Asian (A), Hispanic (H).

FTC measurements (2.6% of total measures) that were physiologically implausible. These were removed from the dataset and the population model re-run. Minor differences were noted for TFV in the CL (51.5 vs. 52.4 L/h) and Vp/F (1,160 L vs. 1,120 L). A larger change was observed in the Vc/F (359 vs. 252 L).

In the FTC population model, CL did not change; however, the central volume of distribution changed from 90.7 to 66.9 L and the peripheral volume of distribution changed from 195 to 166 L.

TFV model

A two-compartment model with first order absorption adequately described the pharmacokinetics of TFV in this population (Table 2); the diagnostic plots and VPCs indicated good agreement between observed and predicted values (Figures 1, 2). Our final model overestimated the TFV trough concentration in the Coleman et al. study, as seen in Figure 2. Inclusion of trimester as a covariate in the apparent clearance significantly reduced the objective function value (OFV) by 48.809. The typical value of the apparent clearance of TFV increased by 1.214, 1.339, and 1.639-fold in the 1st, 2nd, and 3rd trimester, respectively, compared to the non-pregnant baseline values; these data are comparable to the previously reported clearance increment during each trimester. The proportional error of the Partners Demonstration Project (71.2%) was higher than the Coleman et al. study (21.2%).

TABLE 2 Final estimates of TFV pharmacokinetic parameters, between subject variability, and residual variability[a].

Parameter	Estimate	RSE%
CL/F (L/h)	52.4	7
V2/F (L)	252	57
Q/F (L/h)	295	18
V3/F (L/h)	1120	18
KA (/h)	2.56	91
CL/F increment during 1st trimester (%)	21.4%	55
CL/F increment during 2nd trimester (%)	33.9%	34
CL/F increment during 3rd trimester (%)	63.9%	29
BSV on CL/F	35.9%	13
BSV on V2/F	41.4%	145
BSV on Q/F	67.6%	29
BSV on V3/F	56.7%	28
BSV on KA	56.4%	87
σ1(prop; Coleman study)	21.2%	6
σ2(prop; partner demonstration project)	71.2%	5
σ2(add; partner demonstration project) (ng/ml)	0.109	253

[a]CL/F, apparent clearance; V2/F, apparent volume of distribution of the central compartment; Q/F, apparent intercompartmental clearance; V3/F, apparent volume of distribution of the peripheral compartment; KA, absorption rate constant; BSV, between-subject variability; σ1, proportional residual error; σ2, additive residual error; RSE, relative standard error.

FTC model

We selected a two-compartment model with first-order absorption as the final structural model (Table 3). Since the simulated changes in FTC clearance (compared to pre-pregnancy) for each trimester were commensurate with the change when from pre-pregnancy to pregnancy (all trimesters combined), we used combined data from all trimesters in the final model. Pregnancy increased the apparent clearance by 63.1% compared to the non-pregnant baseline value, reducing the OFV by 27.685. As with TFV, we found a high proportional error of the Partners Demonstration Project data (85.4%). The diagnostic plot (Figure 3) showed some bias. The VPC (Figure 4) indicated the satisfactory performance of the final model. Our final model overestimated FTC plasma concentrations compared to those found in the Coleman et al. study.

Clinical trial simulation

In the non-pregnant population, the simulated median steady-state trough plasma concentration was 62.5 ng/ml for TFV and 158 ng/ml for FTC. Our simulation indicated that 13.9% and 16.4% of the participants on a standard "pre-pregnancy" regimen would have steady-state trough plasma TFV and FTC concentrations below the estimated protective threshold, respectively. In the standard TDF/FTC dosing arm (arm 1), the simulated median steady-state plasma TFV trough concentration dropped to 45.9 ng/ml, 39.3 ng/ml, and 27.3 ng/ml in the 1st, 2nd, and 3rd trimesters, respectively. According to our simulations, steady-state median TFV plasma concentrations decrease by 26.5–56.3% throughout pregnancy from a pre-pregnant baseline. Accordingly, we found that 34.0%, 43.8%, and 65.1% of steady-state plasma trough concentrations dropped below the estimated protective TFV trough concentration (35.5 ng/ml) due to the progressively increased clearance in the three trimesters. By comparison, in the simulated arm 2 pregnancy-adjusted double-dose group, the simulated median steady-state plasma trough concentration were 91.8 ng/ml, 78.7 ng/ml, and 54.6 ng/ml in the 1st, 2nd, and 3rd trimesters. Only 10.7%, 14.4%, and 27.8% of participants in the pregnancy-adjusted double-dose arm had

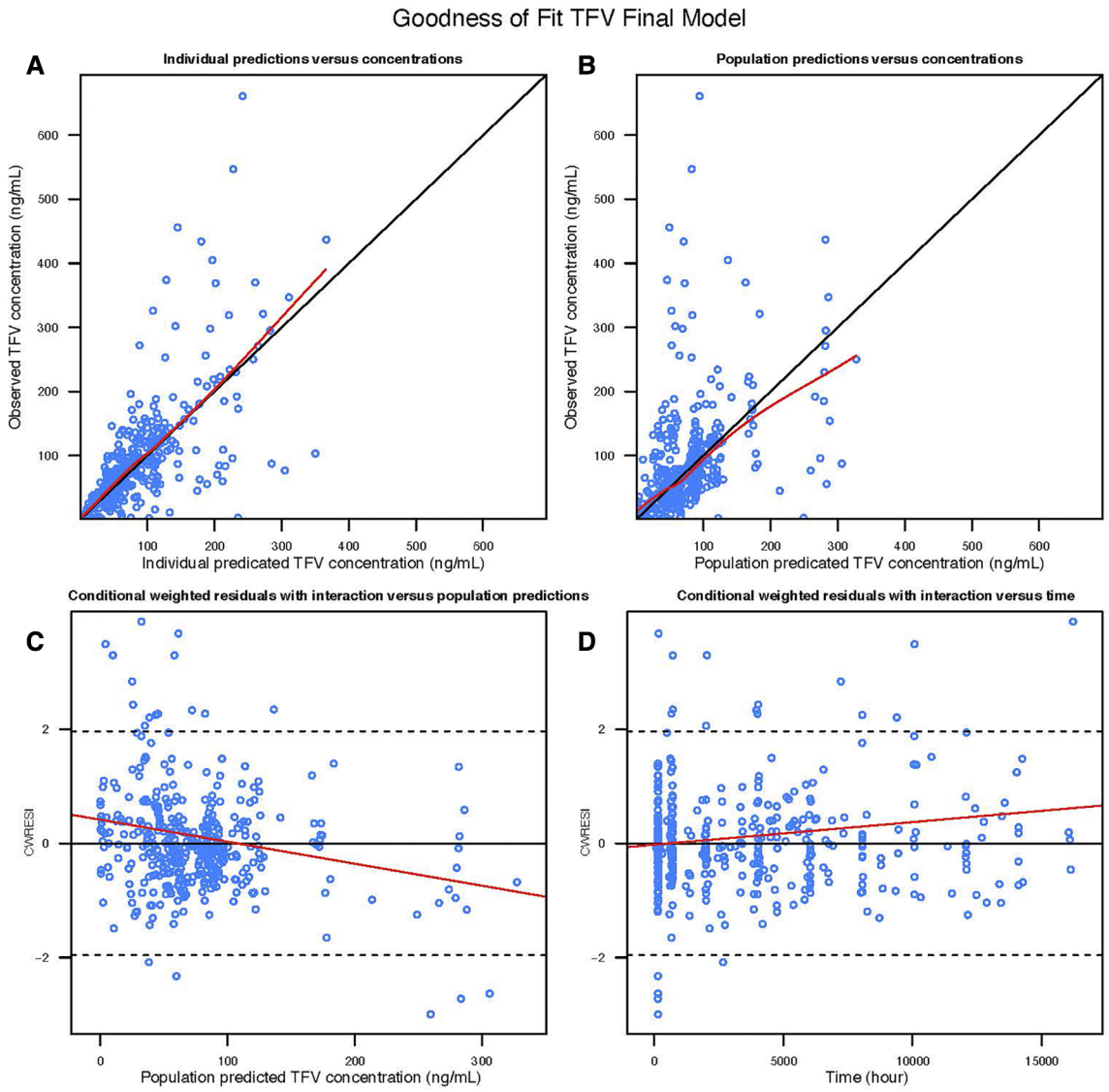

FIGURE 1
Goodness of fit plot of the TFV final model: (A) observed TFV concentration vs. Individual predicted TFV concentration; (B) observed TFV concentration vs. population predicted TFV concentration; (C) conditional weighted residuals with interaction vs. population predicted TFV concentration; (D) conditional weighted residuals with interaction vs. time.

steady-state trough plasma concentrations less than 35.5 ng/ml (Figure 5).

For FTC, since all trimesters were combined in the final model, the simulated steady-state trough concentration estimates trough concentrations throughout pregnancy. In the arm 1 typical dosing group, the median simulated steady-state trough plasma concentration during the pregnant period was 62.4 ng/ml During pregnancy, 42.1% of the steady-state trough concentrations dropped below the estimated protective trough concentrations for FTC (49.1 ng/ml). In the pregnancy-adjusted double-dose arm, the median simulated steady-state trough plasma concentration was 125 ng/ml; 22.4% of participants had trough concentrations less than 49.1 ng/ml, similar to the non-pregnancy group (Figure 6).

Discussion

We analyzed sparsely sampled PK data from the Partners Demonstration Project and intensively sampled PK data from the Coleman et al. study for both plasma TFV and FTC using a nonlinear modeling framework. Removal of outlier values had a modest impact on the popPK parameter estimates, but resulted in significantly improved model performance measures (pcVPC). The central volume of distribution estimate after removal of the outliers is consistent with that reported in the literature (15, 34).

We observed a progressive increase in clearance for TFV throughout pregnancy, with a nearly two-fold increase in clearance in the 3rd trimester compared to the non-pregnant baseline, and an associated progressive decrease in trough plasma levels. For

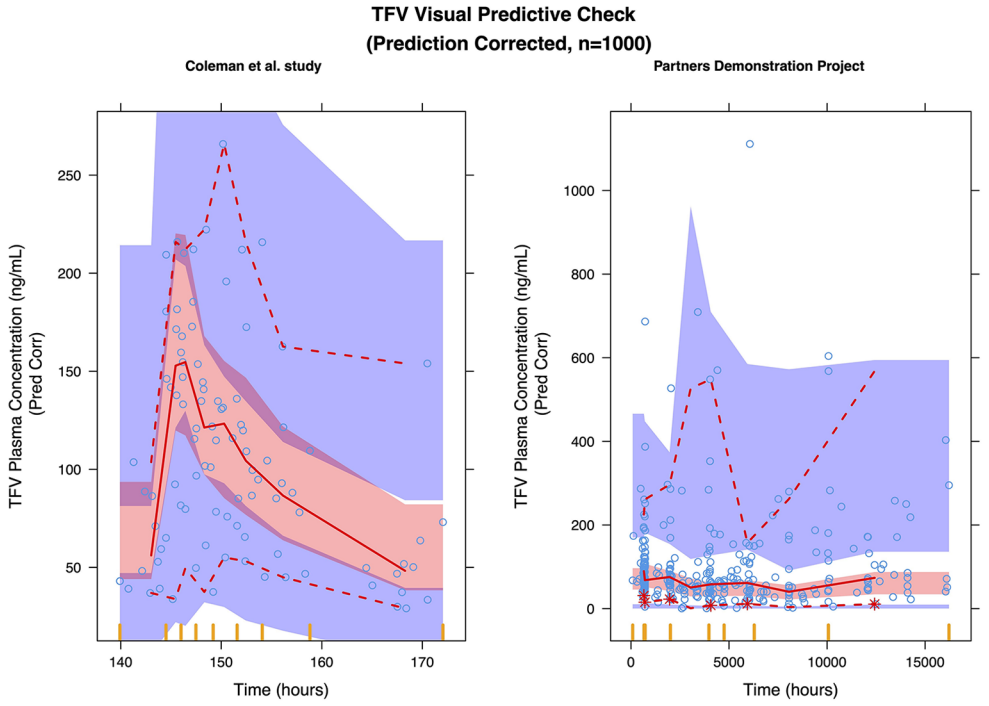

FIGURE 2
Prediction corrected visual predictive check (pcVPC) of the TFV final model: (left) coleman, et al. study; (right) partners demonstration project.

TABLE 3 Final estimates of FTC pharmacokinetic parameters, between subject variability, and residual variability[a].

Parameter	Estimate	RSE%
CL/F (L/h)	16.7	9
V2/F (L)	58.8	62
Q/F (L/h)	13.8	22
V3/F (L/h)	190	18
KA (/h)	0.616	56
CL/F increment during pregnancy (%)	63.1%	23
BSV on CL/F	50.6%	9
BSV on Q/F	62.5%	43
BSV on V3/F	41.6%	60
BSV on KA	20.5%	26
σ1(prop; Coleman study)	29.3%	8
σ2(prop; partner demonstration project)	85.4%	6
σ2(add; partner demonstration project) (ng/ml)	12.5	31

[a]CL/F, apparent clearance; V2/F, apparent volume of distribution of the central compartment; Q/F, apparent intercompartmental clearance; V3/F, apparent volume of distribution of the peripheral compartment; KA, absorption rate constant; BSV, between-subject variability; σ1, proportional residual error; σ2, additive residual error; RSE, relative standard error.

FTC, we observed a smaller increase in clearance in pregnancy, and an associated decrease in trough concentrations; these changes were consistent throughout pregnancy. Clinical trial simulation of standard vs. pregnancy-adjusted double-dose TDF/FTC regimens revealed that, compared to non-pregnant women, a clinically significant proportion of pregnant individuals on the standard dose would have exposures below the estimated protective thresholds for both TFV (35.5 ng/ml) and FTC (49.1 ng/ml) in part or all, respectively, of pregnancy. In contrast, the pregnancy-adjusted dosing regimen significantly reduced the proportion of pregnant individuals falling below the estimated protective threshold from 34%, 43.8%, and 65.1%, to 10.7%, 14.4%, and 27.8% for TFV during the 1st, 2nd, and 3rd trimesters and from 42.1% to 22.4% for FTC during pregnancy. For context, the simulated 1st trimester steady-state plasma TFV trough concentrations with doubled TDF/FTC dosing—10.7% below and 89.3% above the 35.5 ng/ml daily dosing benchmark—is consistent with the 90% sensitivity threshold used in HPTN 066 to select the 35.5 ng/ml benchmark. Even so, the doubled TDF/FTC daily dose did not fully correct plasma TFV in the 2nd and 3rd trimester or FTC during pregnancy to pre-pregnant levels.

Consistent with our findings, physiological changes in renal blood flow are known to be progressive in pregnancy and are associated with progressive increases in clearance and decreases in exposure for renally excreted drugs, such as TFV and FTC. Although not identified in our final model, the increased volume of distribution during pregnancy may also contribute to lower plasma concentrations of TFV and FTC. The 26.5–56.3% reduction we estimated in simulated TFV trough plasma concentrations throughout the pregnancy is consistent with the 45%–58% reduction in TFV concentration reported by Pyra et al. in the averaged TFV concentrations in the Partners Demonstration Project (1). A popPK analysis by Benaboud et al. found a 39% increased clearance during pregnancy in women with HIV on TDF/FTC-containing regimens (2). A whole body physiologically based pharmacokinetic (PBPK) model by De Sousa Mendes et al. in pregnancy predicted a 40% increase in TFV apparent clearance

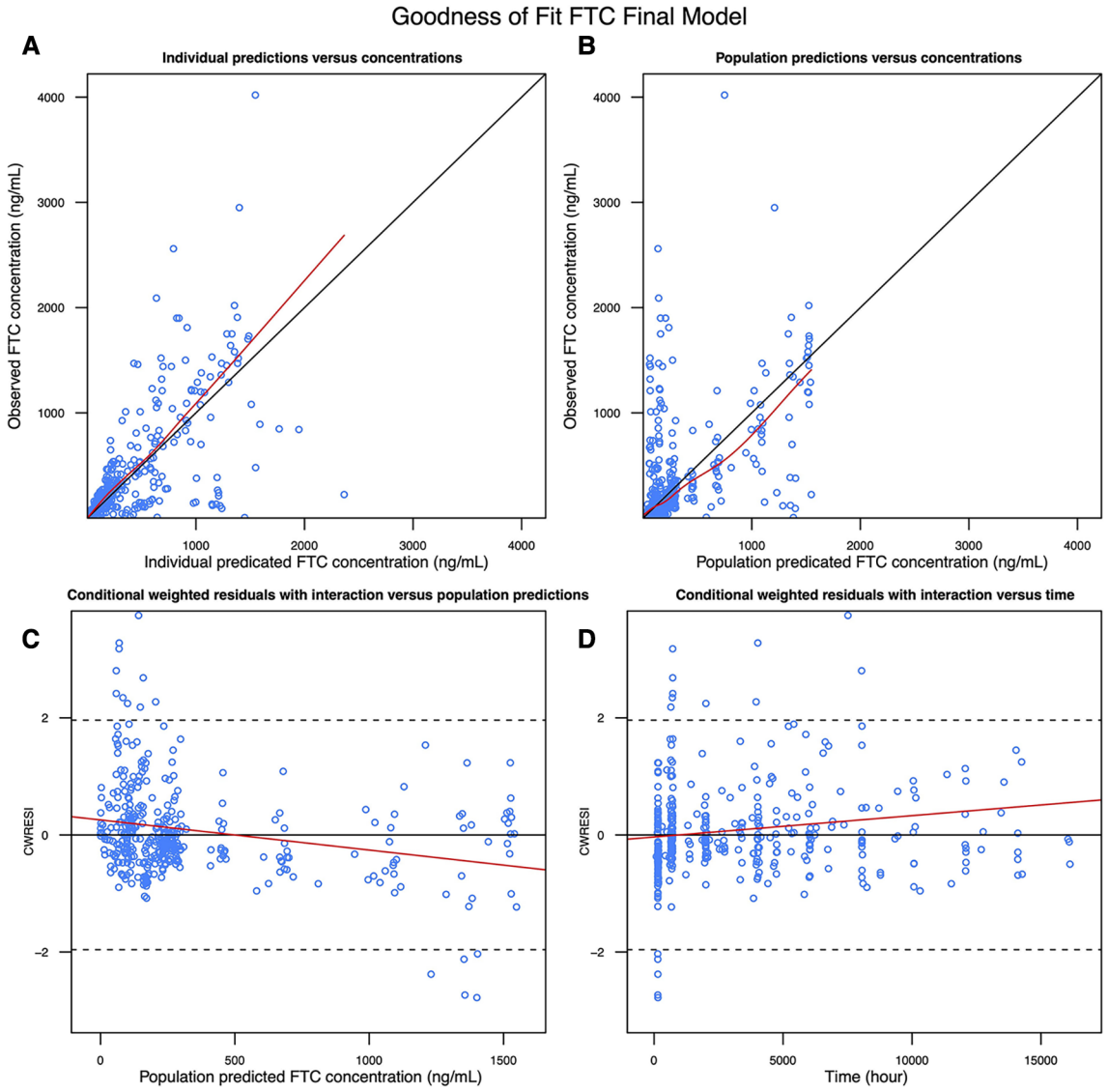

FIGURE 3
Goodness of fit plot of the FTC final model: (A) observed FTC concentration vs. Individual predicted FTC concentration; (B) observed FTC concentration vs. population predicted FTC concentration; (C) conditional weighted residuals with interaction vs. population predicted FTC concentration; (D) conditional weighted residuals with interaction vs. time.

at approximately 33 weeks gestational age (35). A popPK model in women with HIV during pregnancy developed by Hirt et al. showed up to a 50% increase in the apparent clearance of FTC compared with the non-pregnant population (11), similar to our final estimates. A simplified pregnant-PBPK model developed by Xia et al. predicted a 1.39-fold change in the renal clearance of FTC in late pregnancy due to increased in renal secretion and filtration (36). The whole body PBPK model mentioned above predicted a 1.29-fold clearance change, which is slightly lower than our estimates (35). Liu et al. predicted the PK profiles of FTC at different stages of pregnancy using a maternal-fetal PBPK model. They predicted an up to 27.7% decrease in median FTC AUC at 26 weeks of gestation (37).

Despite the availability of newer PrEP modalities, TDF/FTC remains the main stay of HIV prevention in pregnancy. Although there are safety and PK data for HIV treatment in cisgender women, including during pregnancy, tenofovir alafenamide (TAF)/FTC is not yet recommended in cisgender women for PrEP given the lack of efficacy data. There are only limited safety and PK data for long-acting Cabotegravir in pregnancy (38, 39) and although there are reassuring safety data on the use of the Dapivirine ring in pregnancy (40, 41), its approval is limited globally. Decreased protective efficacy of TDF/FTC PrEP during pregnancy due to lower TFV and FTC exposures, as indicated in the clinical trial simulation, is cause for considerable concern, especially as the baseline HIV incidence among pregnant and postpartum women is two to four times that of non-pregnant women (42, 43). Modeled infectivity from the Partners in Prevention HSV/HIV Transmission Study and the Partners PrEP study demonstrated that the probability of

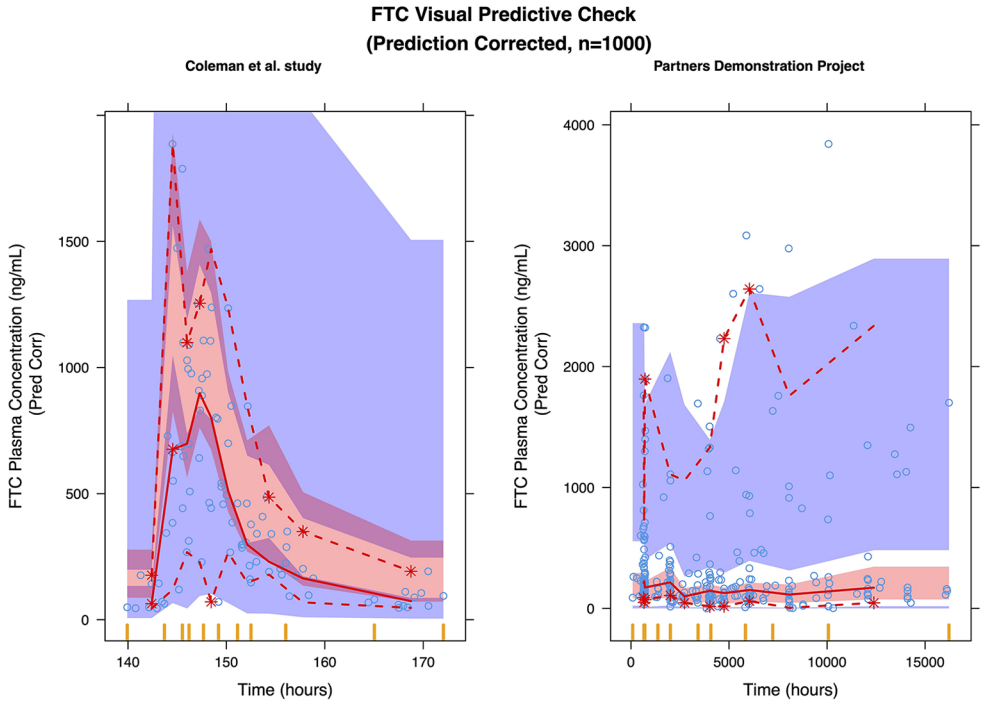

FIGURE 4
Prediction corrected visual predictive check (pcVPC) of the FTC final model: (left) coleman et al. study; (right) partners demonstration project.

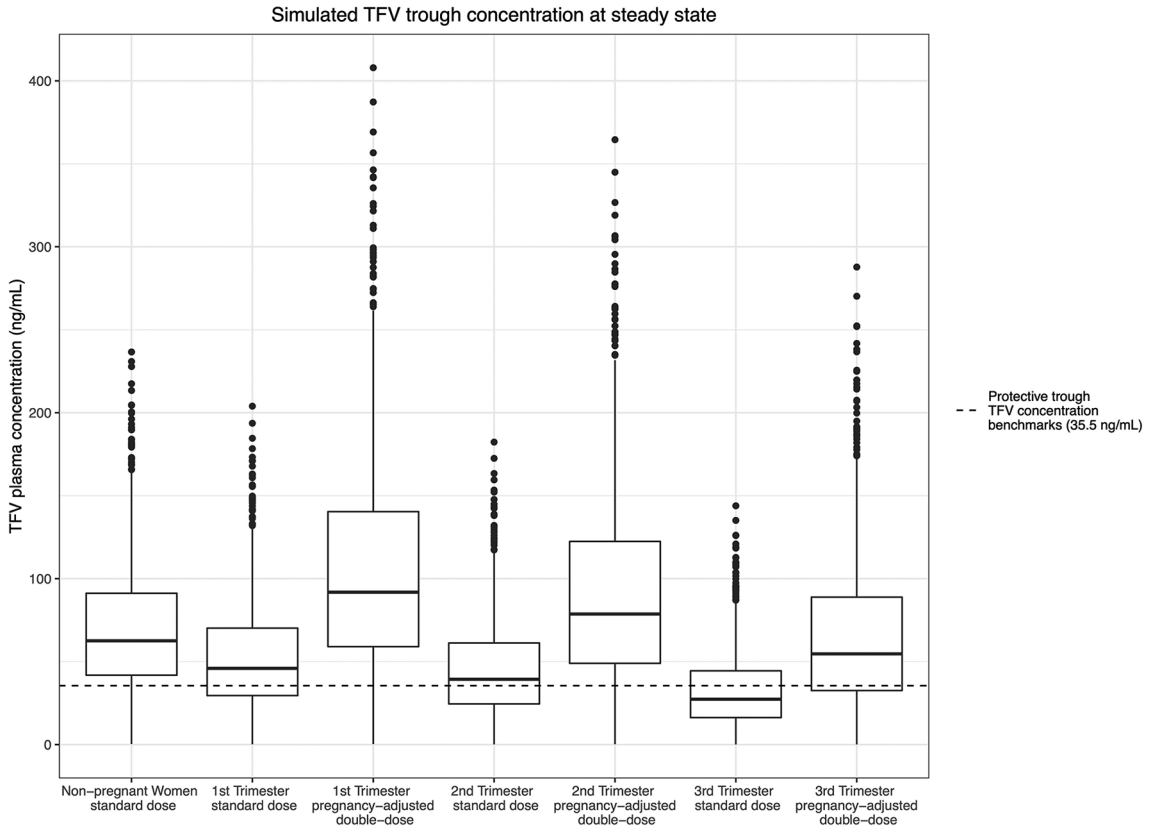

FIGURE 5
Simulated TFV trough concentration at steady state and the estimated protective trough concentration of TFV.

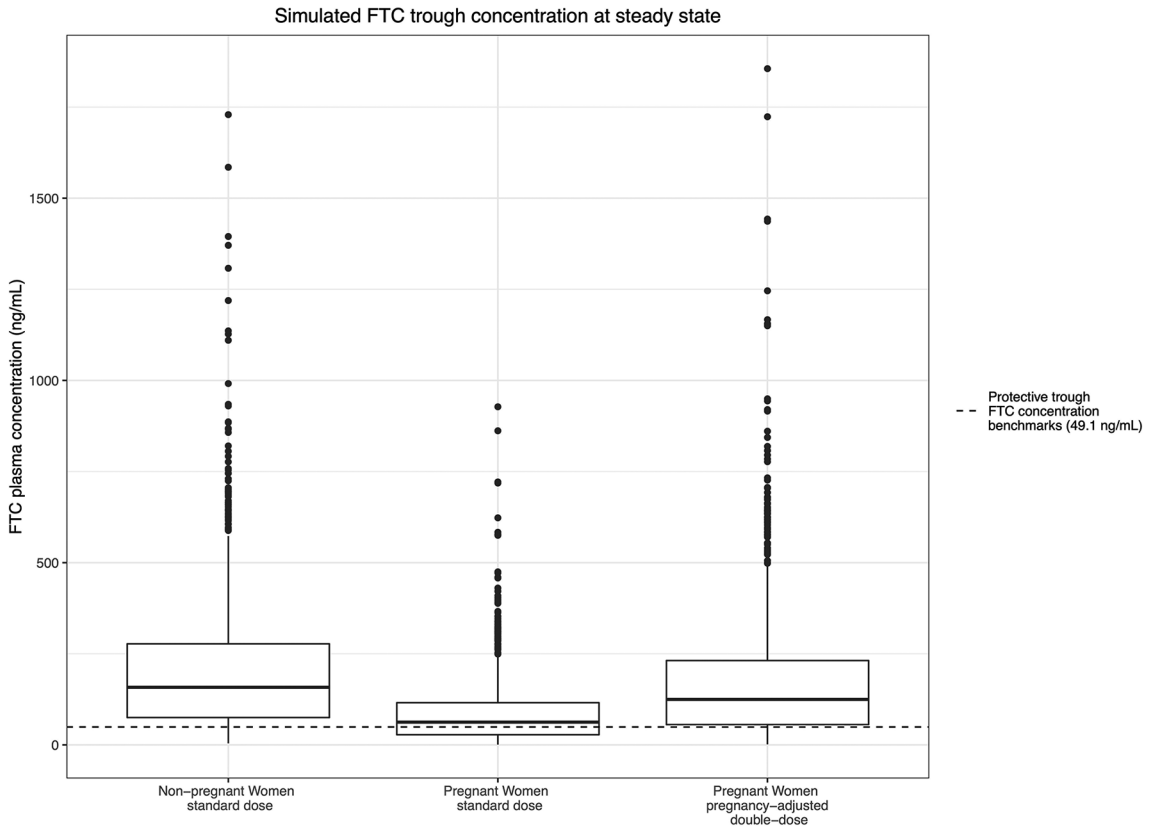

FIGURE 6
Simulated FTC trough concentration at steady state and the estimated protective trough concentration of FTC.

HIV acquisition per condomless sex act increases starting in early pregnancy and peaks postpartum [adjusted RR 3.97 (1.50, 10.51) $p < 0.001$]) (43). Data from several observational studies corroborate that model's findings of increased male-to-female transmission in pregnancy (42–48). This increased incidence is attributed to both behavioral and biological changes (including immunological, vaginal microbiome, and vaginal epithelial integrity) during pregnancy and delivery (42, 46, 49–51). Prevention of HIV is especially critical in pregnant individuals secondary to the additional and increased risk of perinatal transmission. The risk of perinatal transmission is 9–15-fold higher in women diagnosed with HIV during (vs. prior to) pregnancy (22 vs. 1.8%) (52, 53). Increased HIV acquisition attributable to decreased protection of TDF/FTC PrEP against HIV during pregnancy has not been reported, but it is unclear if this is due to the adequacy of TDF/FTC PrEP protection in pregnancy vs. underutilization of PrEP in pregnancy and a dearth of large-scale research on PrEP in pregnancy. Limited clinical trials and epidemiologic research have focused on oral PrEP in pregnancy, but none in sufficient size to evaluate increased incidence due to TDF/FTC PrEP failure.

Limitations of the current analysis include the availability in pregnancy of only sparse PK data and only plasma drug concentrations, rather than active intracellular phosphorylated analytes. Additionally, we did not include body weight and renal clearance as covariates or intracellular metabolite concentrations in our model. Neither study controlled for diet nor timing of dose related to meals, which could introduce additional variability (54, 55). Regarding the differences in CrCl between populations, kidney estimation equations were primarily derived in non-Black populations, and the equations used in the United States at the time the original data were collected (e.g., Coleman et al.) are not always applicable to African populations (e.g., Partners Demonstration Project). Previously published models found body weight (10) and creatinine clearance (10, 34, 56–58) to be significant covariates for TFV and FTC clearance. Even without inclusion of these covariates, the model still captures the global effect of trimester on clearance for TFV and underscores the need for a pooled analysis of all clinical trial data in pregnancy to better understand the dose optimization needs and for prospective PK research on dosing in pregnancy. For FTC, we were unable to identify the different changes in its clearance over different trimesters. An additional limitation was the need for a separate residual error model for Partners Demonstration Project; of particular concern was the large proportional error potentially attributable to differences in PK sampling and ascertainment of the dosing history. During our clinical trial simulation, we discovered that up to 65.1% of the TFV trough concentration and 45.2% of the FTC trough concentration in pregnant population may fall below the protective threshold.

However, we also observed that our final model tended to overestimate the TFV and FTC concentration in the non-pregnant population. As a result, the proportion of pregnant individuals with trough concentrations below the protective threshold (based on empiric observations) may have been underestimated. An additional limitation is that although Partners Demonstration Project utilized MEMS to measure adherence, doses were not observed and activation of the MEMS without taking a dose or taking a double dose ("catch up dosing") prior to a study visit could bias CL/F. Lastly, as noted above, our sample size and that of published studies are insufficient to assess any impact of pregnancy on TDF/FTC PrEP efficacy.

Our popPK model and clinical trial simulation found that steady-state TFV and FTC trough plasma concentrations decreased during pregnancy, which puts pregnant individuals receiving standard TDF/FTC dosing at significantly greater risk of falling below the protective thresholds for both TFV and FTC compared to participants taking the pregnancy-adjusted double dose. This simulation provides the quantitative basis for the design of prospective TDF/FTC studies during pregnancy to evaluate the safety and appropriateness of pregnancy-adjusted dosing.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Available upon request. Requests to access these datasets should be directed to chendrix@jhmi.edu.

Ethics statement

The studies involving humans were approved by Johns Hopkins University Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

RS and CH conceived of the study. YY and RB developed the model and performed the in-silico simulation. RS and YY wrote the manuscript with support from CH and RB All authors discussed the results and contributed to the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

CH holds two patents related to HIV prevention and is founder of Prionde Biopharma, LLC, an HIV prevention product company. RB serves as a consultant for Advanced Bioscience Laboratories (NIAID). RS is the recipient of grant funding from Gilead Sciences, Inc. and ViV Healthcare, managed by MedStar Health. MM is the recipient of grant funding from Gilead Sciences, Inc. and Merck. CH is the recipient of grant funding from Gilead Sciences, Inc. and Merck.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Safety surveillance for PrEP in pregnant and breastfeeding women

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The risk of HIV acquisition is higher during pregnancy and postpartum than other times. Newly acquired maternal HIV infection associated with high primary viraemia, substantially increases the risk of vertical HIV transmission. Pre-exposure prophylaxis (PrEP) reduces the risk of HIV acquisition. Currently available products include oral tenofovir/emtricitabine (TDF/FTC) and tenofovir alafenamide (TAF)/FTC), long-acting cabotegravir (CAB-LA) and the dapivirine ring (DVR). All except oral TDF/FTC have limited safety data available for use in pregnant and breastfeeding women. The safety of new PrEP agents for pregnant women and the fetus, infant and child, either exposed *in utero* or during breastfeeding is an ongoing concern for health care workers and pregnant and breastfeeding women, particularly as the safety risk appetite for antiretroviral (ARV) agents used as PrEP is lower in pregnant and breastfeeding women who are HIV-uninfected, compared to women living with HIV taking ARVs as treatment. With the widespread rollout of TDF/FTC among pregnant women in South Africa and other low-middle income countries (LMIC) and the potential introduction of new PrEP agents for pregnant women, there is a need for safety surveillance systems to identify potential signals of risk to either the mother or fetus, measure the burden of such a risk, and where appropriate, provide specific reassurance to PrEP users. Safety data needs to be collected across the continuum of the product life cycle from pre-licensure into the post-marketing period, building a safety profile through both passive and active surveillance systems, recognising the strengths and limitations of each, and the potential for bias and confounding. Pharmacovigilance systems that aim to assess the risk of adverse birth outcomes in pregnant women exposed to PrEP and other agents need to consider the special requirements of pregnancy epidemiology to ensure that the data derived from surveillance are sufficiently robust to inform treatment policies. Here we review the known safety profiles of currently available PrEP candidates in women of child-bearing potential, pregnancy and breastfeeding and discuss pragmatic approaches for such surveillance in HIV-endemic LMICs.

KEYWORDS

pregnancy, breastfeeding, post-marketing surveillance, pre-exposure prophylaxis (PrEP), pharmacovigilance, teratovigilance

1. Background

Young cisgender women in high HIV-burden countries remain at substantial risk for HIV acquisition: Birdthistle et al., estimated a pooled incidence of 5% in 20–24 year olds in a systematic review and meta-analysis that included data from 10 high prevalence African countries (1). Another study estimated a 10% incidence of HIV infection in 15–24 year old women in 15 high prevalence sub-Saharan African (SSA) countries between 2015 and 2019 (2). Risks of HIV acquisition during pregnancy and breastfeeding are also extremely high. In cisgender women in sero-different relationships in 7 countries in Southern and Eastern Africa, HIV incidence per hundred person years was 1.25 (CI 95% 0.95–1.62) in non-pregnant women, 3.75 (CI 95% 1.22–8.75) in early pregnancy, 7.02 (CI 95% 3.74–12.01) in late pregnancy and 4.68 (CI 95% 1.72–10.18) postpartum (3). Similarly, a recent systematic review and meta-analysis conducted in SSA, estimated HIV incidence at 3.6 per 100 person years (95% PI: 1.2–11.1) during pregnancy and breastfeeding combined (4). These high rates of maternal HIV infection increases the risk of HIV transmission to the fetus or baby during pregnancy, delivery, or breastfeeding. The transmission risk is especially high when the woman is unaware of her HIV status, is not yet receiving antiretroviral therapy (ART) as treatment, and has a high HIV viral load (5). High rates of HIV acquisition among young women of child-bearing potential (WOCP) and among women who are pregnant or breastfeeding, highlight the importance of including these groups in HIV prevention programmes.

Significant progress has been made in the development of biomedical products for prevention of HIV infection. The incidence of new HIV infections in pregnant and breastfeeding women, as well as adolescent girls and young women (15–24 years), has declined (although at a slower rate compared to adolescent male counterparts) with Graybill et al., reporting HIV incidence of 4.1 per 100 person years (95% PI: 1.1, 12.2) pre-2010, compared to 2.1/100 person years (95% PI: 0.7, 6.5) post-2014 (4, 6, 7). Several studies have clearly demonstrated the efficacy and acceptability of pre-exposure prophylaxis for HIV (PrEP) in pregnant as well as non-pregnant and breastfeeding women (8–15). National HIV programmes globally are implementing policies that include the rollout of products for the prevention of HIV in all populations considered to be at risk, including WOCP, pregnant and breastfeeding women (16–18). Currently the World Health Organization (WHO) recommends three products for PrEP – (i) oral tenofovir (TDF)/emtricitabine (FTC) PrEP available in fixed dose combination (FDC), (ii) the dapivirine vaginal ring (DVR) and iii) intramuscular long-acting cabotegravir (CAB-LA) (16–18). There is a pipeline of new agents that could be used for HIV prevention in pregnant women including oral/subcutaneous lenacapavir, antiretroviral-containing vaginal films and subcutaneous patches, and new oral antiretrovirals such as TAF/FTC. A well-established surveillance system would support the safe introduction of these products in pregnant women and WOCP as they become available. Specific safety indicators that clinical trials may not collect in a large enough sample, but surveillance systems would be able to collect include congenital anomalies, pregnancy and birth outcomes (stillbirth, prematurity, birth weight, neonatal mortality), exacerbation of pregnancy-related conditions such as gestational hypertension, gestational diabetes mellitus and child health outcomes including growth, neurodevelopment and malignancies (19). We summarise available safety data in PrEP agents in WOCP, pregnant and breastfeeding women, as well as discuss in detail approaches to surveillance in this population, specifically related to PrEP rollout.

1.1. Data on PrEP in pregnant and breastfeeding women

Oral TDF/FTC, which has an estimated efficacy of 97% in cisgender women when taken as prescribed, has been recommended by WHO since 2017 in pregnancy and breastfeeding, to complement other HIV prevention mechanisms in women at "substantial risk" of HIV infection (16, 17). Initial safety data were based on the use of TDF/FTC in combination with other ARVs in women living with HIV (WLHIV), requiring it for treatment, and later, in women without HIV receiving TDF/FTC as preventative therapy during pregnancy and breastfeeding (20–24). Published clinical trials and systematic reviews report reassuring safety data with minimal concerns regarding the use of TDF/FTC in pregnancy/breastfeeding for women or/and their infants (8, 20, 25–27). However, common side effects include gastrointestinal symptoms (nausea, vomiting, loss of appetite), headache and rashes, all of which may compound common pregnancy-related symptoms. In addition, elevated creatinine and subsequent renal damage may occur rarely, as well as reduction in bone mineral density (28). The PRIMA study in Kenya found that oral TDF/FTC uptake was higher in pregnant women at higher risk of HIV acquisition. Adherence was higher in pregnancy compared to postpartum and having a partner with a known HIV infection was the most significant predictor of initiation, adherence, and continued use. Interestingly tolerance to ARVs side effects was not an important predictor of adherence (9). The PrIYA program in Kenya evaluated pregnancy outcomes in 1530 mother-child pairs in Kenya, including 206 women who initiated TDF/FTC pre-conception compared to 1,324 with no TDF/FTC exposure (29). No increased rates of prematurity or low birth weight were seen in the TDF/FTC-exposed group, there were no congenital anomalies reported in the TDF/FTC-exposed group (5 in the PrEP-unexposed group) and at six weeks of age growth was similar in both groups (29). A study from Durban, South Africa, compared immediate initiation of TDF/FTC in pregnant young women, to deferred initiation post breastfeeding cessation, and found no increase in prematurity or low birth weight infants in those women receiving TDF/FTC during pregnancy (14). In addition, very low TDF/FTC concentrations are secreted in breast milk (30). Data from infants exposed to maternal TDF/FTC compared to those unexposed, from Maternal-Child and Vertical transmission programmes in Kenya, showed no differences in infant anthropometry at birth, 6- or 9-months (10).

Increasingly, country-based National Programmes are offering TDF/FTC to WOCP, pregnant and breastfeeding women, although roll-out progress remains slow, particularly in some high HIV-burden countries (12, 31).

The Dapivirine Vaginal Ring (DVR) which contains 25 mg of dapivirine, a non-nucleoside reverse transcriptase inhibitor, has been studied in cisgender women in SSA, and was shown to reduce risk of HIV infection by 27%–35% in clinical trials and by over 50% when adherence to the product is optimal (32, 33). Side effects may include cervical inflammation, reddening or swelling; urinary tract infections as well as bladder control problems; headache, pelvic pain and pain during sex, although all were rare and of mild severity in clinical trials (26). Data in pregnancy and breastfeeding are limited, but the Microbicide Trial Network (MTN) is conducting studies specifically focussed on these populations. The MTN 016 study evaluated pregnancy outcomes in 169 women who conceived while using the DVR on study (179 incident pregnancies) and discontinued the product when their pregnancy became known, at median gestational age of 5.4 weeks. In this study there were 105 (58%) full-term live births, nine (5%) preterm births, 39 (22%) spontaneous abortions, 22 (12%) elective abortions, four (2%) stillbirths and eight (7%) congenital anomalies (all minor). There was no statistical difference in pregnancy outcomes between the DVR and placebo arms (34). The ongoing MTN 042/DELIVER (NCT03965923) study is evaluating safety and acceptability of the DVR in pregnant women, beginning with the enrolment of women with more advanced gestational age: 3rd trimester in cohorts 1 (> 36 weeks, $n = 148$) and 2 (30–35 weeks, $n = 154$) respectively, and 2nd trimester in cohort 3 (12–29 weeks). Data from cohorts 1 and 2 have been published and showed low rates of pregnancy complications. Hypertension in pregnancy was the most common adverse outcome and there was one stillbirth and one neonatal death in each cohort, balanced across arms (35). Premature delivery occurred in 2% of cohort 1, and 6% of cohort 2 (35). To provide background pregnancy outcome rates as a comparison, MTN 042B, which was a cross sectional systematic chart review, was conducted in the same sites as MTN 042/DELIVER. Adverse outcomes in MTN 042/DELIVER were similar to background rates in MTN 042B for cohorts 1 and 2 (36, 37). However, in MTN 042/DELIVER, participants were enrolled late in pregnancy and carefully screened to exclude those with increased risk of prematurity and other potential complications. The study is currently fully enrolled, and all delivery outcomes completed by mid-2023. The MTN-043 B-PROTECTED (NCT04140266) study that enrolled postpartum women exclusively breastfeeding, also reported no safety concerns and minimal maternal systemic detection of dapivirine on pharmacokinetic measurement. There was negligible secretion of dapivirine in breastmilk and in infant pharmacokinetic sampling (38). Although efficacy of DVR is lower than TDF/FTC and CAB-LA, the advantage of providing choice of product to pregnant/breastfeeding women, particularly since extremely low exposure to product occurs for the fetus, is potentially compelling. DVR is registered in several high HIV-burden countries in SSA, including South Africa, Zimbabwe and Zambia (39). Due to the high cost, rollout in routine public health settings beyond demonstration projects (implementation science projects where products not yet readily available in public facilities are made available to enrolled participants) is not yet under consideration. Demonstration projects in SSA countries are planning to deliver DVR to WOCP in 2023, some of whom may become pregnant. Although the product is not registered for pregnant/breastfeeding women yet, and pregnant women will not be enrolled currently, women participating in the demonstration projects, who become pregnant while using DVR may have the option to continue using the product should they wish to, although this is project-dependant.

Long-acting cabotegravir (CAB-LA) is an integrase inhibitor, administered intramuscularly 2-monthly, which showed an 88% lower HIV acquisition risk in young cisgender women compared to TDF/FTC in the HVTN 084 study (40). Side effects may commonly include localised reactions at the injection site, as well as gastrointestinal side effects, sleep disturbances including abnormal dreams, anxiety and tiredness (26). The HVTN 084 study did not specifically enrol pregnant women, and CAB-LA was withheld if participants tested positive for pregnancy. Participants who became pregnant while on the study were offered the option of switching to TDF/FTC for the duration of the pregnancy. In 27 women who became pregnant while receiving CAB-LA, compared to 18 women who conceived on TDF/FTC, there were no significant differences in pregnancy or infant outcomes between the two groups (41). Pharmacokinetic (PK) drug levels measured by apparent terminal phase half-life were similar in pregnant and non-pregnant women. Because CAB-LA was stopped once pregnancy was diagnosed, PK levels from the 2nd or 3rd trimester were not evaluated (41). Given the long half-life of CAB-LA, even in women who have stopped treatment pre-pregnancy, the product may still be classified as active treatment and exposure during pregnancy, which has consequences for surveillance (42). Open-label extension studies, due to start in 2023, as well as upcoming demonstration projects, will allow continuation of CAB-LA during pregnancy, if desired by the participant, providing an opportunity to collect much-needed safety data on CAB-LA's safety in pregnancy CAB-LA is currently registered in a number of countries including South Africa, Botswana, Zambia and Zimbabwe but, due to the high cost, rollout in routine public health settings beyond demonstration projects is not yet under consideration (39).

2. The importance of sufficient robust PrEP safety data in pregnancy and breastfeeding

Whilst the increasing availability of PrEP products provides hope for prevention of HIV infection in WOCP, pregnant and breastfeeding women, safety data in pregnancy and breastfeeding remain limited and inadequate. Arguably, the greatest concern with respect to both fetal and maternal risk is during pregnancy, since breastfeeding women return to pre-pregnancy metabolism within about 6 weeks post-delivery, and as long as limited

product is secreted in the breastmilk, which is largely the case with the products described above, there is less concern regarding safety during lactation (29). Clinical trials are essential to provide data regarding product dosage, pharmacokinetics, efficacy, safety, and acceptability. Pregnant women are generally excluded from these early phases of drug development and data, particularly regarding efficacy can be extrapolated from adult trials in non-pregnant individuals. In terms of safety, clinical trials are usually too small and too short to provide adequate data to understand the real risk-benefit profile of a product. In clinical trials involving pregnant women only reasonably healthy participants with no or well-controlled co-morbidities, and no preceding pregnancy complications, or risks for complications such as multiple gestation are included. Additionally, adolescents are frequently excluded from clinical trials and may be at higher risk of adverse complications, as well as more likely to access PrEP, therefore the absence of data is problematic (44). Moreover, in pregnant populations, different pharmacokinetics and possibly pharmacodynamics, and the presence of a developing fetus expands the scope of safety assessment of products such as PrEP. Populations in which PrEP will be used are far more diverse than clinical trial participants, use the product for longer periods than the duration of clinical trials, and use products in combination with other comorbidities and medicines which are often excluded in the clinical trial population (19).

Frameworks for safe approaches to inclusion of pregnant women as early as possible in clinical research have been developed (19, 43). Proposed steps include the following:

Figure 1 describes the framework that could be used for evaluation of new drugs, including PrEP, in pregnant women (34, 35).

Common pregnancy and birth adverse outcomes such as prematurity, small for gestational age, hypertension etc. may occur with high enough frequency to require a smaller sample sizes to detect a significant difference in risk of these outcomes. However, outcomes such as specific birth defects, which occur far less frequently, require much larger sample sizes to detect a significant difference in risk of these outcomes (45). For example, if overall congenital disorders occur at around 3%, at least 200 exposures are required to exclude a 2-fold increase in risk, whereas specific rare anomalies such as neural tube defects (0.1%) require at least 2000 exposures during the gestational period of risk to exclude a 3-fold increase in risk (45). Clearly, clinical trials are unlikely to enrol such numbers, nor should they, as requiring such large studies would further delay registration and availability of necessary products for pregnant women. Therefore, all steps in the framework, culminating in surveillance, are important.

Surveillance systems need to be able to identify signals of adverse events not detected in clinical trials that are associated with the use of PrEP products. WOCP, pregnant women and their products of conception and children exposed *in utero* or during breastfeeding are the key populations to include in any PrEP safety surveillance plan. Each of these exposed populations have specific outcomes that should be monitored for in terms of the risk of PrEP exposure. Figure 2 provides an overview of key safety-related outcomes that need to be assessed as part of any PrEP rollout plan. Ensuring that key safety outcomes are adequately and systematically assessed is particularly pertinent for HIV-*prevention* products, where the threshold of acceptable risk may be lower than with HIV-*treatments* in which benefits

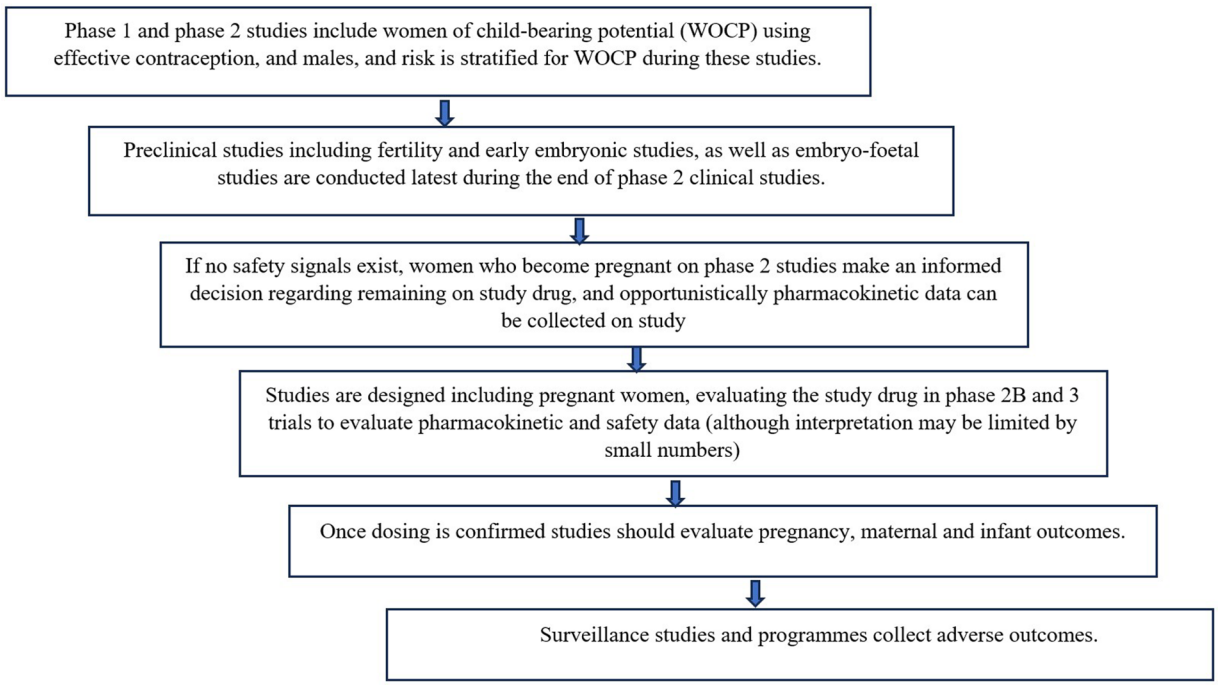

FIGURE 1
Framework for the safe inclusion of pregnant women in clinical trials.

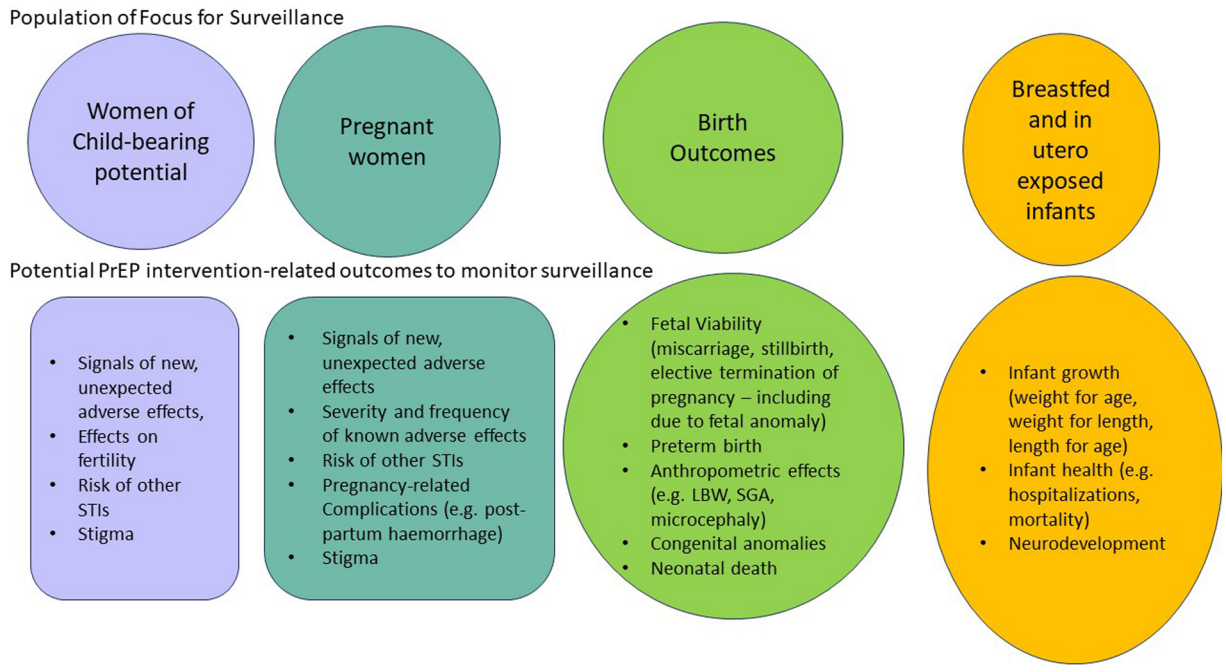

FIGURE 2
Populations and related key safety-related outcomes to include in surveillance of Pre-exposure prophylaxis (PrEP) products.

are proven. In contrast, in situations where pregnant women require specific ARV regimens to treat a resistant HIV virus, the risk/benefit balance may sway towards treating HIV in order to achieve virological control, improve maternal health and prevent HIV infection through vertical or horizontal transmission, even if the required therapy has minimal safety information in pregnancy. Similarly, if a more favourable HIV treatment drug becomes available and is rolled out to the general population, the risk/benefit balance may shift to encourage use in pregnant women, living with HIV even with limited safety information about the drug, as it would be potentially inequitable to exclude pregnant women. For example, in the Tsepamo study in 2018, a signal was detected for the increased risk of neural tube defects in babies born to mothers who conceived on dolutegravir, compared to WLHIV receiving other ART regimens and to women without HIV (46). An interim analysis initially reported an increased risk of 0.94% (compared to around 0.1% in WLHIV on other ART and HIV-negative women). However, the risk decreased to 0.11% in 2022 after repeat analyses including a larger number of women (47). Importantly, despite the initial, apparent increased risk, and the resultant recommendation to exercise caution with the use of DTG periconception, the benefits of DTG including a more favourable side effect profile, faster viral suppression and reduced risk of developing HIV resistance resulted in ongoing use and advocacy supporting its use even in pregnant women (49). This study highlighted the need for bridging studies when products are prescribed for pregnant and breastfeeding populations, as well as the need for epidemiologically robust surveillance of HIV treatment and prevention products in the post-marketing period.

3. Safety surveillance systems

Given that many PrEP products are new, and considering the approaches to safety surveillance in WOCP, pregnant and breastfeeding women described previously, surveillance systems are required to enhance and confirm available data from clinical trials, implementation trials and demonstration projects. These systems form the final tier in evaluating PrEP safety and there are numerous types of surveillance that can be implemented. Safety surveillance systems for PrEP need to incorporate both passive and active surveillance systems. Active surveillance systems must have the capacity to measure risk by reliably comparing collected rates of adverse outcomes of interest between exposed and unexposed populations whether these unexposed groups are contemporary or historic controls.

Passive surveillance systems are usually implemented nationally or across many countries and therefore provide an inexpensive option for the detection of signals of previously unknown or poorly understood adverse events. Active safety surveillance systems are best placed within environments where a high number of exposures are expected in WOCP or pregnancy, and specifically where the disease is common, or medication required for treatment or prevention is commonly used. For example, in South Africa where around 7.5 million people are living with HIV (50), active safety surveillance systems for HIV treatment and prevention are much needed. Unintended pregnancies are common, 33.9% overall and 55.9% in WLHIV in two pooled analyses from SSA, and as high as 71% in a recent study from Cape Town, South Africa in WLHIV (51–53). This increases the chance that conception on treatment may occur, even if a drug is

not licenced in pregnancy. Although the high rate of unintended pregnancy needs to be addressed urgently, this provides an opportunity for surveillance and to ensure that signals for adverse outcomes are reported as early as possible and closely monitored.

Standardisation of key maternal, pregnancy, birth and infant outcomes to be measured in surveillance programs allows for data pooling with other national and international programs, where increased numbers of exposures across differing geographical locations and populations adds strength to ascertainment of exposure-associated risk/s provided that the methods for data collection are comparable. A component of antenatal care which frequently presents challenges, is accurate gestational dating. Calculated using early ultrasound, reliable last menstrual period, gestational age assessment at birth or fundal height, gestational dating is critical to ascertain the timing of exposure of interest as well as outcomes such as prematurity, distinguishing stillbirth from miscarriage based on gestational age, and estimating low-for-gestational-age birth weight (54).

Teratovigilance studies the exposure of the fetus to external factors (drugs, substances, environmental factors, etc) and any resultant foetal developmental abnormalities and their impact on public health using epidemiological approaches (55). Teratovigilance is not confined to structural malformation but includes effects such as fetal loss, preterm delivery, impaired fetal and infant growth and development (55). Often such studies are designed to assess the risk of specific teratogenic effects that may have a biological plausibility or hypothesis based on animal and human studies with the specific drug in question or from drugs in the same class. For instance, long term follow-up studies aimed at assessing the safety of integrase inhibitors may form a critical component of the rollout plan for CAB-LA given early signals of neurodevelopmental and neurological effects associated with integrase inhibitor use (56–58). In establishing teratovigilance systems, a number of factors must be considered. Although pre-clinical data may be reassuring, animal models do not reliably predict congenital anomalies in humans. Therefore, unexpected findings may arise and may require verification in other settings or populations. Teratovigilance systems need to be designed based on the key objectives of the system, the health-seeking behaviour of pregnant women in the communities where medicines of interest are commonly prescribed, the key risk drivers of the medicine/s being investigated and the threshold of acceptable risk for these medicines in pregnant women, considering their benefit profile. Classification systems such as EUROCAT and WHO have different categories for minor and major anomalies, resulting in a lack of uniformity across surveillance systems when reporting rates of congenital anomalies (59, 60). Usually, surveillance systems are only able to capture surface examination findings of congenital anomalies at the time of delivery. Internal congenital disorders such as cardiac, renal or other anomalies may only be detected much later on as well as longer term effects on growth and neurodevelopment. This is expected and needs to be noted as a potential limitation of such systems. Stillborn surface examination is difficult, depending on the state of the fetus, and may be inaccurate in macerated stillbirths. Health care workers often prefer not to conduct stillbirth surface exams and may require support and training to highlight the clinical importance of identifying and recording potential congenital anomalies. In addition, autopsies are rarely conducted in stillbirths. Very few surveillance systems have the capacity to include miscarriages or medical/elective pregnancy termination, and birth defects are likely to be missed in these cases. Surveillance approaches may also need to be augmented with social science research and other research to assess the impact of the introduction of PrEP on stigma, health-seeking behaviour, fertility, risky sexual behaviour and the rates of other STIs.

Longer term studies aimed at assessing the effect of in-utero exposures on growth and neurodevelopment will be important given that such studies are lacking even in cases where there are early studies suggesting a potential risk (61–63).

A sustainable surveillance model which integrates health system strengthening is central to improved quality and monitoring of care for pregnant women. Periodic reporting from surveillance systems and feedback to health care workers accompanied by relevant training is likely to build confidence in providing the necessary care. Such data may also be required by regulators, particularly where clinical trial data is limited, to expand labelling of drugs to include pregnant and breastfeeding women, subsequently increasing access. Resources are required for such surveillance systems as they are usually not implementable within the confines of a busy, already over-burdened health care system; external funding is almost always required. It may be possible for the cost of surveillance systems to be reduced over time as these outcome measure become standard of care and with increasing digitisation of health records, making them more sustainable within the routine health care system. However, this usually occurs sometime after implementation and does not completely negate the need for ongoing surveillance support.

4. Approaches to safety surveillance

Below we describe passive and active surveillance systems that could be considered for PrEP safety surveillance, exploring their strengths and limitations as safety surveillance and teratovigilance methods (summarised in **Table 1**) with some discussion on how these relate to PrEP surveillance (64). The decision regarding which system/s to choose depends on what the key risk drivers are likely to be based on available evidence, knowledge gaps, feasibility of implementation and end-user preference. Consideration of the primary objectives of the surveillance system should made by key stakeholders including regulatory authorities, HIV/AIDS and Maternal and Neonatal Health departments, academic researchers, and pregnant women themselves.

4.1. Passive surveillance reporting systems

4.1.1. Case reports (spontaneous reporting)

Spontaneous reporting systems of individual case reports of suspected adverse reactions are a standard pharmacovigilance approach applied globally. These regulatory systems are an

TABLE 1 Description of different surveillance types, examples, advantages and disadvantages.

Type of surveillance	Example	Approach	Passive/ active	Advantages	Disadvantages
Case reports, Medicines information systems, Pharma-driven Registries	Vigibase (65) OTIS (66) and ENTIS (67) Medicines Information Centre SA (68) Antiretroviral Pregnancy Registry (69)	Voluntary reporting of adverse events by clinical staff to a central body	Passive	Detection of signal for congenital anomalies or other adverse outcomes, potential to detect miscarriage.	Sample size usually small, denominator uncertain, difficult to quantify extent of risk, reporting bias
Hospital-based surveillance	Tsepamo (46) Eswatini (70) Uganda and Malawi Birth Defects Surveillance projects (74)	Data collection on pregnancy, exposures and outcomes, + - consented photographs of congenital anomalies, routine case record review + - interview of mothers	Active	Large cohort, comparator/ control groups, good quality data when coupled with health system strengthening	Missed miscarriage, home delivery, reliant on accuracy of maternal records
Case-control studies	National Birth Defects Prevention study (71)	Matched control group without the outcome of interest enrolled with group where infants born with outcome of interest. Exposures and any other potential risk factors captured from each group and compared	Active/ Passive	Detailed data on specific defects Indication of risk for factors associated with outcome, information bias, information on outcomes not included in the case definition may be limited	Small cohort depending on number of facilities involved, may not be generalisable to different socio-economic, environmental circumstances
Prospective cohort studies	Ubomi Buhle (SA) (72) Western Cape Pregnancy Register (73, 74)	Prospective collection of data from first ANC visit, through pregnancy and outcome	Active	Health system strengthening focus to improve exposure history, outcome ascertainment, embedded in routine care	Time-consuming, additional resources required, may miss miscarriages, data quality dependant on maternal record
Healthcare Data Bases	Western Cape Provincial Health Care Data Base (74)	Clinical records including laboratory tests and other specialist investigations collected electronically as part of standard of care	Active	Large, representative cohort, Data linked to pharmacy dispensing records, laboratory results, specialist services, using unique identifier	Date of conception and gestational age usually unknown Challenges in controlling for bias and confounding

inexpensive but effective way of monitoring the safety of all health products, enlisting the support of health professionals and the public to provide information on the safety performance of these products in the country. In recent years, systems have been digitised allowing for easier and more timely reporting. Important signals related to teratogenic exposures have been detected through the reporting of individual clinical case reports. The risk of phocomelia and other major limb malformations with thalidomide, the teratogenic risk of isotretinoin and mycofenolate in pregnancy are well-known examples of teratogens identified through case reports and spontaneous reporting (75). However, the system depends on *voluntary* registration of events by clinical staff, and underreporting and reporting biases remain key challenges affecting the reliability of the data. In the case of pregnancy-related events, the delay between the timing of exposure during pregnancy and manifestation of the adverse outcome at birth, confounded by events and other exposure in-between means that spontaneous reporting has some limitations as a signal detection tool in pregnancy exposure cases. Nevertheless, it remains a useful tool for maternal adverse reactions and adverse reactions that WOCP may encounter. In addition, given the lack of a denominator and a reliable comparator group, spontaneous reporting is not able to accurately assess the magnitude of risk. Nevertheless, efforts are underway to optimise spontaneous reporting forms to collect better data from pregnancy-related reports (76).

4.1.2. Medicines/teratology information centres

Medicine information centres are a valuable resource to support health care professionals with therapeutic decision-making. In high income countries, bespoke centres are in place to support pregnant and breastfeeding women and their clinicians with therapeutic decision-making in pregnancy. Teratology information centres leverage the opportunity of clinical enquiries to support collection of data on pregnancy exposures to medicines that are poorly studied. After obtaining an initial query about the safety of a particular medicine in pregnancy, the healthcare workers or the patient are contacted post-partum to determine additional pregnancy exposures and the birth outcome, including information on the presence of any birth defects. These teratology information centres are often based in academic institutions or at health facilities, are usually independent of the pharmaceutical industry and are supported by clinicians and researchers with relevant expertise in the area. That these cases are identified before the birth outcome is known and are followed up prospectively, minimizes the likelihood of recall bias. The Organization of Teratology Information Specialists (OTIS) and European Network of Teratology Information Services (ENTIS) have pooled case reports to create a "control pool" of cases of women who have been exposed to a non-teratogenic substance (67, 77). This control pool is used to conduct risk analyses for women exposed to products with an unknown risk profile (78).

Limitations include, certain information such as failed elective termination of pregnancy, self-prescribing or illicit drug use may not be disclosed/captured by these centres and there may be a bias towards more motivated responders having higher education status and more social stability resulting in selection bias. The latter may also be an advantage as data on other exposures, for example over the counter (OTC) and herbal medications, can be collected. This approach was used to identify the increased risk of birth defects with methotrexate use (79). Unfortunately, medicines information centres are currently scarce in HIV-endemic countries, with only South Africa having a maturely developed information resource in the SSA region, hence limiting the opportunities for leveraging these resources for PrEP surveillance. The Medicines Information Centre in South Africa, however is only accessible to health professionals and does not interact directly with the public (68).

4.2. Exposure registries managed by the pharmaceutical industry

An example of such a registry is the Antiretroviral Pregnancy Registry (APR) established in 1989, mainly for exposure to ART as treatment in pregnant women living with HIV, but also includes PrEP exposures and is still ongoing (69). This registry type is established by the manufacturers for specific drugs/drug classes such as antiretrovirals or anti-epileptic agents and are usually global (80). The APR requires voluntary enrolment of women receiving a specific ART or combination ART, resulting in a case collection. This may assist with signal detection for specific drug exposures and may be a regulatory requirement in some circumstances.

Limitations include the lack of background rates of adverse outcomes from the source population, selection bias, low levels of enrolment, particularly from LMIC settings, frequent missing data, and difficulty ascertaining risk due to the lack of background rates or comparator groups. In some instances, manufacturers create a pregnancy exposure registry for an individual product rather than a class of products. Such registries are unlikely to provide adequate data to identify signals or the controlled data needed to estimate risks of harm.

4.3. Hospital-based surveillance of birth outcomes

Data are collected from the maternal records or other maternity registers at pregnancy outcome in high volume delivery facilities, with a specific focus on capturing exposures and outcomes related to pre-conception (where possible) and pregnancy. These systems use records designed for recording of pregnancy-related information such as gestational age, exposures, comorbidities, as well as infant surface examination with photographs if there is a birth defect and consent is given. Examples of such surveillance systems focussing on ART include the Tsepamo study in Botswana (48) (discussed previously), ViiV study in Eswatini and the Ugandan and Malawi Birth defect surveillance programmes (70, 81, 82). The advantages of such systems are that large numbers of records of exposures and pregnancy, maternal and infant outcomes can be collected with good ascertainment of variations in frequency of birth outcomes. These surveillance models usually collect data on *all* women seeking perinatal care including HIV-exposed and unexposed women, ART exposure with different drugs (treatment and prevention) and without drug exposure, providing concurrently enrolled control groups for various risk analyses. These surveillance projects are usually conducted in a specific country or region and may not be representative of countries/regions where there are programmatic variations, socioeconomic, geographic, ethnic, or genetic variations. This model requires reliable, accurate and consistent capture of drug exposure data as part of routine maternal care and is best augmented with concurrent health system strengthening initiatives targeting data collection on medicines use so that data on exposures are elicited or captured reliably. Missing outcomes can occur in situations such as miscarriage, early stillbirths, elective and medical termination of pregnancy and home-based deliveries, although this is a limitation of most surveillance models.

4.4. Case control surveillance

Case control studies involve the collection and comparison of data on exposures and risk factors on infants born with the outcome of interest against similar data on an appropriately matched control group without the outcome of interest. Cases are usually derived from a number of hospitals or facilities where birth defect surveillance is being conducted. Matched controls are then selected using birth registration or hospital records to evaluate whether there are any associated risk factors for particular birth defects including data on medicine exposures. Data are collected retrospectively (e.g., by telephonic interview with the mother and/or health care provider) after delivery and includes pregnancy, family and obstetric history, medical care, diet, lifestyle, and medicine used during pregnancy. The potential pitfalls of this approach are recall bias of drug exposures history and compromised accuracy with respect to the timing of exposure as this information is elicited retrospectively. National Birth Defect Notification systems can be leveraged to identify relatively rare malformations, using matched controls from the reporting institutions. With the development of the Global Birth Defect Detection and Coding App, birth defect cases can be collected across multiple sites across the globe using a single system facilitating remote pooled coding and assessment of all cases (83).

4.5. Prospective cohort studies

Pregnant women are enrolled prospectively, and data are collected from their first antenatal clinic visit onwards. As with the other active surveillance approaches, this model works best when combined with health system strengthening and capacity building initiatives aimed at ensuring that maternal care and record-keeping are linked across facilities, that some identifier such as a sticker placed on the clinical record makes participants easily identifiable and that clinical record-keeping is as complete and as accurate as possible. The approach

works best when rates of facility-based delivery are high, referral pathways are well-defined and clinical record-keeping during antenatal and perinatal care is linked. Gestational dating during the antenatal period and at the time of delivery allows the determination of accurate timing of exposures of interest and the assessment of prematurity as a birth outcome. Data on confounding factors for the outcome of interest including additional exposures and risk factors for adverse outcomes should be systematically collected. This prospective model requires investment in data capture embedded at sentinel sites and training and mentorship of facility staff to support high quality clinical record-keeping. This approach is time-consuming, functions best in a reasonably well-functioning health system, and benefits from the use of unique patient identifiers to facilitate record linkage and reduce loss to follow-up between enrolment and pregnancy outcome. With this approach, miscarriages, medical or elective abortions that occur after the first antenatal visit and stillbirths are less likely to be missed compared to hospital-based studies. An example of this is the Western Cape Pregnancy Exposure Registry linked to the UBOMI BUHLE pregnancy exposure registry project in South Africa (72, 73).

4.6. Healthcare databases

This mechanism is usually integrated within relatively sophisticated routine state or private health care information systems, where a unique patient identifier allows for all data from each patient receiving care and treatment to be linked electronically into a single patient record. There is no specific focus on a particular life period, such as pregnancy or breastfeeding, and these periods may not be accurately be ascertained from the data. Data include longitudinal follow-up and tracking through different life and health stages and across different health facilities. In these databases, maternal and infant records are linked allowing for ongoing assessment of infant outcomes beyond birth into childhood which is advantageous. Reliable exposure ascertainment using electronic prescription and dispensing records is possible. Accurate coding of pregnancy and birth outcomes is essential, and this mechanism provides large numbers of pregnant women and their infants who have been exposed and unexposed to an infection such as HIV, with or without ART, with basic information on outcomes (e.g., Caesarean Section, livebirth, stillbirth, birth weight, maternal and neonatal death). Data on exposure to over-the-counter, complementary and traditional agents and medicines dispensed via ward stock may be missing (84) as well as data on outcomes of home-based deliveries and miscarriages. Gestational age and conception dates are often missing and require computational estimation of timing of exposure, which may limit accuracy of the timing of exposure related to pregnancy or breastfeeding. Depending on the health system in question, outcomes that require higher levels of expertise and diagnostic capacity such as specific congenital malformations may be inaccurate, incomplete or missing. An example of such a platform is the Western Cape Provincial Health Data Centre in South Africa, which has already been used to assess the safety performance of isoniazid preventive therapy in women with HIV (74).

5. Longer term safety outcomes

A limitation of all current surveillance systems is not extending through to the postnatal and breastfeeding period and longer term, to assess growth and neurodevelopmental effects in childhood following in-utero exposures (85). Existing and future cohort studies to assess the growth and development of HIV-exposed and HIV-unexposed uninfected infants could be leveraged to assess the effect of PrEP exposures in pregnancy and breastfeeding. Healthcare databases are often able to link maternal and infant records allowing for longer term follow-up of exposed infants into childhood as well as detecting adverse birth outcomes and congenital disorders only identified in infancy and childhood (e.g., through linkage to paediatric cardiology, surgery and renal services). Studies assessing growth and neurodevelopment need to use measurement tools and approaches that have been validated in the local population while ensuring that data can be pooled across sites and settings.

6. Surveillance during breastfeeding

Most of the approaches above do not focus on safety issues that may arise in the infant as a result of breastfeeding alone. Very often, exposures to medicines occurs as a continuum from pregnancy into the breastfeeding period. Early infancy is fraught with confounding factors including the coincidental manifestation of infections and underlying clinical conditions. For this reason, attribution of causal association between exposure of a medicine during breastfeeding and the occurrence of an adverse effect is challenging and complex. Exposures are also difficult to measure, particularly with reliance on maternal history of breastfeeding and limited information on the extent to which medicines are excreted into breastmilk. Current knowledge suggests that accumulation of PrEP medicines in breastmilk is minimal (29). Passive surveillance systems and regular review of the international biomedical literature for signal case reports of potential harms associated with breastfeeding may be the first approach to determining the need for more active targeted surveillance approaches for infants exposed during breastfeeding.

7. Selecting a surveillance mechanism

Given the strengths and challenges of the various approaches outlined above, a number of factors need to be considered when developing a safety surveillance plan for PrEP products in pregnant and breastfeeding women and their children. First and foremost, strategic aims and objectives of such a plan need to be developed based on a thorough assessment of what is known and remains to be studied in terms of the safety and tolerability of PrEP products. These plans will vary according to country, region or even within-country. Perhaps most important would be consideration of the extent to which these products are likely to be used in pregnant and breastfeeding populations in the country

and hence the public health importance of ensuring that these products have a favourable risk-benefit profile in the local context. Ideally, in high HIV-endemic settings, both active and passive surveillance systems should form part of the surveillance plan. In such settings, a landscape analysis could identify existing research and surveillance systems that can be leveraged to support PrEP safety surveillance. Political support for such surveillance will be critical in ensuring that the findings of such surveillance projects can inform policy. The spontaneous reporting system usually overseen by the national regulatory authority remains the mainstay of passive surveillance for all medicines including medicines used in pregnancy. The custodians of these systems need to work closely with public health researchers and policymakers engaged in developing and implementing the active surveillance system in order to ensure that signals can be detected, validated and assessed in collaboration.

The resources required to implement the chosen surveillance plan and feasibility thereof are strong considerations and include financial, implementation (for example, electronic devices, network availability), and human resources, particularly regarding how much surveillance can occur within the public health system and how much support is needed. Some models, such as a prospective surveillance system, are more costly but allow more accurate data to be collected; others may be more easily implemented within a routine public health system but produce less accurate results. The numbers of potentially eligible patients need to be considered in choosing the surveillance approach, for example in an environment where high prevalence of disease and drug use exists, it may be cost-effective to select a prospective or hospital-based surveillance system whereas in a lower prevalence environment, data could contribute to a global registry such as the APR. There is growing appreciation of the need for a signal surveillance platform to assess a variety of exposures in pregnant women and infants rather than bespoke projects looking at specific drugs or clinical conditions. A surveillance system may include a hybrid of high quality (such as prospective) and cross-sectional approaches (such as hospital-based or case-collection), ensuring that data can be compared in order to improve our understanding of the findings while expanding the data sources on which policies will be based. As far as possible, aligning surveillance system data points between different projects and geographical areas will allow later analysis across these diverse areas, increasing the generalisability of signals or risk factors across different populations.

8. Conclusions

As options for PrEP products, and access increases in WOCP, pregnant and breastfeeding women, pharmacovigilance systems that encompass both active and passive surveillance, provide an important opportunity to monitor the safety of current and new PrEP products in women and their infants. These surveillance systems also provide reassurance to both public health programmes, clinicians, and clients, that efforts are underway to ensure that recommended PrEP products have a favourable risk-benefit profile based on robust evidence. In establishing surveillance systems in-country, existing systems should be identified and strengthened, and there should be coordination across systems in-country regarding data triangulation, involvement of relevant stakeholders, avoiding duplication of new initiatives and allowing the design and implementation of new systems to be relevant and informed by experts.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LF, UM and DL conceptualised and developed the first draft of the manuscript. All authors reviewed, contributed and approved the submitted version of the article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Adherence to daily, oral TDF/FTC PrEP during periconception among HIV-exposed South African women

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Background: Daily, oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as pre-exposure prophylaxis (PrEP) reduces HIV acquisition for African women. Adherence is key to efficacy and patterns of adherence can be highly variable in real-world settings. Using group-based trajectory modeling (GBTM), we sought to identify distinct patterns of periconception PrEP adherence and evaluate potential baseline predictors of such adherence trajectories.

Methods: We conducted a single-arm longitudinal study for women aged 18–35 years living in Durban, South Africa with personal or partner plans for pregnancy with a partner with HIV or of unknown serostatus. Participants were offered safer conception counseling, including daily oral PrEP; women who initiated PrEP were given a bottle with an electronic pillcap that recorded when device opens. Weekly adherence to daily PrEP was modeled using GBTM with a censored normal outcome distribution as a function of weeks since PrEP initiation. The number and functional form of the adherence trajectory groups were primarily selected based on Bayesian information criteria (BIC) and confirmed by mean estimated probabilities of group membership. A multivariable version of the selected model assessed baseline predictors of membership in adherence trajectory groups.

Results: Overall mean (95% CI) adherence to PrEP was 63% (60%, 67%). We identified four groups of women with distinct patterns of adherence: (1) high (i.e., ≥6 doses per week) steady adherence throughout follow-up (22% of PrEP initiators); (2) moderate (i.e., 4–5 doses per week), but steady adherence (31%); (3) initially high, but consistently declining adherence (21%); and (4) initially moderate adherence, followed by a rapid decline and subsequent rebound (26%). In multivariable-adjusted analyses, older age was associated with membership in the high, steady adherence group as compared to the group identified with an adherence trajectory of initially high, then decline, and finally a rebound.

Conclusions: GBTM is useful for exploring potential heterogeneity in longitudinal patterns of medication adherence. Although a large proportion of women in this study achieved high levels of adherence by electronic pillcap initially, far fewer women maintained these levels consistently. Knowledge of different adherence trajectories could be used to develop targeted strategies for optimizing HIV prevention during periconception.

KEYWORDS

HIV prevention, oral pre-exposure prophylaxis (PrEP), adherence, women, periconception, group-based trajectory modeling (GBTM)

Introduction

Women of reproductive age constitute the majority of new HIV infections in South Africa (1). It is vital to ensure that women who wish to conceive with a partner with HIV or of unknown HIV-status have access to strategies to lower the risk of HIV acquisition during conception. Daily, oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as pre-exposure prophylaxis (PrEP) is an important individually-controlled method for reducing risk of HIV acquisition during conception and throughout pregnancy (2, 3).

PrEP has high efficacy for HIV protection in African women and is safe to use during pregnancy; however, adherence is key to maintaining protection (4–7). Uptake of and adherence to PrEP in real-world settings is highly variable (8–10). Changes in adherence can be driven by multiple factors including intentional breaks in PrEP use (11) (i.e., no risk of HIV perceived) or gaps in adherence due to challenges overcoming known barriers to use such as medication fatigue, drug side effects, and partner relationship dynamics. This presents an implementation challenge as no gold standard exists for measuring adherence, especially when it changes over time (12, 13). Common approaches to measuring and describing adherence include using prescription refill data or pill bottle openings as a proxy measure of medication consumption and cross-sectional assessments of drug levels to approximate average historical adherence. However, these methods report a single value to summarize medication use and may miss potentially informative trends in the existence and corresponding behavior of sub-groups. Analytic approaches that allow for the identification and subsequent stratification of these sub-groups represent a critical first step to designing effective targeted interventions.

Group-based trajectory modeling (GBTM) is a method first developed in the field of criminology for assessing individual-level differences in criminal career patterns (14–16). The use of GBTM has since been expanded to look at other behavior patterns like medication adherence (12, 17, 18), sexual risk-taking (19), and healthcare expenditures (20). A key advantage of GBTM is that it allows for individual-level heterogeneity in propensity for the outcome without assuming an underlying distribution for that propensity. This both allows for unmeasured variables to impact the outcome and enables the detection of sub-group trajectories within the data (14, 15).

The current analysis uses data collected as part of a single-arm interventional trial in Durban, South Africa to evaluate the use of TDF/FTC as PrEP among women with potential for HIV-exposure and planning for pregnancy (21). A cohort of 330 women aged 18–35 were enrolled and offered safer conception counseling, including daily oral PrEP. Participants were followed for 12-months (or longer if they became pregnant), and those who initiated PrEP were given a pill bottle with an electronic cap that recorded when the device was opened, providing an assessment of day-to-day dosing behavior. Using the electronic pill cap data, we applied GBTM to (a) identify distinct patterns of longitudinal PrEP adherence within trial participants and (b) evaluate potential baseline predictors of any identified adherence trajectory groups.

Materials and methods

Study design and population

The Zivikele ngaphambi kokukhulelwa (ZINK) ("Protecting yourself before pregnancy study" in Zulu) was a single-arm longitudinal study conducted in Durban, South Africa. ZINK participants included women aged 18–35 years who tested HIV-negative at enrollment and reported personal or partner plans for pregnancy within the next 12 months with a partner with HIV or of unknown serostatus. All participants were offered safer conception education emphasizing the importance of couples-based HIV counseling and testing, antiretroviral therapy (ART) for partners living with HIV, treatment for sexually transmitted infections (STIs), and safer conception strategies, such as limiting sex without condoms to peak fertility. We also offered daily TDF/FTC, oral PrEP during periconception and pregnancy with adherence support. Recruitment was conducted by field teams reaching out directly to women at local Department of Health (DoH) primary health care clinics within the eThekwini District, gathering spots near the research site, and through word-of-mouth promotion from enrolled participants and others who knew of the study.

The primary aims of the study were to determine PrEP uptake and use during the periconception period and pregnancy. The current manuscript reports on PrEP adherence during periconception (the period from enrollment until study exit or incident pregnancy).

Study procedures

A complete description of the study procedures including the safer conception education, visit schedules, adherence support, and questionnaires can be found elsewhere (21). Briefly, at the enrollment visit, women were offered a package of safer conception counseling based on South African guidelines (22). Safer conception counseling occurred at baseline and at each quarterly visit thereafter for non-pregnant women.

Participants who chose to use PrEP were offered oral, daily TDF/FTC PrEP. Women were counseled to use PrEP for 7 days

(as per WHO 2016 guidance) before engaging in sex without condoms or other backup protection. Women could choose to initiate/discontinue PrEP at any time during the periconception period. At the time of initiation, women were provided with a 30-day supply of PrEP, consistent with South African guidelines at the time. At each quarterly visit thereafter, a 90-day supply was provided.

Laboratory

Participants completed beta-HCG urine pregnancy testing, individual HIV counseling and testing (HCT), and syndromic screening for STIs at each study visit. Participants who seroconverted were followed to promote linkage to care and conduct genotyping. Participants with a positive pregnancy test were referred to antenatal care and those with STI symptoms were referred to a local clinic for treatment.

Women who chose to initiate PrEP completed blood testing for renal function (creatinine) and for hepatitis B infection consistent with CDC and WHO guidelines at the time. Women with abnormal renal function or active hepatitis B infection were instructed to stop PrEP. Renal function testing was repeated quarterly PrEP could be re-started if serum creatinine and/or eGFR levels returned to normal.

Questionnaires

Baseline questionnaire was administered to assess constructs within our conceptual framework for periconception risk behavior (e.g., risk perception, reproductive autonomy, HIV stigma) (23, 24) using instruments validated in this setting. Questionnaires were administered via face-to-face interviews with a trained research assistant fluent in English and the dominant local language, isiZulu.

COVID 19 study adaptations

Due to the COVID-19 pandemic, South Africa was on a nationwide lockdown from March 27, 2020, to May 1, 2020. During that period, telephonic data collection was conducted for study activities to ensure the safety of participants. Only essential clinical visits were allowed and participants were screened for COVID-19 symptoms before their visits. Non-essential in-person clinic visits were allowed for up to 6-months for non-pregnant participants with 6-month PrEP prescriptions.

Measuring periconception adherence to PrEP

To measure daily pill-taking behavior, women were provided with a pill bottle with an electronic cap [Medication Electronic Monitoring System (MEMS) (AARDEX, Switzerland)] that recorded when the device was opened, providing an objective assessment of day-to-day dosing behavior. Among women who initiated PrEP, defined as collection of at least one month's supply of PrEP within 12 months of enrollment, we assessed adherence to PrEP as the number of days with a time-stamped record of a pill bottle opening (capped at one opening per day) divided by the number of days the participant was in active PrEP follow-up. Women were only monitored for adherence while in active PrEP follow-up, which we define as continued attendance of follow-up visits and acceptance of PrEP refills. For the purposes of defining adherence follow-up, women were censored at the earlier of the following: end of study, positive pregnancy test, HIV seroconversion, lost to follow-up, relocation outside the study area, or withdrawal from study. Women who became pregnant during the study were eligible to continue or start taking PrEP, but for the current analysis we restricted their data to the periconception period due to smaller numbers of pregnant women. A separate analysis will report on PrEP uptake in the pregnant cohort. During our study, PrEP was not widely available in the public health system in South Africa and was contra-indicated among women planning for or with pregnancy. Therefore, we assumed that any participant who missed a refill for any reason was no longer in active PrEP follow-up and could be censored at that time point; however, censored women contributed adherence data up through censorship and were eligible for any adherence pattern.

Statistical analysis

We used GBTM to identify sub-groups of PrEP initiators who followed distinct adherence trajectories over time. GBTM is an application of discrete mixture modeling that uses maximum likelihood estimation to fit multiple regression models simultaneously (25). More specifically, given the number of potential groups, the procedure fits (a) an intercept-only multinominal logistic regression model for the probability of membership in each group along with (b) separate regression models for the conditional distribution of the longitudinal data (conditional on group) as a smoothed function of time using higher-order polynomials.

For the current study, we modeled weekly adherence to PrEP (range: 0–7 doses per week) using a censored normal distribution as a function of weeks since PrEP initiation. We fit models with 2, 3, 4, and 5 potential adherence groups with up to a third-order polynomial (i.e., cubic term for time). The final model specification—including the number of groups and functional form of each group trajectory—was selected primarily based on the Bayesian information criteria (BIC). That is, models with lower BIC values indicate better fits to the observed data. The output from GBTM not only includes the estimated coefficients for the shape of each trajectory group, but also the estimated probability of group membership per group per participant and the proportion of participants "assigned" to each group. GBTM assigns individuals to groups according to the group with highest estimated probability of membership for that individual. As

recommended by Nagin (2005) and Nagin and Odgers (2010), we confirmed the adequacy of the identified model fit by ensuring that the mean estimated probability of group membership for individuals assigned to each group was high (i.e., >0.7) with reasonably narrow confidence intervals (25, 26). To assess the potential for informative censoring, we compared baseline characteristics of women who were lost to follow-up, moved, or withdrew with women who were retained (women who became pregnant or seroconverted were not considered lost, as their censoring was part of the study design).

Lastly, using the selected model specification, we performed multivariable-adjusted analyses to assess predictors of membership in adherence trajectory groups. Candidate predictors were selected *a priori* based on our periconception HIV risk conceptual framework (24) and factors associated with adherence measured by tenofovir concentrations at 3 months (manuscript under review), and included age, education, perceived HIV risk (27), and PrEP optimism (28). All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC, USA) and PROC TRAJ (29).

Ethics

The protocol was approved by the Human Research Ethics Committee at the University of the Witwatersrand (Pretoria, South Africa) and the Institutional Review Board of Partners Healthcare (Boston, MA, USA) and University of Alabama at Birmingham. The protocol is registered with the South African Health Products Regulatory Agency (SAHPRA), MCC#20170131) and at ClinicalTrials.gov (NCT03194308).

Results

Between October 2017 and January 2020, we enrolled 330 women, of whom 195 (59%) initiated PrEP as a primary HIV-prevention method (Figure 1). A total of 180 (92% of PrEP initiators) were included in the current analysis. Fifteen women who initiated PrEP were excluded due to either no available pillcap adherence data ($n = 13$) or no pillcap adherence data prior to first positive pregnancy test result ($n = 2$). Among the 180 PrEP initiators with periconception pillcap adherence data, median (25th, 75th percentile) age was 24.4 (21.7, 27.2) years with 152 (84%) reporting education through or beyond grade 12 and 46 (25%) were employed. Most women ($n = 110$; 61%) had at least one prior pregnancy and 171 (96%) had been in a steady relationship for at least 6 months. Nearly all participants ($n = 172$, 96%) reported not knowing the HIV serostatus of their primary pregnancy partner at enrollment (Table 1).

For the current analysis of periconception pillcap adherence, the most common reason for discontinuing follow-up was pregnancy ($n = 31$) followed by loss to follow-up ($n = 19$) and relocation outside the study area ($n = 11$). Six women acquired HIV during follow-up, none of whom had detectable drug concentrations (Figure 1). Supplementary Table S1 summarizes

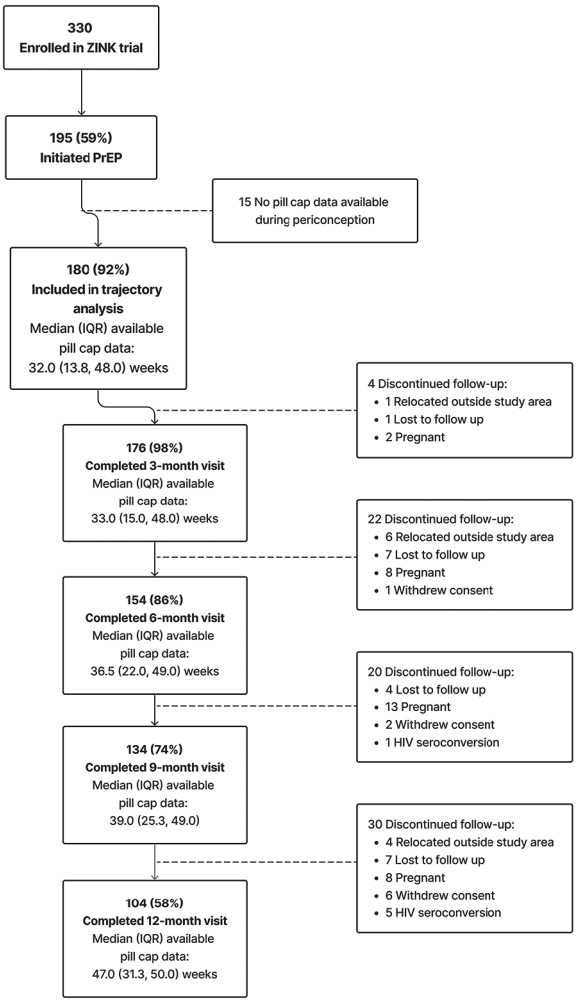

FIGURE 1
Summary of enrollment, eligibility, and retention of cohort included in trajectory analysis.

the baseline characteristics of women lost to follow up with those who remained under study. Briefly, women lost to follow up were less likely to have prior pregnancies. Other demographics were similar, with women lost to follow up having slightly higher income and education. The total amount of observed PrEP follow-up time ranged from 1 to 52 weeks with most women contributing >32 weeks [overall median (25th, 75th percentile): 32 (13.8, 48.0)] weeks. Among women who completed the 9-month follow-up visit the median (25th, 75th percentile) duration of PrEP follow-up was 39 (25.3, 49.0) weeks (Figure 1). Overall mean (95% CI) adherence to PrEP through 39 weeks was 63% (60%, 67%).

Figure 2 presents and compares the observed (bold lines) and predicted lines (dashed lines) weekly adherence to PrEP using 2–5 trajectory groups with third-order polynomial terms for time since PrEP initiation. The maximum observed follow-up time for adherence was 52 weeks. However, in analyses using all observed follow-up time, trajectory shapes became highly sensitive to outliers during later time periods. This loss of data was due to multiple reasons, including late initiation of PrEP, administrative

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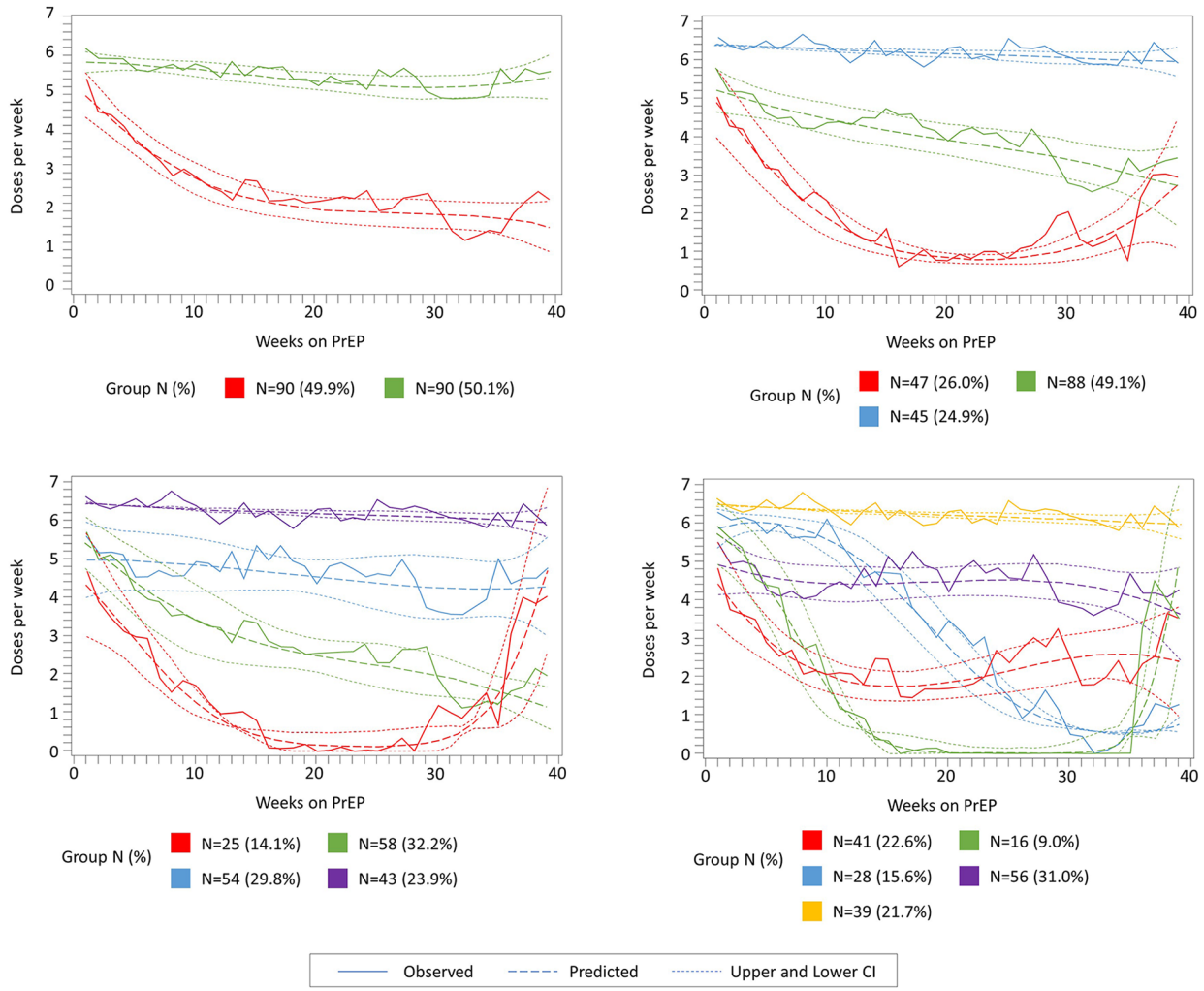
TABLE 1 Summary of baseline characteristics of $N = 180$ women initiating PrEP and enrolled in a single arm trial of a safer conception intervention for HIV prevention in Durban, South Africa 2017–2020, overall and by adherence trajectory group.

Characteristics (n with available data)	Overall $N = 180$	Adherence trajectory group[a]			
		1: High steady adherence $N = 40$ (22%)	2: Moderate but steady adherence $N = 55$ (31%)	3: Consistently declining adherence $N = 38$ (21%)	4: Rapidly declining adherence then rebound $N = 47$ (26%)
Age (years) ($n = 180$)					
Mean	24.8	25.8	25.1	24.8	23.5
Median (25th, 75th percentile)	24.4 (21.7, 27.2)	25.5 (23.1, 29.1)	24.9 (22.8, 26.7)	24.4 (20.9, 27.8)	22.3 (20.7, 25.8)
Education ($n = 180$)					
Grade 7–11	28 (16%)	7 (18%)	7 (13%)	8 (21%)	6 (13%)
Grade 12 or beyond	152 (84%)	33 (83%)	48 (87%)	30 (79%)	41 (87%)
Currently employed ($n = 180$)	46 (25%)	16 (40%)	15 (27%)	7 (18%)	8 (17%)
Income, per month ($n = 131$)[b]					
<$116	48 (36%)	9 (32%)	12 (31%)	11 (41%)	16 (42%)
$116-$232	41 (31%)	11 (39%)	12 (31%)	8 (30%)	10 (26%)
>$232	42 (32%)	8 (28%)	14 (37%)	8 (30%)	12 (31%)
Prior pregnancies ($n = 180$)					
0	70 (39%)	16 (40%)	17 (31%)	17 (45%)	20 (42%)
1	71 (39%)	13 (32%)	23 (42%)	13 (34%)	22 (47%)
2+	39 (22%)	1 (27%)	15 (27%)	8 (21%)	5 (11%)
Sexual partners, past 3 months ($n = 179$)					
1	156 (87%)	39 (97%)	43 (80%)	36 (95%)	38 (81%)
2+	23 (13%)	1 (2%)	11 (20%)	2 (5%)	9 (19%)
HIV serostatus of pregnancy partner ($n = 179$)					
Known to be HIV negative	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Known to be HIV positive	7 (4%)	6 (15%)	0 (0%)	1 (3%)	0 (0%)
Unknown HIV serostatus	172 (96%)	34 (85%)	54 (100%)	37 (97%)	47 (100%)
Relationship status with pregnancy partner ($n = 179$)					
Ongoing casual partner/one-time encounter	2 (1%)	0 (0%)	1 (2%)	0 (0%)	1 (2%)
Boyfriend/main partner for <6 months	6 (3%)	2 (5%)	0 (0%)	2 (5%)	2 (4%)
Boyfriend/main partner for ≥6 months	164 (92%)	36 (90%)	51 (94%)	35 (92%)	42 (89%)
Spouse or living as married ≥6 months	7 (4%)	2 (5%)	2 (4%)	1 (3%)	2 (4%)
Any alcohol consumption, past year ($n = 179$)	93 (52%)	17 (42%)	33 (61%)	18 (47%)	25 (53%)
Depression score ≥ 1.75 ($n = 177$)[c]	9 (5%)	2 (5%)	5 (9%)	1 (3%)	1 (2%)
Sexual Relationship Power Score ($n = 156$)[d]					
Mean	2.6	2.6	2.6	2.6	2.6
Median (25th, 75th percentile)	2.6 (2.4, 2.8)	2.7 (2.5, 2.9)	2.6 (2.4, 2.8)	2.6 (2.5, 2.8)	2.6 (2.3, 2.8)
Perceived HIV risk ($n = 170$)[e]					
Mean	19.7	20	20	19.7	19.1
Median (25th, 75th percentile)	20 (18, 22)	20 (18, 23)	21 (18, 21)	19.5 (18, 21)	19 (17.5, 21)
PrEP optimism ($n = 177$)[f]					
Mean	5.7	5.9	6	5.3	5.7
Median (25th, 75th percentile)	6.0 (5.0, 7.0)	5.0 (5.0, 7.0)	6.0 (5.0, 7.0)	5.0 (5.0, 6.0)	6.0 (5.0, 6.0)

[a]N (%) unless otherwise noted; column percentages calculated among those with non-missing covariate data.
[b]Converted to $USD from ZAR.
[c]Hopkins Symptom Checklist was used to derive depression scores.
[d]Developed by Pulerwitz et al., the Sexual Relationship Power Score assesses Relationship Control and Decision-Making Dominance between a male and female partner.
[e]Developed by Napper et al., the HIV-risk score assesses a person's perception of their risk of acquiring HIV based on their sexual and lifestyle habits.
[f]Adapted from Kalichman SC., the PrEP optimism score assess a person's attitudes about taking PrEP for HIV prevention.

censoring of women after pregnancy or seroconversion, and women moving or withdrawing consent. Therefore, we restricted the follow-up period for the current analysis to 39 weeks; corresponding to median adherence follow-up time for women completing the 12-month visit (Figure 1). The 5-group trajectory model was discarded because one group contained <10% of the cohort. A 4-group trajectory model was selected over 2- and 3-group models based on having the lowest BIC value (Supplementary Table S2).

From the final 4-group model specification, we identified groups of women with (1) high (i.e., ≥6 doses per week) steady adherence over time (22% of PrEP initiators); (2) moderate (i.e.,



Note: Observed and predicted number of doses per week depicted with solid and dashed lines, respectively. Participants were assigned to a trajectory group based on the group with the highest predicted probability of membership; the number and percentage of participants assigned to each group are shown below each plot.

FIGURE 2
Observed (solid lines) and predicted (dashed lines) weekly adherence to PrEP over 39 months of follow-up assuming 2, 3, 4, and 5 trajectory groups and third-order polynomial terms for time since PrEP initiation.

4–5 doses per week), but steady adherence (31%); (3) initially high, but consistently declining adherence (21%); and (4) initially moderate adherence, followed by a rapid decline and subsequent rebound (26%) (Figure 3). The mean predicted probability of group membership for women assigned to each trajectory group was consistently high (all >0.7), indicating adequate model fit. Additionally, the width of the 95% CIs for the mean predicted probability of group membership was reasonably narrow with the widest CI observed for trajectory group 3 (95% CI: 0.76, 0.90 for an absolute width of 0.14). The lower bound for all CIs was above the suggested threshold of 0.7, also confirming the adequacy of model fit (Figure 3).

Table 1 summarizes the baseline characteristics of the adherence cohort overall and according to assigned trajectory group. Women with the high or moderate, but steady adherence over time (i.e., trajectory groups 1 and 2, respectively) were older, more likely to be currently employed, and report higher levels of optimism for PrEP at enrollment as compared to women with consistently or rapidly declining levels of adherence (trajectory groups 3 and 4, respectively). Among women assigned to trajectory groups 2 and 4, approximately 20% reported multiple sexual partners during the past three months, compared with less than 6% reporting the same in groups 1 and 3. Perceived HIV risk and sexual relationship power scores were similar across all four trajectory groups (Table 1).

Table 2 presents and compares a subset of baseline individual predictors (i.e., age, education, perceived HIV risk, and PrEP optimism) of group membership modeled using a multivariable-adjusted version of GBTM. In multivariable-adjusted analyses, age was inversely associated with membership in trajectory group (4) (i.e., initially moderately

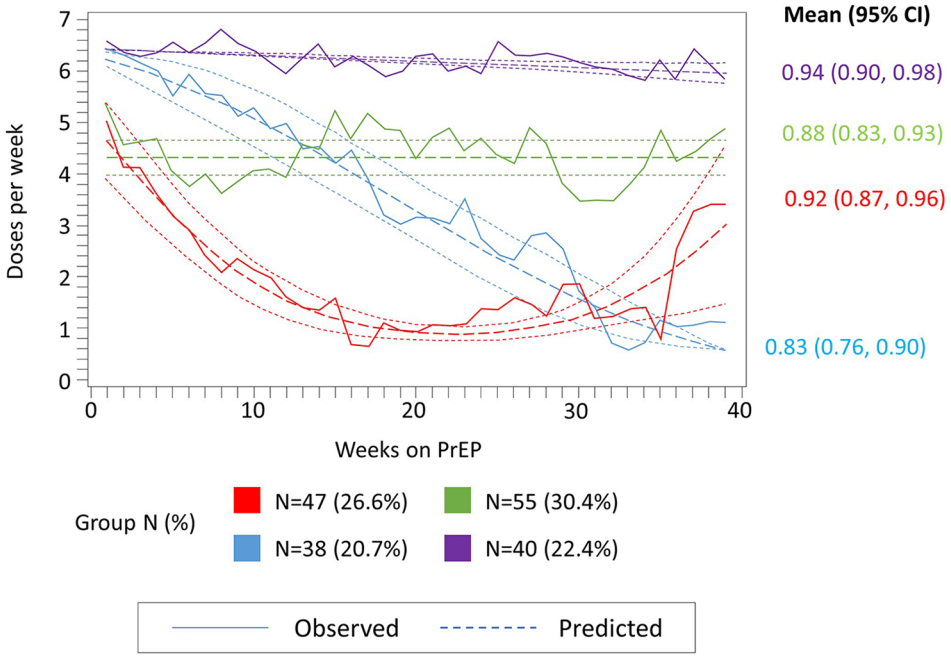
TABLE 2 Summary of multivariable-adjusted mean change in probability of membership in an adherence trajectory group among $N = 180$ women initiating PrEP and enrolled in a single-arm trial of a safer conception intervention for HIV prevention in Durban, South Africa 2017–2020.

	Estimate (95% CI) and *P*-value					
	2: Moderate but steady adherence		3: Consistently declining adherence		4: Rapidly declining adherence then rebound	
	(vs. 1: High steady adherence)					
Baseline characteristic						
Age (years)	−0.04 (−0.16, 0.08)	0.46	−0.07 (−0.23, 0.09)	0.34	−0.19 (−0.33, −0.05)	0.01
Education	0.69 (−0.58, 1.96)	0.29	0.11 (−1.36, 1.58)	0.88	0.02 (−1.41, 1.45)	0.98
Perceived HIV-risk	0.002 (−0.16, 0.16)	0.98	−0.03 (−0.23, 0.17)	0.76	−0.14 (−0.32, 0.04)	0.13
PrEP optimism	0.01 (−0.26, 0.28)	0.97	−0.23 (−0.60, 0.14)	0.23	−0.08 (−0.23, 0.39)	0.62

high adherence, followed by a rapid decline and subsequent rebound trajectory group). More specifically, one additional year of age was associated with a 19% decreased probability of membership in trajectory group (4) as compared with trajectory group (1) (i.e., high steady adherence) ($P = 0.01$). The other two adherence trajectory groups also had negative point estimates for age (i.e., decreased probability of membership as compared to trajectory group (1) (i.e., high steady adherence); however, neither were statistically significant. None of the other baseline covariates we examined were associated with membership in an adherence trajectory group.

Discussion

Among women living in an HIV endemic area and planning pregnancy with either a partner with HIV or of unknown serostatus, most chose PrEP as a safer conception strategy. These data indicate high demand for and acceptability of periconception PrEP in South Africa. The overall adherence summary suggests mean adherence by pillcap was 63% (corresponding to approximately 4.4 doses per week on average); our analysis of these data exposes that this mean includes women with excellent adherence (≥6 pills per week), moderate (4–5 pills per week), and two groups comprised of women who did not sustain adherence longitudinally, with one group



Note: Observed and predicted number of doses per week depicted with solid and dashed lines, respectively. Participants were assigned to a trajectory group based on the group with the highest predicted probability of membership; the number and percentage of participants assigned to each group are shown below each plot.

FIGURE 3
Observed (solid lines) and predicted (dashed lines) weekly adherence to PrEP over 39 months of follow-up assuming four trajectory groups and up to second-order polynomial terms for time since PrEP initiation.

having some rebound around 30 weeks of follow-up. Importantly, over half (52%) of those taking PrEP consistently took 4–6 doses per week over the follow-up period. Without GBTM, we miss important heterogeneity in how women planning for pregnancy use PrEP. Understanding and being able to identify these distinct adherence patterns may inform future efforts to tailor support for women accessing PrEP.

A few studies described patterns of PrEP adherence among women of reproductive age using GBTM with different results (12, 13, 30). An open-label demonstration project conducted in Kenya and Uganda used GBTM to identify four patterns of PrEP adherence (via daily electronic monitoring) among 233 women in HIV-serodifferent partnerships: high steady adherence, moderate steady, late declining, and early declining adherence (13). Approximately 55% of women were consistently and highly adherent. This is consistent with prior studies indicating that many women in mutually-disclosed HIV-serodifferent partnerships are successful in overcoming challenges in maintaining high adherence to PrEP (6, 31) A separate PrEP demonstration project conducted in Kenya—The Monitoring PrEP among Young Adult women (MPYA) study—used GBTM to identify three PrEP adherence patterns among 348 women aged 18–24 years: steady high adherence, moderate but declining, and low and declining (12). In contrast to the current study, only 5% of women exhibited steady, high adherence. The higher proportion of moderate to high PrEP adherence patterns in our study may result from motivations to achieve pregnancy while avoiding HIV and/or the reproductive-goals focused adherence support counseling, Healthy Families-PrEP, that was offered (21, 32).

Over half of our participants accessing PrEP consistently took 4–6 doses per week with about one-fifth taking at least 6 doses per week. Women in the other 2 groups were distinguished within 12 weeks of monitoring. We believe this early distinction in PrEP use could be a useful target for future interventions. The lone sociodemographic characteristic significantly associated with trajectory group was age: older women were more likely to display steady high levels of adherence to PrEP. This result is consistent with previously published findings (9). However, a more nuanced understanding of why young women experience worsening PrEP adherence over time will help to further optimize existing HIV prevention programs. In addition, over a quarter of women who had declining PrEP use experienced a rebound around 30 weeks of follow-up. Women participated in quarterly adherence support; it is possible that the 6-month session boosted use. It is also possible that life circumstances changed for this group (perhaps evolving decisions re. pregnancy plans). Future qualitative work to understand PrEP use by trajectory could be used to better understand factors informing how women choose to use PrEP and thus optimize support strategies offered. PrEP adherence support groups or interventions could be personalized especially for early or late PrEP decliners. Additionally, implementation studies that prioritize identifying PrEP adherence patterns early on, as well as developing optimal strategies for women with early declining adherence patterns would be desirable.

A key strength of this study is the combination of electronic monitoring of PrEP adherence via the MEMS caps and the GBTM analysis method. Using a measure of daily adherence allows for sufficiently granular data to make trajectory analysis possible. This contrasts with other measures of adherence, such as weekly or monthly prescription refill data, or drug concentration data collected at intervals. Although MEMS caps are not without measurement error, they have been demonstrated as more reliable than self-reported adherence, and the data correspond well with biomarkers of tenofovir intake (33). Another strength is that while our study population allowed for the inclusion of women who knew their partner was living with HIV, most women (96%) were unaware of the HIV status of their partner, making the findings more generalizable to women who live or interact in high HIV prevalence communities without concrete knowledge of their partner's HIV status. A limitation of this study is that our small sample size may have inhibited us from detecting meaningful demographic differences between the trajectory groups (12, 13). In addition, this analysis was limited to periconception PrEP use due to smaller numbers of pregnant women accessing PrEP (which will be addressed in a separate analysis).

In conclusion, women of reproductive age in HIV endemic regions remain susceptible to acquiring HIV. PrEP is an effective biomedical HIV prevention intervention when used consistently, however adherence remains a challenge. GBTM is a useful method for assessing how sub-groups of a population split into different patterns of longitudinal medication adherence. We found evidence of four different patterns of PrEP adherence behavior among a prospective cohort of women with potential for HIV exposure planning pregnancy, and age was associated with being in the rapid decline trajectory group. Nearly half of the women did not sustain steady adherence over the follow-up period. These findings indicate that younger women planning for pregnancy may be at risk of not adhering to PrEP over time and may benefit from novel strategies that address their unique needs and adherence barriers. Further research should explore the possibility of developing risk scores based on early adherence patterns to screen for women who may be at risk for declining adherence. Finally, given that current guidelines in South Africa are permissive of continuing PrEP during pregnancy, future implementation studies stake should into consideration different PrEP adherence trajectories among African women throughout their reproductive cycle to inform models of support.

Data availability statement

The datasets presented in this article are not readily available because primary analyses are ongoing. Once final analyses are complete, data will be shared to the Harvard Dataverse. In the interim, requests to access the datasets should be directed to the corresponding author. Requests to access the datasets should be directed to LM: lynnmatthews@uabmc.edu.

Ethics statement

The studies involving humans were approved by the Human Research Ethics Committee at the University of the Witwatersrand (Pretoria, South Africa) and the Institutional Review Board of Partners Healthcare (Boston, MA, USA) and the University of

Alabama at Birmingham. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by all participants.

Author contributions

KEH: Formal Analysis, Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. OI: Formal Analysis, Data curation, Visualization, Writing – review & editing. KRH: Writing – original draft, Writing – review and editing. MJ: Investigation, Project administration, Writing – review & editing. YK: Data curation, Investigation, Project administration, Writing – review & editing. PS: Data curation, Project administration, Writing – review & editing. MM: Data curation, Investigation, Project administration, Writing – review & editing. KB: Data curation, Formal Analysis, Writing – review & editing. CP: Funding acquisition, Resources, Supervision, Writing – review & editing. JB: Methodology, Resources, Writing – review & editing. DB: Funding acquisition, Writing – review & editing. JH: Methodology, Writing – review & editing. JS: Funding acquisition, Investigation, Supervision, Writing – review & editing. LM: Conceptualization, Funding acquisition, Methodology, Supervision, Validation, Writing – review & editing.

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Conflict of interest

LM received operational support from Gilead Sciences for this project. JH has been a consultant for Merck and owns stock in Natera. JB is an employee of Gilead Sciences, outside of the present work. KEH, KRH and KB are employed by and own equity in Target RWE, which has received fees from Amgen, Baxter International, Gilead Sciences, Janssen Research & Development (Janssen R&D), and Merck outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1263422/full#supplementary-material

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Uptake of and intention to use oral pre-exposure prophylaxis for HIV among pregnant and post-natal women in Eswatini: a cross-sectional survey

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Introduction: In Eswatini, HIV incidence among women of childbearing age is 1.45%. Eswatini introduced oral pre-exposure prophylaxis (PrEP) for HIV prevention in 2016 and requires that all HIV-negative pregnant and post-natal women (PPW) visiting health care facilities be offered PrEP.
Methods: Between September-November 2021, we conducted a survey among HIV-negative PPW from 16 purposively selected healthcare facilities in the Hhohho and Shiselweni regions in Eswatini. We interviewed consenting HIV-negative PPW using a structured questionnaire to collect data on PrEP knowledge, attitudes, intentions, and practices, as well as information on partner HIV status and stigma. Multivariate logistic regression was used to determine predictors of PrEP use and intention, adjusted for significant covariates.
Results: Of 1,484 PPW women approached, 1,149 consented and were interviewed, of whom 704 (61.3%) were post-partum and 445 (38.7%) pregnant. The median age was 25 years [Interquartile Range (IQR) = 21–30 years], with 533 (46.4%) 18–24 years old. Among the 1,149 women, 930 (80.7%) had ever heard about PrEP; 635 (55.3%) had knowledge about PrEP; 183 (15.9%) were currently using PrEP; and 285 (24.8%) had ever used PrEP. Increased odds of PrEP use were associated having HIV-positive male partner (aOR:7.76, 95%CI 3.53- 17.04); positive attitudes to PrEP (aOR:1.56, 95% CI: 1.02–2.40); and high self-efficacy (aOR:1.49, 95%CI:1.13–1.98). Among 864 women who never used PrEP, 569 (65.3%) intended to use PrEP in the future. Odds of intention to use PrEP were higher among women with low levels of education (aOR:2.23, 95% CI: 1.32–3.77); who ever heard about PrEP (aOR:1.69, 95%CI: 1.12–2.56); and had high self-efficacy (aOR:1.57, 95%CI: 1.31–1.87). Regarding stigma, among all women, 759 (66%) either agreed or strongly agreed that people would think they have HIV if they were to use PrEP; 658 (57.3%) reported they would be labelled as having multiple sex partners; 468 (40.7%) reported that their partner would think they are having risky sex with other people. Of 102 women who had discontinued PrEP, a majority stopped due to side effects 32 (35.2%).
Conclusion: Only about 50% of women had knowledge of PrEP, and PrEP uptake among PPW was low, though intention to use appeared high. More efforts to reduce stigma and promote PrEP use, including adequate information on side effects, are needed.

KEYWORDS

pregnant and post-natal women, HIV pre-exposure prophylaxis, PrEP, uptake, intention, Eswatini

Introduction

In 2016, the World Health Organization (WHO) strongly recommended offering oral pre-exposure prophylaxis (PrEP) containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention (1). Oral PrEP reduces the risk of HIV acquisition if used correctly as part of a combination prevention strategy. Several controlled trials have provided rigorous evidence that oral daily PrEP is protective against HIV infection among heterosexual sero-discordant couples (2, 3); women (4); men who have sex with men (MSM) (5); and injecting drug users (6). Evidence also shows that PrEP is safe to use by pregnant or lactating women (7–10). However, there are few surveys on knowledge and use of PrEP for HIV among pregnant and lactating women (11), and most of them have been conducted in South Africa. Data from the existing surveys showed low levels of awareness and knowledge about PrEP among pregnant and lactating women (12–14).

Eswatini has an HIV prevalence of 24.8% among adults 15 years and older, with a prevalence of 30.4% among women overall (15), and 35.4% among pregnant women aged 15–49 years (16). This is much higher than the prevalence among similarly-aged men of 18.7% (15). The annual HIV incidence rate among adults 15–49 years is 0.77% (0.20% among males and 1.45% among females) (15). With the high HIV prevalence and incidence rates, pregnant and post-natal women (PPW) in Eswatini are at substantial risk of HIV infection (11). Women who get infected with HIV during pregnancy or breastfeeding risk transmitting HIV to their infants (11). In 2019, the Eswatini Ministry of Health scaled-up the provision of PrEP as part of combination HIV prevention, with a particular focus on HIV-negative PPW, adolescent girls and young women (AGYW) aged 16–24 years, men aged 30–34 years, HIV-negative partners in sero-discordant sexual relationships, clients with sexually transmitted infections (STIs), and key populations (sex workers, men who have sex with men and transgender clients) (11). In Eswatini, clients are eligible for PrEP if at substantial risk after an assessment; age is 16 years and above; HIV test is negative on the day of PrEP initiation; there is no presence of symptoms indicating acute HIV infection (AHI) in combination with an exposure for HIV in the previous 14 days; willing to attended PrEP visits until 28 days after risk period; no contraindication to TDF + lamivudine (3TC); and bodyweight is 30 kilograms (kg) and above. PPW women are considered to be at substantial risk for HIV infection and are offered PrEP upon testing HIV-negative and having no contraindications for PrEP.

In Eswatini there is paucity of data on facilitators and barriers among PPW. Understanding the levels of knowledge, intention, use and potential gaps related to PrEP among PPW could help to identify opportunities for education and program implementation. The information could also be used to monitor the impact of social behavior change activities aiming to improve knowledge, attitudes and practices related to PrEP in antenatal and postpartum women. This study aimed to determine oral PrEP related levels of knowledge, attitudes, intention and practices PPW in Eswatini, and also to determine factors associated with use and intention to use PrEP among PPW.

Materials and methods

Study design

We conducted a cross-sectional survey among HIV- negative PPW between September 2021 and November 2021. All HIV-negative women receiving antenatal care (ANC) and postnatal care (PNC) services in the study sites were invited to participate in the study. Individual interviews were conducted using a structured questionnaire covering topics on socio-demographic characteristics, HIV risk behaviors, PrEP knowledge, PrEP access and sources of information, PrEP experiences (e.g., adherence, discontinuity, and side effects), intention to use PrEP and PrEP stigma. Only women who provided written informed consent were interviewed.

Study sites

The study was conducted in 16 purposively selected PEPFAR-supported health facilities and regions (Hhohho and Shiselweni) in Eswatini which were offering oral PrEP to PPW. By November 2020 there were 55 health facilities providing PrEP to PPW in Hhohho and Shiselweni regions, of which 34 were in Hhohho and 21 were Shiselweni region. Among the health facilities, six were public health units (PHUs) and 49 were clinics. Public health units provide primary healthcare services and are the basis for outreach services in Eswatini while clinics only provide primary healthcare services. Since there was a small number of PHUs, all six PHUs were included in the study and five clinics were randomly selected from each region using a random number generator in Microsoft Excel. Nine sites were selected from Hhohho region and seven sites were from Shiselweni region. The study sites comprised of four sites located in urban areas and 12 sites located in rural areas.

Sample size

The sample size calculation aimed to provide a sufficient sample size to estimate the proportion of PPW with knowledge about PrEP with ±3% precision (half width of 95% Wilson confidence intervals) or better. Since the proportion of PPW with knowledge about PrEP in Eswatini was unknown, the sample size calculation assumed that 50% PPW would have knowledge about PrEP. In addition, the sample size had to be large enough to allow a detection of significant differences of at least 10% with 80% power in knowledge and attitudes between current PrEP users and non-users, and also large enough to perform multivariate analysis to determine factors associated with PrEP use and intention to use PrEP. A sample size of at

least 1,064 was required to be able to meet the study objectives. We also factored in 10% refusal and non-response rate. Probability proportional to size was used to select the number of PPW to be interviewed from each site.

Study population and eligibility

The study population comprised of HIV-negative PPW seeking antenatal and post-natal care in the study sites. Women were eligible to participate in the study if they were accessing antenatal or post-natal services at the sites; were 18 years or older; were pregnant or reported to have delivered within 24 months; had a documented HIV-negative status; willing to provide consent to participate, and able to read and/or speak one of the study languages of English and SiSwati. Women were excluded if they had an illness that could prevent their participation, which included display of pain, inability to focus on the conversation or to talk or to sit throughout the interview.

Participant recruitment and data collection procedures

Women were recruited within Maternal Child and Neonatal Health (MNCH) departments in the study sites with the support of healthcare workers (HCWs) who worked in the study sites. The HCWs informed potential study participants about the study after providing them with the required clinical services for the day. Interested women were referred to trained research assistants (RAs) who were stationed in the study sites. After obtaining written informed consent, RAs interviewed the women in a quiet space using a structured questionnaire designed in EpiInfo 7, entering the responses directly into the database on Wi-Fi enabled tablets. The questionnaire had built-in controls and checks to assure data accuracy and quality.

Data collection instrument and definition of terms

A questionnaire was developed specifically for the study by adapting already validated questions from similar Knowledge, Attitude and Practices (KAP) surveys in multiple populations (12, 14, 17, 18). Adaptation included removing or rephrasing words and statements which did not apply to the study population. The interviewer-administered questionnaire collected data on socio-demographic characteristics, HIV risk behaviors, PrEP awareness and knowledge, PrEP access and sources of information, PrEP experiences (e.g., adherence, discontinuity, side effects), PrEP attitudes, PrEP motivation, PrEP self-efficacy, PrEP willingness, PrEP potential uptake (intention), and PrEP stigma. The questionnaire was translated from English to SiSwati, and participants had the interview in English or SiSwati depending on their preference.

Socio-demographic characteristics and sexual behavior questions were adapted from a PrEP demonstration survey conducted in Nigeria (17) and from a survey of knowledge and PrEP use among pregnant and breastfeeding women (PBFW) in South Africa (12). Socio-demographic variables included age, level of education, marital status, employment status, health related decision making and characteristics of male partners such as their age, HIV status, and employment. Sexual behavioral variables included number of sexual encounters, number of sexual partners, condom use, use of post exposure prophylaxis (PEP) for HIV, and testing and treatment for sexually transmitted illnesses (STIs).

Questions about **PrEP awareness, sources of information and places to access PrEP** were adapted from the survey of knowledge and PrEP use among PBFW in South Africa (12). Participants were asked if they have ever heard about PrEP, and where they have heard about PrEP. They were also asked where they would like to get information about PrEP and access PrEP pills in the future.

The questions about PrEP experience were adapted from the PrEP demonstration survey in Nigeria, the Durbar Mahila Samanwaya Committee (DMSC) case study and the Ashodaya Samithi Demo and Feasibility Project, and from the AIDS Clinical Trials Group (ACTG) Adherence Baseline Questionnaire (17). Participants were asked to self-report on the use of PrEP, experience of side effects, adherence to PrEP medication, PrEP disclosure and reasons for discontinuing PrEP for those who had discontinued PrEP.

For the study **PrEP users** were defined as women who were using PrEP at the time of the survey and **PrEP non users** were women who had never used PrEP and those who had previously used PrEP but had stopped taking PrEP at the time of the survey. Two questions were used to determine use of PrEP (1) Have you ever taken PrEP pills and (2) Are you currently taking PrEP pills. The response options were "Yes", "No" and "Do not remember/ Refused to answer". Only respondents who answered "Yes" were considered to have ever used or were currently using PrEP.

Knowledge about PrEP: was measured using four items as follows: (1) Consistent use of PrEP reduces HIV risk among HIV-negative individuals, (2) People using PrEP are recommended to continue using condoms, (3) Inconsistent use of PrEP decreases its effectiveness and (4) PrEP does not help prevent other STIs. The items were adapted from a survey of PrEP functional knowledge among MSM conducted in 2018 and were validated as part of scale on "Functional Knowledge of HIV Prevention Strategies" in the survey "Prioritizing U, 2015" (18). The response options were "True", "False", and "Do not know". If a respondent answered "True" to ALL of the four items, then they were considered to have knowledge about PrEP otherwise considered not having knowledge about PrEP.

Before introducing respondents to PrEP scales, a summary of the meaning of PrEP was orally presented as follows. "*There is a new way to prevent HIV infection for people who may be exposed to the virus. It is called Pre-Exposure Prophylaxis or PrEP. It involves an HIV-negative person taking a pill daily, on an ongoing basis (starting before an exposure and continuing after for as long as the person is at risk) to reduce their risk of HIV infection.*

Research suggests that PrEP is generally safe and is highly effective (over 90%) in preventing HIV infection if taken every day. It is much less effective if not taken every day and does not protect against other sexually transmitted infections. Taking PrEP would require a visit to a doctor every three months in order to be tested for HIV, STIs and side effects (19)."

PrEP Attitudes: was measured using a 5-items scale which sought to assess the participant's beliefs around PrEP's safety and effectiveness at preventing HIV (**Supplementary Table S1**). The items were taken from the article on applying the Information-Motivation-Behavioral Skills Model to understand PrEP intentions and use among MSM (20).The response options were 1 = Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly agree. The scale was constructed by summing the item scores and dividing by the number of items. The scale score range was 1–5, and a higher scale score indicated a higher level of positive PrEP attitudes. Using Factor Analysis, the scale was reliable to measure attitudes towards PrEP with Cronbach's Alpha (α) = 0.7.

PrEP Self-efficacy: was measured using a 5-items scale (α = 0.8) which sought to assess the participant's perceived ability to take PrEP consistently and as required (19) (**Supplementary Table S1**). The response options were: 1 = Not at all confident, 2 = Slightly confident, 3 = Somewhat confident, 4 = Fairly confident, 5 = Completely confident. The scale was constructed by summing the item scores and dividing by the number of items. The scale score range was 1–5, and a higher scale score indicated a higher level of self-efficacy (belief in self to use PrEP correctly).

PrEP Motivation: was measured using a 6-items scale (α = 0.6) which sought to assess circumstances under which participants would take or not take PrEP (19). These included assessing if clients would want to take PrEP if they knew about PrEP side effects, if they had to disclose to their sexual partners about taking PrEP, if they knew someone taking PrEP, if they had social support and if they trusted the efficacy of PrEP to prevent HIV transmission (**Supplementary Table S1**). The response options were: 1 = Strongly disagree, 2 = Disagree, 3 = Neutral, 4 = Agree, 5 = Strongly agree. The scale was constructed by summing the item scores and dividing by the number of items. The scale score range was 1–5, and a higher scale score indicated a higher level of motivation to use PrEP.

PrEP Stigma: was measured using a 13-items scale (α = 0.8) which covered fear of being perceived as promiscuous and fear of being shunned or rejected within social circles (**Supplementary Table S1**). The items were adapted from "The Pre-Exposure Prophylaxis (PrEP) Stigma Scale" (14, 21). The response options were: 1 = Strongly agree, 2 = Agree, 3 = Neutral, 4 = Disagree and 5 = Strongly Disagree. The scale was constructed by summing the item scores and dividing by the number of items. The scale score range was 1–5, a lower score indicated a higher level of stigma about PrEP.

PrEP Intention: was measured using three items as follows: (1) During the next three months, I will talk to a health care provider about PrEP; (2) During the next three months, I will seek out more information about PrEP and (3) During the next three months, I will get a prescription for PrEP (20). The response options were: 1 = No, definitely not; 2 = No, probably not; 3 = Yes, probably; 4 = Yes, definitely. A women was considered to have intention to use PrEP if they responded with either option "3 = Yes, probably" or option "4 = Yes, definitely" across all the three statements.

PrEP Willingness: was measured using a 6-items scale (α = 0.8) adapted from a study on willingness to take PrEP for HIV prevention among Thai MSM (22) (**Supplementary Table S1**). The items assessed participants' willingness to take PrEP if available, even if they would still have to use condoms, if it could cause temporary mild side effects, if they had to pay for it and if they would still need to test regularly for HIV. The response options were: 1 = No, definitely not; 2 = No, probably not; 3 = Yes, probably; 4 = Yes, definitely. The scale was constructed by summing the item scores and dividing by the number of items. The scale score range was 1–4, a higher score indicated a higher level of willingness to use PrEP.

Data analysis

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 26.0. Categorical variables were summarized using frequencies and percentages of participants. Continuous variables were summarized using means and standard deviations or medians and interquartile ranges, as appropriate. Factor analysis was used to confirm reliability among the scale items. Scales were considered reliable if the Cronbach's alpha was 0.5 and above. Pearson's chi-squared test was used to measure the association among categorical variables, and a rank-sum test was used to measure association between continuous variables. The precision around PrEP awareness, knowledge, use and intention estimates was assessed by 95% confidence intervals. Additionally, we used multivariate logistic regression to identify predictors of PrEP use and intention to use PrEP. Odds ratios and their respective 95% confidence intervals were used to quantify the effects. Variables for the multivariate model, were initially compiled informed by background knowledge, and these included region, age, education, marital status, decision making about health-related issues, HIV testing, male partner's characteristics, sexual risk behavior, self-efficacy, social support, perceived benefits and barriers of PrEP and stigma association with taking PrEP (14, 23–25). The potential factors were subsequently screened using simple (i.e., univariate) logistic regression and included in the multivariate model if the association with the respective dependent variable had a *p*-value of 0.05 or lower. Missing cases were excluded in a listwise fashion.

Ethical considerations

The protocol was implemented with human subject oversight provided by the Eswatini Health and Human Research Review Board (EHHRRB) (IRB: 00011253) in Eswatini, and the Advarra IRB (IORG0000468) in the United States of America. In addition, administrative approvals were obtained from the Eswatini National AIDS Program; Regional Health Management Teams, and senior

management teams at the study sites. No monetary incentives were provided to the women for being part of this study. To enhance confidentiality, study participants were assigned unique study identification numbers to identify and link study records.

Results

A total of 1,484 PPW were referred to the Research Assistants by Healthcare Workers (HCWs) in study sites, and 252 (17.0%) were not eligible to participate in the study, 1,157 (78.0%) consented to participate in the study and 75 (5.0%) did not consent. Of the 75 women who did not consent to participate, 23 (30.7%) refused (did not want/ not interested/not comfortable), 46 (61.3%) did not have enough time to sit through the interview/in a hurry to leave health facility, 6 (8.0%) had their children crying endlessly. Among the 1,157 PPW who consented to participate in study, 1,149 completed the interview. Figure 1 presents the flow of study participant screening and enrollment.

Characteristics of respondents

A total of 1,149 PPW women were interviewed for the study: 704 (61.3%) women were post-partum and 445 (38.7%) were pregnant (Table 1). The median age was 25 years [Interquartile Range (IQR) = 21–30 years], with 46.4% (533) 18–24 years old. Most women ($n = 902$, 78.8%) said that they are the ones who usually make decisions regarding their health, 100 (8.7%) had their male partners making the decisions, 111 (9.7%) their parents. Nearly two-thirds, 748 (65.3%) had HIV-negative male partners, 83 (7.2%) had HIV-positive male partners and 318 (27.7%) did not know the HIV status of their male partners. Of the women who reported that their male partners were HIV-positive, 70 (84.3%) reported that the HIV-positive male partners were on antiretroviral therapy (ART).

Sexual behavior of respondents

Of the 1,149 women interviewed, 353 (30.8%) reported to have used a condom in their last sex encounter while 154 (21.8%) reported to have used a condom every time they had sex in the last month and 415 (58.6%) had never used a condom during sex in the last month (Table 2). About 370 (32.3%) had tested for a sexually transmitted infection (STI) in the past 6 months; 55 (4.8%) had been treated for a Sexually Transmitted Infection (STI) in the past 3 months; 28 (2.5%) had engaged in anal sex in the past 3 months; and 127 (11.1%) had taken post-exposure prophylaxis (PEP) following a potential exposure to HIV in the past six months.

PrEP awareness and knowledge

Over 80% ($n = 930$, 80.7%) of the women had ever heard about oral PrEP for HIV prevention, while 219 (19.3%) had never heard

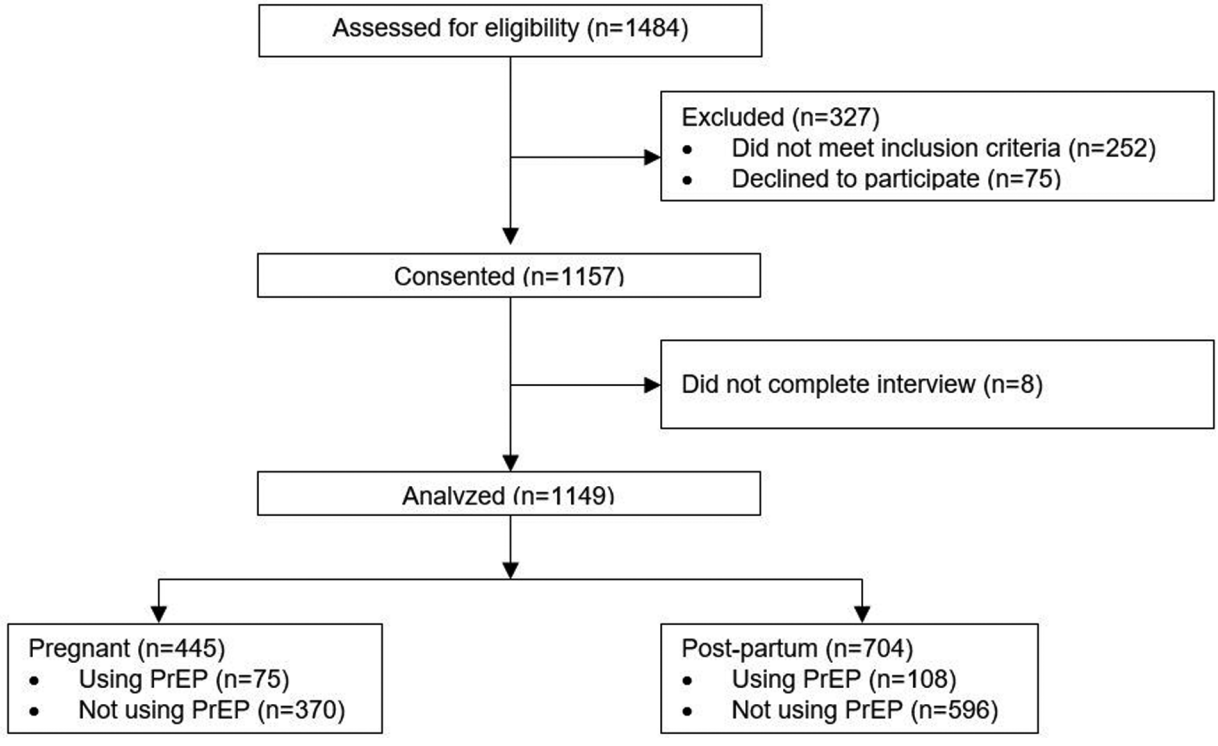

FIGURE 1
Flow of study screening and enrollment.

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TABLE 1 Characteristics of study participants.

Characteristic	Total (*N* = 1,149)	Pregnant (*N* = 445)	Postpartum (*N* = 704)
	n (%)	*n* (%)	*n* (%)
Age (years)			
Median (IQR)	25 (21–30)	24 (21–29)	26 (22–31)
Categories			
18–24	533 (46.4)	227 (51.0)	306 (43.5)
25–29	304 (26.4)	107 (24.0)	197 (28.0)
30–34	203 (17.7)	81 (18.2)	122 (17.3)
36–39	84 (7.3)	24 (5.4)	60 (8.5)
40+	25 (2.2)	6 (1.4)	19 (2.7)
Level of education			
None	9 (0.8)	4 (0.9)	5 (0.7)
Primary (first 7 years of school)	156 (13.6)	54 (12.2)	102 (14.5)
Secondary (1–3 classes post primary)	337 (29.4)	126 (28.4)	211 (30.0)
High school (4–5 classes post primary level)	470 (40.9)	181 (40.8)	289 (41.1)
Tertiary (Post high school)	176 (15.3)	79 (17.8)	97 (13.8)
Missing	1	1	0
Marital status			
Married	396 (34.5)	154 (34.6)	242 (34.5)
Cohabiting	129 (11.2)	50 (11.2)	79 (11.3)
Not married	622 (54.2)	241 (54.2)	379 (54.3)
Missing	2	0	2
Employment status			
Unemployed	759 (66.1)	275 (61.8)	484 (68.8)
Student	65 (5.7)	37 (8.3)	28 (4.0)
Employed	325 (28.3)	133 (29.9)	192 (27.3)
Person who makes decisions regarding health			
Myself	902 (78.8)	351 (79.1)	551 (78.6)
My partner	100 (8.7)	29 (6.5)	71 (10.1)
Parent/s	111 (9.7)	51 (11.5)	60 (8.6)
Someone else	32 (2.9)	13 (2.9)	19 (2.7)
Missing	4	1	3
Period tested for HIV			
Before the pregnancy	140 (12.2)	56 (12.6)	84 (12.0)
During pregnancy	466 (40.7)	366 (82.4)	100 (14.2)
After delivery	540 (47.1)	22 (5.0)	518 (73.8)
Missing	3	1	2
Region			
Hhohho	850 (74.0)	323 (72.6)	527 (74.9)
Shiselweni	299 (26.0)	122 (27.4)	177 (25.1)
Male partners' age (years)			
Median (IQR)	31 (26–36)	30 (25–35)	32 (27–38)
Categories			
18–24 years	169 (14.7)	82 (18.4)	87 (12.4)
25–29 years	277 (24.1)	110 (24.7)	167 (23.7)
30–34 years	267 (23.2)	118 (26.5)	149 (21.2)
36–39 years	183 (15.9)	63 (14.2)	120 (17.0)
40 years and above	167 (14.5)	44 (9.9)	123 (17.5)
Unknown	86 (7.5)	28 (6.3)	58 (8.2)
Age gap between participants and their male partners			
1–5 years	593 (51.6)	239 (53.7)	354 (50.3)
6–10 years	346 (30.1)	141 (31.7)	205 (29.1)
11 years and above	124 (10.8)	37 (8.3)	87 (12.4)
Age gap unknown	86 (7.5)	28 (6.3)	58 (8.2)
Occupation of male partner			
Not working	189 (16.4)	58 (13.0)	131 (18.6)
Student	41 (3.6)	21 (4.7)	20 (2.8)
Working	914 (79.5)	364 (81.8)	550 (78.1)
Missing	5	2	3
HIV status of male partner			
HIV-negative	748 (65.1)	300 (67.4)	448 (63.6)
HIV-positive	83 (7.2)	28 (6.3)	55 (7.8)
Do not know	318 (27.7)	117 (26.3)	201 (28.6)
HIV-positive male partner on ART			
No	5 (6.0)	4 (14.3)	1 (1.8)
Yes	70 (84.3)	20 (71.4)	50 (90.9)
Do not know	8 (9.6)	4 (14.3)	4 (7.3)
HIV-negative male partner on PrEP			
No	698 (93.1)	283 (94.3)	413 (92.2)
Yes	7 (0.9)	0 (0.0)	7 (1.6)
Do not know	45 (6.0)	17 (5.7)	28 (6.2)

TABLE 2 Sexual behavior.

Characteristic	Total (*N* = 1,149)	Pregnant (*N* = 445)	Post-partum (*N* = 704)
	n (%)	*n* (%)	*n* (%)
Had sexual intercourse in the last month			
No	404 (35.2)	93 (20.9)	311 (44.2)
Yes	745 (64.8)	352 (79.1)	393 (55.8)
Number of times a condom was used with partner in the past month			
Never	415 (58.6)	230 (67.1)	185 (50.7)
Sometimes	117 (16.5)	59 (17.2)	58 (15.9)
Most of the time	22 (3.1)	5 (1.5)	17 (4.7)
Every time	154 (21.8)	49 (14.3)	105 (28.8)
Missing	37	9	28
Condom use during the last sex encounter			
No	793 (69.2)	347 (78.0)	446 (63.6)
Yes	353 (30.8)	98 (22.0)	255 (36.4)
Tested for a sexually transmitted infection (STI) In the past 6 months			
No	769 (67.2)	261 (59.5)	508 (72.6)
Yes	370 (32.3)	178 (40.5)	192 (27.4)
Treated for an STI in the past 3 months			
No	1,087 (95.1)	425 (96.4)	662 (94.4)
Yes	55 (4.8)	16 (3.6)	39 (5.6)
Engaged in anal sex in the past 3 months			
No	1,088 (97.50	425 (98.2)	663 (97.1)
Yes	28 (2.5)	8 (1.8)	20 (2.9)
Taken post-exposure prophylaxis (PEP) following a potential exposure to HIV in the past six months			
No	1,019 (88.7)	392 (88.5)	627 (89.2)
Yes	127 (11.1)	51 (11.5)	76 (10.8)

about PrEP. Most women, 706 (76.2%) heard about PrEP at a clinic or hospital, followed by 150 (16.2%) who had heard about PrEP at a community or outreach event (Supplementary Table S2). Similarly, the most preferred source of information about PrEP among the women was a clinic or hospital ($n = 1{,}039$, 90.4%), followed by the community or outreach event ($n = 151$, 13.1%). The clinic or hospital was also preferred by a majority ($n = 1{,}112$, 96.8%) of the women for accessing PrEP pills, followed by the community or outreach event ($n = 101$, 8.8%). The proportion of PPW who knew all four facts (1) Consistent use of PrEP reduces HIV risk among HIV-negative individuals, (2) People using PrEP are recommended to continue using condoms, (3) Inconsistent use of PrEP decreases its effectiveness and (4) PrEP does not help prevent other STIs) about PrEP was 635 (55.3%) (95 CI: 52.3, 58.2).

PrEP attitudes and stigma

The women had positive attitudes towards PrEP. A majority of the women, 1,032 (89.8%) either agreed or strongly agreed that taking PrEP is safe; 974 (84.8%) agreed that PrEP is effective for preventing HIV; and 859 (74.8%) felt that it was not going to be difficult to adhere to PrEP every day (Table 3). Regarding stigma, a majority of the women either agreed or strongly agreed that if they were to use PrEP people would think they have HIV ($n = 759$, 66.0%), and that people would think that they have sex with a lot of different people ($n = 658$, 57.3%) (Table 3). Nearly half of the women ($n = 511$, 44.5%) felt that if they brought-up the subject of PrEP with their partners, then their partners would think that they are having risky sex with other people.

TABLE 3 PrEP attitudes and stigma among respondents.

Statement	Agree/strongly agree ($N = 1{,}149$)
	n (%)
Attitudes	
Taking PrEP is safe	1,032 (89.8)
PrEP is effective at preventing HIV	974 (84.8)
The government makes certain that drugs like PrEP are safe	956 (83.2)
People who take PrEP are responsible	935 (81.4)
It would be no trouble to take PrEP every day	859 (74.8)
Stigma-fear of being perceived as promiscuous	
If I were to use PrEP, people would think that I have HIV	759 (66.0)
If I were to use PrEP, people would think that I have sex with a lot of different people	658 (57.3)
If I were to use PrEP, people would think that I like having strange types of sex	612 (53.3)
If I were to bring up the subject of using PrEP with my partner, he would think that I am having risky sex with other people	511 (44.5)
Stigma-fear of being shunned	
My friends would think less of me if they found out I was using PrEP	449 (39.1)
People would feel uncomfortable with me if they found out that I used PrEP	359 (31.2)
People would avoid me if they found out that I used PrEP	289 (25.2)
If I used PrEP, I would worry that people would tell others that I am using PrEP	342 (29.8)
My family would think less of me if they found out I was using PrEP	291 (25.3)
I would worry about telling people that I take a medicine like PrEP for my health's sake	278 (24.2)
If I were going to use PrEP, I would feel a need to hide that from other people	266 (23.2)

Use and experiences with using PrEP

Among all the 1,149 PPW interviewed for the study, the number of PPW who have ever used PrEP was 285 (24.8%), and the number of PPW who were currently using PrEP was 183 (15.9%) (Supplementary Table S3). Among the 285 women who have ever used PrEP, 102 (35.8%) had stopped using PrEP. Seventy eight (76.5%) PPW had stopped taking PrEP within the past 12 months, and 12 (13.3%) in more than a year. Thirty-five (35.2%) PPW had stopped taking PrEP due to side effects; and 59 (64.8%) stopped due to other reasons including unavailability of PrEP pills ($n = 15$, 27.8%), perceived lack of HIV acquisition risk ($n = 7$, 13.0%) and partners/husbands' refusal ($n = 6$, 11.1%). When asked if they would like to re-start taking PrEP, 62 (60.8%) wanted to start taking PrEP again, among which 23 (42.6%) wanted to protect themselves from getting infected with HIV, 8 (14.8%) because they did not trust their partners, and the remaining due to a variety of reasons. Of the 183 PPW who were still on PrEP during the survey; 63 (34.4%) reported to have experienced side effects as a result of taking PrEP; 142 (77.6%) had disclosed to their male partners about taking PrEP; 91 (49.7%) had disclosed to their parents; and 54 (29.5%) had disclosed to other family members (Supplementary Table S3). When asked if they would want to continue taking PrEP in the next month, 174 (95.6%) wanted to continue using PrEP for the next month and 8 (4.4%) did not.

Factors associated with PrEP use

Using multivariate logistic regression, we determined factors associated with the use of PrEP. We first used univariate logistic regression to measure association of potential factors to "PrEP use" and only included in the final multivariate model factors that were significant with a $p =$ value of 0–05 or lower. PrEP use, comparing women on PrEP against women not on PrEP, was associated with HIV status of male partner, PrEP attitudes, and self-efficacy (Table 4). Women with an HIV-positive male partner were more likely to use PrEP compared to women with a HIV-negative partner [adjusted odds ratio [aOR] = 7.8, 95% confidence interval (CI) (3.5, 17.0)]. PPW with positive PrEP attitudes [aOR = 1.6, 95% CI (1.0, 2.4)]; and high self-efficacy about taking PrEP correctly [aOR = 1.5, 95% CI (1.1, 2.0)] were more likely to use PrEP.

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TABLE 4 Factors associated with PrEP use among pregnant and post-partum women.

Factors	Un-adjusted odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95%CI)	*p*-value
Region				
Shiselweni	REF		REF	
Hhohho	2.9 (1.8, 4.7)	<0.001	1.5 (0.8, 2.6)	0.207
Pregnant or post-partum				
Post-partum	REF			
Pregnant	1.1 (0.8,1.5)	0.495		
Age groups		***0.270***		
40 + years	REF			
18–24 years	1.2 (0.4,3.4)	0.798		
25–29 years	0.8 (0.3,2.4)	0.652		
30–34 years	0.8 (0.3,2.6)	0.765		
36–39 years	1.2 (0.4,4.1)	0.730		
Level of education		***0.265***		
Tertiary (post high school education)	REF			
No schooling or primary (first 7 years of school)	1.7 (0.9,3.2)	0.078		
Secondary (1–3 classes post primary level)	1.4 (0.8,2.5)	0.210		
High school (4–5 classes post primary level)	1.6 (1.0,2.7)	0.069		
Marital status		***0.152***		
Not married	REF			
Married	1.1 (0.8,1.5)	0.628		
Cohabiting	1.6 (1.0,2.6)	0.053		
What is your occupation?		***0.565***		
Employed	REF			
Unemployed	1.2 (0.8,1.8)	0.289		
Student	1.1 (0.5,2.3)	0.796		
Age gap between male partner and participant		***0.293***		
Age gap unknown	REF			
1–5 years	0.7 (0.4,1.2)	0.190		
6–10 years	0.8 (0.4,1.4)	0.428		
11 years and above	1.0 (0.5,2.0)	0.944		
Decision maker regarding respondent's health		***0.159***		
Someone else	REF			
Myself	1.1 (0.4,2.9)	0.843		
My partner	0.8 (0.3,2.5)	0.707		
Parent/s	0.5 (0.2,1.7)	0.288		
Male partner's HIV status		***<0.001***		**<0.001**
HIV negative	REF		REF	
HIV positive	13.5 (7.5, 24.4)	<0.001	7.8 (3.5,17.0)	<0.001
HIV status unknown	1.8 (1.1, 2.8)	0.001	1.6 (0.9,2.8)	0.141
Condom use during the last sex encounter				
No	REF			
Yes	1.0 (0.7,1.4)	0.912		
Tested for an STI in last 6 months				
No	REF		REF	
Yes	0.5 (0.4, 0.7)	<0.001	0.7 (0.4,1.1)	0.086
Treated for an STI in the past 3 months				
No	REF			
Yes	0.8 (0.4,1.5)	0.411		
Engaged in anal sex in the last 3 months				
No	REF			
Yes	0.6 (0.2,1.3)	0.181		
Taken PEP in last 6 months				
No	REF		REF	
Yes	0.5 (0.4, 0.7)	<0.001	0.1 (0.0, 0.1)	<0.001
PrEP perceptions				
Attitudes	2.5 (1.8, 3.3)	<0.001	1.6 (1.0, 2.4)	0.042
Motivation	1.4 (1.1, 1.8)	0.004	1.3 (0.9,1.8)	0.152
Self-efficacy	1.8 (1.5, 2.3)	<0.001	1.5 (1.1,2.0)	0.005
Stigma	1.5 (1.2,1.9)	<0.001	1.3 (1.0,1.7)	0.087

The bold italics indicate that the *p*-values for the associated of the covariates (as a whole) with the dependent variable.

Intention to use PrEP

Regarding intention to use PrEP, among 864 PPW who had never used PrEP, 65.3% intended to use PrEP in the future and 34.1% did not. The intention to use PrEP, comparing women who intended to use PrEP against women who did not intend to use PrEP, was associated with level of education, PrEP awareness, willingness to use PrEP, and self-efficacy (Table 5). PPW who had attained high school education [aOR = 1.7, 95% CI (1.1, 2.8)], secondary education [aOR = 2.2, 95% CI (1.3, 3.9)] and had primary education or no schooling [aOR = 2.0, 95% CI (1.1, 3.9)] are more likely to intend to use PrEP compared to those who have attained tertiary education. PPW who have ever heard about PrEP [aOR = 1.7, 95% CI (1.1, 2.6)]; high willingness to use PrEP [aOR = 3.1, 95% CI (2.3, 4.1)]; and with high self-efficacy (believe that they are capable of taking PrEP as required) [aOR = 1.6, 95% CI (1.3, 1.9)] are more likely to intend to use PrEP.

Discussion

This study identified that a majority of the PPW had ever heard of PrEP, however, about 19% did not know anything about it. Additionally, only about half of PPW possessed the correct knowledge about PrEP. This is an indication of gaps in health education, particularly within health facilities, which is where the women were recruited for the study. Whilst this study shows slightly higher proportions of PPW aware and also having correct knowledge about PrEP, several studies in similar populations in different settings in Sub-Saharan Africa and the United States of America have reported relatively low awareness and knowledge about PrEP (12, 26–32). In South Africa, in a study among pregnant women from Cape Town knowledge about PrEP was only 33% (12) and in a study among young pregnant women aged 18–24 years old in KwaZulu Natal, none of the women had ever heard about PrEP before the survey (32). In Zambia, knowledge about PrEP among pregnant and

TABLE 5 Factors associated with intention to use PrEP among pregnant and post-partum women.

Factors	Un-adjusted odds ratio (95% CI)	*p*-value	Adjusted odds ratio (95%CI)	*p*-value
Region				
Shiselweni	REF			
Hhohho	1.1 (0.8,1.6)		0.376	
Pregnant or post-partum				
Post-partum	REF			
Pregnant	1.1 (0.8,1.4)	0.644		
Age groups		***0.672***		
40 + years	REF			
18–24 years	1.3 (0.5,3.6)		0.632	
25–29 years	1.0 (0.3,2.8)		0.990	
30–34 years	1.2 (0.4,3.3)		0.789	
36–39 years	1.1 (0.4,3.6)		0.819	
Highest level of education attained		***0.001***		***0.022***
Tertiary (post high school education)	REF		REF	
No schooling or primary (first 7 years of school)	2.5 (1.5, 4.3)	<0.001	2.0 (1.1, 3.9)	0.028
Secondary (1–3 classes post primary level)	2.2 (1.5, 3.4)	<0.001	2.2 (1.3,3.9)	0.003
High school (4–5 classes post primary level)	1.9 (1.3,2.8)	0.002	1.7 (1.1,2.8)	0.025
Marital status		***0.104***		
Not married	REF			
Married	0.9 (0.7,1.2)	0.436		
Cohabiting	1.6 (0.9,2.7)	0.081		
What is your occupation?		***0.580***		
Employed	REF			
Unemployed	1.2 (0.9,1.6)	0.300		
Student	1.2 (0.6,2.2)	0.651		
Decision maker regarding respondent's health		***0.024***		***0.901***
Someone else	REF		REF	
Myself	1.1 (0.4,2.5)	0.886	1.0 (0.3,3.0)	0.981
My partner	1.3 (0.5,3.4)	0.591	0.9 (0.2,3.0)	0.846
Parent/s	2.4 (0.9,6.4)	0.074	1.2 (0.4,4.2)	0.742
Age gap between male partner and participant		***0.459***		
Age gap unknown	REF			
1–5 years	1.5 (0.9,2.6)	0.114		
6–10 years	1.5 (0.8,2.6)	0.188		
11 years and above	1.3 (0.7,2.6)	0.380		
Male partner's HIV status		***0.112***		
HIV negative	REF			
HIV positive	0.8 (0.6,1.1)	0.259		
HIV status unknown	2.3 (0.8,7.0)	0.134		
Condom use during the last sex encounter				
No	REF			
Yes	1.0 (0.7,1.4)	0.998		
Tested for an STI in last 6 months				
No	REF			
Yes	1.2 (0.9,1.6)	0.256		
Treated for an STI in the past 3 months				
No	REF			
Yes	1.4 (0.7,2.8)	0.320		
Engaged in anal sex in the last 3 months				
No	REF			
Yes	1.0 (0.4,2.7)	0.918		
Taken PEP in last 6 months				
No	REF			
Yes	1.2 (0.4,3.7)	0.739		
Ever heard about PrEP (PrEP awareness)				
No	REF		REF	
Yes	1.5 (1.1, 2.1)	0.015	1.7 (1.1,2.6)	0.013
PrEP Perceptions				
Willingness	4.3 (3.4, 5.5)	<0.001	3.1 (2.3,4.1)	<0.001
Attitudes	2.3 (1.9,2.9)	<0.001	1.2 (0.9,1.5)	0.306
Motivation	2.3 (1.9,2.8)	<0.001	1.2 (1.0,1.6)	0.094
Self-Efficacy	2.2 (1.9,2.5)	<0.001	1.6 (1.3,1.9)	<0.001
Stigma	1.5 (1.3,1.8)	<0.001	1.1 (0.9,1.4)	0.298

The bold italics indicate that the *p*-values for the associated of the covariates (as a whole) with the dependent variable.

breastfeeding was only 36% (28). In the United States approximately two thirds of pregnant women had never heard of PrEP before participating in the study (26). Of note is that even if the women were aware about PrEP, a majority tended to have incorrect knowledge about PrEP as an option for HIV prevention and also tended to have concerns about potential effects to their babies during pregnancy or breast feeding (27, 31).

Limited PrEP awareness and knowledge among the PPW is concerning because if women possess little or no knowledge on PrEP, then they are less likely to utilize the service even if it is offered at the healthcare facilities. From the studies it emerged clearly that high acceptability of PrEP is associated with knowledge about its efficacy in preventing the acquisition of HIV, and once PrEP was explained to the women, most of them reported positive attitudes towards PrEP and an interest to initiate PrEP (27, 29, 30, 32). PrEP programs targeting women at ANC or PNC need to develop appropriate interventions to increase health education on HIV PrEP among PPW both within health facilities and communities. Health education should aim to increase accurate PrEP knowledge and also motivate PPW to use PrEP as PPW are considered to be at high-risk of acquiring HIV.

In this study, the most cited source of PrEP information for women was the health facility. This finding indicates possible locations for health education interventions which could be implemented when the clients come for other health services. It could also be an indication of missed opportunities for health education outside the health facility environment. Extending PrEP promotion to the community can help to reach populations who do not regularly attend health facilities (34). Other studies have reported similar findings where health facilities and healthcare workers are the most cited sources of PrEP information (12, 28, 30, 31, 34). In this regard, HCWs play a critical role in delivering PrEP in antenatal and postpartum care

to PPW. However, studies from South Africa and France showed that less than half of HCWs knew about PrEP, described inaccurate PrEP knowledge regarding effectiveness, and lacked clinical detail (35–38). The limited PrEP knowledge among HCWs will hinder their ability to educate patients correctly about PrEP and the confidence to prescribe PrEP There is therefore a need to address this gap by providing trainings to HCWs on information about PrEP safety, efficacy, and how to prescribe it to pregnant and breastfeeding women, and other population groups.

The study also revealed that there was stigma attached to PrEP use. Most women agreed that if they were to use PrEP, people would think they have HIV, have sex with a lot of different people and/or like having strange types of sex. The PPW also agreed that their partners would think they were having risky sex with other people. A similar study conducted in Uganda, South Africa and Zimbabwe, mentioned that participants would refrain from taking PrEP because of its association with antiretroviral therapy and HIV related stigma (39). Likewise, findings from Malawi and Zambia showed that PrEP stigma was linked to being perceived as promiscuous and being on ART due to the appearance of PrEP packaging (29). This stigma associated with PrEP leads to challenges in PrEP initiation, retention, and adherence (14, 30, 34, 40–43). Interventions to address stigma and public education on HIV/AIDS prevention should address the social and cultural norms that undermine PrEP's optimal use (44, 46). HIV prevention programs should also consider introducing long-lasting injectable PrEP, as it comes with benefits of administration only once every two months and invisibility as no pills are required to be carried and taken by the individual (44–46).

Despite WHO's recommendation to offer PrEP to all population groups at substantial risk of HIV infection, the uptake is persistently low (11). In this study, only a quarter of PPW women have ever used PrEP and an even lower percentage were on PrEP at the time of the study. On the other hand, a large proportion of the women engaged in sex with men who were HIV-positive or had unknown HIV status, and many of the women's sexual encounters did not involve the use of condoms. This low coverage of PrEP among the women engaged in unprotected sex is worrying and may explain the continued high incidence of HIV in Eswatini. The factors associated with PrEP use identified by this study included having a known HIV-positive male partner, a male partner with unknown HIV status, positive attitudes towards PrEP, high self-efficacy, having tested for an STI in the last 6 months, and having taken PEP in the last 6 months. This finding aligns with previous studies conducted in Zambia and Kenya among PPW where factors associated with PrEP use were: being a sero-different couple, having a partner of unknown HIV status, having a positive attitude towards PrEP (47), and a reactive syphilis test result (7). Some studies identified other pertinent factors for PrEP use such as: engaging in sex without a condom in the past six months, having experienced intimate partner violence (7, 29), the desire to safely conceive a child (23), being a drug injector, being homeless (48) and rape (29). Worth noting is that most factors associated with PrEP use are factors know to be associated with the risk of HIV acquisition. Literature has shown that understanding the risk of HIV infection strengthens the desire to seek information about PrEP (12) and that women with perceived risk for HIV acquisition had high interest to use PrEP (49). For this reason, it is imperative for HCW to be aware of risk factors for HIV acquisition in order to provide the opportunity to discuss expanded HIV prevention options with women who are at risk of HIV exposure.

Among PPW using PrEP in this study, more than a quarter experienced various side effects, with dizziness and headaches being the most reported. Consequently, 36% of these women stopped taking PrEP due to the side effects. This finding resonates with already existing literature on PrEP where side effects were stated as some of the reasons for stopping PrEP (50, 51). However, studies from Zimbabwe and Mozambique had contradictory findings where the experience of side effects was not perceived as a major reason for discontinuing the use of PrEP, and in such cases women developed coping strategies of dealing with side effects (23, 52). It is critical for HCWs to provide information about PrEP side effects to PPW during initiation and follow up, so that they cope with side effects without stopping PrEP.

Our study found other reasons for PrEP discontinuation including; unavailability of PrEP and being stopped by partner or husband. Consistent findings from regional studies reported PrEP stock-outs and needing partner or husband approval to take PrEP as barriers to PrEP uptake, adherence and retention (23, 39, 47). The lack of autonomy among women to make decisions concerning their health may present a barrier to PrEP uptake. Thus, male involvement in promoting PrEP uptake beyond healthcare spaces including the community and key leaders such as traditional leaders, religious leaders, political leaders and employers could increase the use of PrEP in this target population (56) Also, political will is key in developing interventions and policy reviews to address challenges contributing to PrEP drugs stock-outs.

Some reasons for stopping PrEP unique to other studies were: changes in partner relationships and doubting safety of PrEP in pregnancy (41), changing risk perception, lack of social support, PrEP stigma, pill fatigue, and loss of interest (43, 51). These findings suggest that appropriate education and messaging about PrEP use, effectiveness, and side effects to communities might improve PrEP uptake and persistence. In so doing, partners and family members would also be enlightened about the importance of PrEP and supporting PrEP users. Also, conceptualizing PrEP as an intervention that can be paused and later restarted based on HIV risk may help ease the pill burden (54).

From this study, among women who never used PrEP, 65%, intended to use PrEP in the future. The odds of intention to use PrEP were high among women with low levels of education, awareness of PrEP, high self-efficacy and high willingness to use PrEP. These findings are similar to other studies where women with awareness of PrEP and high self-efficacy showed increased willingness to use PrEP (28, 55). On the contrary, Scott et al. in a research among PPW found that self-efficacy was not associated with PrEP uptake intention (56). Further, positive attitudes, subjective norms (support or approval from significant other), maternal status and breastfeeding were other factors associated

with PrEP use intention reported from existing evidence (28, 55). To increase intention to use PrEP, it is imperative to sensitize women on risk factors for HIV infection, to be empowered with knowledge and make informed choices about using PrEP.

Strengths and limitations

The main strength of this study is that it includes a large sample size of PPW from 16 health facilities. The results reported in this study are specific to PPW, providing important insights to inform scale-up of PrEP services to PPW. However, the study also has some limitations. The main limitation of this study is that it only sampled from the population of those already accessing the health care facility, therefore it may not represent the perspective of those who do not access health care facilities. Additionally, the study relies on self-reported information about PrEP during the interviews which may be biased.

Conclusion

The study showed that there are gaps in PrEP awareness and knowledge and that PrEP uptake among PPW was low. While PPW generally believed that PrEP is safe and effective to prevent HIV, they were concerned about possible side effects and encountering negative experiences if they were to disclose about taking PrEP to their sex partners. There is a need to strengthen health education about PrEP for PPW. This should include improving the integration of PrEP counselling into existing clinic visits at ANC and PNC and offering clients with options for HIV prevention. The program can also improve efforts to identify and educate sero-discordant couples; continue implementing couples' HIV testing to ensure that the women have knowledge of their risk; and identify outreach strategies to be implemented at community level to reduce stigma and misinformation around PrEP. These strategies can reach women who may become pregnant (intentionally or otherwise), and possibly increase acceptability of PrEP early in the antenatal course. In addition, the study suggests that many women are ready for PrEP since more than two thirds of the women had the intention of initiating PrEP. Accordingly, program implementers should use this opportunity to expand PrEP activities nation-wide.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Eswatini Health and Human Research Review Board (EHHRRB) and Advarra IRB. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

PK: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. SM: Writing – review & editing, Writing – original draft. KK: Conceptualization, Investigation, Validation, Writing – review & editing. SM: Conceptualization, Investigation, Writing – review & editing. PD: Conceptualization, Investigation, Writing – review & editing. VT: Writing – review & editing. RM: Conceptualization, Investigation, Validation, Writing – review & editing. GW: Conceptualization, Investigation, Validation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1253384/full#supplementary-material

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An implementation strategy package (video education, HIV self-testing, and co-location) improves PrEP implementation for pregnant women in antenatal care clinics in western Kenya

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Background: Pre-exposure prophylaxis (PrEP) is recommended by the World Health Organization and the Kenyan Ministry of Health for HIV prevention in pregnancy and postpartum for women at risk for HIV. Integration of PrEP into antenatal care is promising, but delivery gaps exist in the face of healthcare provider shortages in resource-limited settings.

Methods: Between May and November 2021, we conducted a difference-in-differences study (3 months pre-intervention data collection and 3 months post-intervention data collection) analyzing four intervention facilities, where the strategies were implemented, and four comparison facilities, where no strategies were implemented. We tested a combination of three implementation strategies—video-based PrEP information in the waiting bay, HIV self-testing, and dispensing of PrEP in the antenatal care rooms—to improve PrEP delivery. We compared absolute changes in the proportion of antenatal attendees screened for PrEP (PrEP penetration), the proportion receiving all PrEP-specific steps in a visit (HIV testing, risk screening, and PrEP counseling) (PrEP fidelity), and client PrEP knowledge, client satisfaction, and waiting time and service time (*a priori* outcomes); *post hoc,* we compared the proportion offered PrEP (PrEP offer) and completing HIV testing. We measured provider perceptions of the acceptability and appropriateness of the implementation strategies.

Results: We observed significant improvements in PrEP penetration, PrEP offer, satisfaction, and knowledge ($p < 0.05$) and improvements in fidelity that trended towards significance ($p = 0.057$). PrEP penetration increased 5 percentage points ($p = 0.008$), PrEP fidelity increased 8 percentage points ($p = 0.057$), and PrEP offer increased 4 percentage points ($p = 0.003$) in intervention vs. comparison facilities. Client PrEP knowledge increased by 1.7 out of 6 total points ($p < 0.001$) and client satisfaction increased by 0.7 out of 24 total points ($p = 0.003$) in intervention vs. comparison facilities. We observed no changes in service time (0.09-min decrease; $p = 0.435$) and a small increase in waiting time (0.33-min increase; $p = 0.005$). HIV testing among those eligible did not change (1.5 percentage point decrease, $p = 0.800$). Providers felt the implementation strategies were acceptable and appropriate (median acceptability: 20/20; median appropriateness: 19.5/20). However, absolute levels of each step of the PrEP cascade remained suboptimal.

Conclusions: An implementation strategy package with video information, HIV self-testing, and co-location of medication dispensing enhanced PrEP delivery across several implementation outcomes and client satisfaction, while not substantially increasing wait time or decreasing provider-client contact time.

Clinical trial registration: ClinicalTrials.gov, identifier, NCT04712994.

KEYWORDS

pre-exposure prophylaxis (PrEP), pregnancy, postpartum, implementation science, video education, HIV self testing, integration

Introduction

Pregnant and postpartum women in high HIV prevalence settings face an elevated risk of HIV acquisition due to biological and social factors (1, 2). Pre-exposure prophylaxis (PrEP) is a safe, effective, and acceptable intervention for use during pregnancy and postpartum (3–7). It is recommended by the World Health Organization and several countries' guidelines (8). Despite this endorsement, the reach and coverage of PrEP during this period remain suboptimal globally due to a range of implementation challenges (9). A systematic review of implementation science studies of PrEP in pregnancy and postpartum noted that implementation challenges exist at the intrapersonal, interpersonal, community, and systems levels. However, most implementation strategies tested to improve implementation intervened at the intrapersonal and interpersonal levels, rather than focusing on the systems level. In addition to demand-generating activities, supply-side interventions to improve implementation are needed to fully realize the population-level benefits of PrEP for HIV prevention (10).

PrEP can be delivered in vertical siloed programs—such as through HIV care clinics (11, 12)—or horizontally in integrated programs—such as through maternal and child health (MCH) or family planning clinics (13–16). Pregnant and postpartum women report preferring integrated service delivery for reasons of convenience and reduced stigma (17). In order to provide integrated PrEP delivery, healthcare workers (HCWs) require specific training in PrEP counseling, prescribing, and documentation. HIV testing providers have a higher volume of clients to test each day in order to initiate PrEP, and clinics within a facility need to determine where to dispense PrEP (either from a central pharmacy or a clinic-specific setting).

Kenya was an early adopter of integrated PrEP delivery in pregnancy and postpartum; Kenyan research teams have conducted a series of qualitative investigations, implementation projects, and trials to identify optimal approaches for integrated PrEP delivery (16–24). An early implementation project focusing on developing integrated models for PrEP delivery in MCH clinics highlighted that services can be delivered by a single nurse delivering antenatal/postnatal and PrEP services or by multiple nurses sequentially, with the service delivery model selection depending on clinic organization, space, and staffing. PrEP activities take additional time, with a median of 13 min for PrEP education and counseling among clients who did not initiate PrEP and 18 min for clients who initiated PrEP; compared to average antenatal clinic (ANC) service times of 9 min and waiting time of 13 min, this represents substantial additional time spent by both clients and HCWs (23). HCWs highlighted insufficient staffing, insufficient staff PrEP knowledge, insufficient space, and high patient volumes as the most impactful barriers experienced while delivering PrEP to pregnant and postpartum populations across 55 facilities in Kenya (25). Implementation strategies to address these additional time demands and patient activity volumes associated with integrated PrEP offers could meaningfully increase the reach and coverage of PrEP for this priority population.

In this study, we tested a combination of three implementation strategies to decrease client waiting time, improve coverage of PrEP education and PrEP offer, improve PrEP knowledge, and maintain satisfaction for clients and HCWs. The package included video education, HIV self-testing (HIVST) for repeat HIV testing, and PrEP dispensing in MCH clinics.

Methods

Setting & design & population

This study is registered at ClinicalTrials.gov (NCT04712994). This study was conducted in three counties in western Kenya: Kisumu, Siaya, and Homa Bay counties. These counties have relatively high HIV prevalence. We focused on MCH clinics at each site, which provide ANC, postnatal (PNC), and child welfare services. We engaged eight facilities in a difference-in-differences design with 3 months of baseline data collection (May through July 2021) and 3 months of intervention period data collection (August through November 2021); four facilities were never exposed to the implementation strategy package and four facilities were exposed to the implementation strategy package during the second 3-month period. The distribution of study sites in each county was balanced between the intervention and comparison facilities (**Supplementary Table S4**). We aimed to select facilities that were of similar size and staffing to other facilities in the region to enhance external validity and generalizability. However, there were factors in the selection process that may have limited generalizability. The eight facilities were selected from among a list of facilities that had previously engaged in either a research trial (24), a demonstration project with staffing support (16), or a mentorship model with no staffing support (22). All prior work was finished at each site

prior to engagement for our study and no additional staff were supporting PrEP delivery in MCH clinics. Facilities that were selected for these research or demonstration projects in the past tended to have somewhat better resourcing, including physical space availability (26). We further note that these eight clinics are not representative of smaller facilities in the region, which were systematically missing due to low numbers of clients served, limiting feasibility as research sites. The original study design was intended as a controlled interrupted time series, which employs the same pre-post and concurrent comparison clinic elements, but differs from the difference-in-differences design by controlling for linear temporal trends during each period; however, due to interruptions in data collection related to COVID-19, flooding, strikes, and other unanticipated events, the calendar time table was interrupted, necessitating the switch to a difference-in-differences analytic approach.

Ethical approval

This study was reviewed and approved by the Kenyatta National Hospital/University of Nairobi Ethics & Research Committee (P907/11/2019) and the University of Washington Institutional Review Board (STUDY00008392). Facilities were engaged to participate by seeking the relevant county, sub-county, and site-level approval.

Implementation strategy package

The implementation strategy package contained three components: (1) video education, (2) HIV self-testing (HIVST) for repeat HIV testing, and (3) PrEP dispensing in MCH clinics rather than in a central or HIV-specific pharmacy. The following descriptions focus on specification using the Proctor specification approach, highlighting actor, action, action target, temporality, dose, implementation outcomes targeted, and theoretical justification (27). Of note, this study did not employ any research staff or additional program staff to deliver clinical services and aimed to test strategies to improve implementation without additional human resources.

The video was created by a local videography company with prior experience creating engaging and informative videos for MCH audiences. The content of the informational video was developed by the study team and informed by quantitative and qualitative data from past PrEP in pregnancy studies (28). The story characters were developed to reflect the most common populations, including a married primigravida who did not know her partner's HIV status. The modes of PrEP information delivery featured in the video mirrored the methods reported to motivate women to initiate PrEP: PrEP-experienced peer conversations and HCW conversations. The PrEP-specific clinical information provided covered the required elements of PrEP counseling as outlined by the Kenyan National AIDS & STI Control Program. The video was presented in three languages (English, Dholuo, and Kiswahili) to reflect the common languages in the region and featured subtitles. The video employed a dramatized, soap opera style to mirror common popular TV programs; it was approximately 13 min in length [the average waiting time was 13 min for a similar population (23)]. The video was played in the waiting room of the MCH clinic at each intervention site on repeat; MCH clients could watch the video in a group setting in the waiting room. Clients were encouraged to ask questions about PrEP to the HCW they saw during their subsequent care. This strategy was selected in order to reduce the amount of time spent by HCW delivering standardized PrEP information, aiming to decrease waiting time and service time and increase PrEP penetration and fidelity. Video education has been used in numerous high-resource and some low-resource settings for HIV pre-test information provision and has shown to be either superior or equivalent to counselor-delivered information (29, 30).

HIVST is utilized in Kenya as a screening test and is endorsed in the national HIV testing services guidelines. The OraQuick test was procured through central government systems and provided by the site. Women were eligible to use the OraQuick for repeat HIV testing if they were not attending their first ANC visit; those attending the first ANC visit were required to complete standard HIV testing services. Privacy booths—such as those described by Oyaro et al. (31)—were provided near the waiting bays. Standardized pictorial and text instructions were provided as part of the OraQuick insert in both English and Kiswahili. Women collected their own samples, submerged them in the reaction fluid, and used a stopwatch to wait for the required 15-minute reaction time. Women read their own results and thereafter showed their test results to an HCW for confirmation of correct interpretation. Women whose HIVST was non-reactive did not undergo additional HIV testing and were considered eligible to initiate PrEP. Women whose HIVST was reactive or had any irregular result underwent standard HIV testing by the site HCW. This strategy was selected in order to reduce the amount of time spent by HCWs waiting for HIV test reactions to take place and to reduce the volume of clients needed to be served by the limited number of HIV testing providers at a given site.

For women who were offered PrEP and decided to initiate or continue PrEP, the pills were dispensed within the MCH clinic, rather than at a central or HIV-specific pharmacy, aligning with the strategy of co-location. This strategy was selected in order to eliminate additional waiting time and to reduce the potential stigma associated with receiving medication at the HIV-specific pharmacy.

Implementation & service outcomes

We measured several PrEP implementation, service, and health outcomes (32), which are shown in **Table 1**. Our primary outcomes were PrEP penetration, PrEP fidelity, client satisfaction, healthcare worker acceptability and appropriateness (33), and waiting time and service time (*a priori* primary outcomes). PrEP uptake, PrEP continuation, PrEP adherence, and client PrEP knowledge were *a priori* secondary outcomes. PrEP offer and HIV testing completion were added as *post hoc* outcomes. During preparation

TABLE 1 Difference in differences comparison of implementation, effectiveness, and service outcomes.

		Comparison sites				Intervention sites				Difference in difference [(Change in intervention sites)—(Change in comparison sites)] *Adjusted for first ANC*		
		Pre ($N = 480$)		Post ($N = 478$)		Pre ($N = 480$)		Post ($N = 481$)		Point estimate	Confidence interval	*p*-value
Outcome	Definition	*n* (%) or median IQR	*N*	*n* (%) or median IQR	*N*	*n* (%) or median IQR	*N*	*n* (%) or median IQR	*N*			
PrEP fidelity[b]	Proportion of women who receive all PrEP-specific steps in a HIV-testing visit, HIV-risk screening, PrEP-counseling/total women receiving antenatal or postnatal services [*Risk screening question: "Please answer yes if you were asked about any of the following behaviors today: (Kenyan risk assessment tool HIV risk factors)"*]	4 (2.5%)	161	5 (3.0%)	164	14 (8.3%)	168	28 (15.5%)	181	7.6%	(−0.2%, 15.4%)	0.057
HIV testing[d]	Proportion of women HIV tested among eligible candidates (not tested in past 6 months, not known HIV positive)	98 (60.1%)	163	107 (65.2%)	164	142 (84.0%)	169	144 (79.6%)	181	−1.5%	(−12.9%, 9.9%)	0.800
PrEP risk screening[d]	Proportion asked questions on HIV risk behavior characteristics (yes vs. no/don't know)	43 (9.0%)	480	104 (21.8%)	478	146 (30.5%)	479	159 (33.1%)	481	−8.8%	(−15.9%, −1.8%)	0.013
PrEP penetration[b]	Proportion of women who are counseled about PrEP / total women receiving antenatal or postnatal services ("*Did anyone talk to you about PrEP today?*")	17 (3.5%)	480	8 (1.7%)	478	30 (6.3%)	480	46 (9.6%)	481	5.4%	(1.4%, 9.3%)	0.008
PrEP offer[d]	Proportion offered to start or continue taking PrEP/total women receiving antenatal or postnatal services	8 (1.7%)	480	9 (1.9%)	478	6 (1.3%)	480	28 (5.8%)	481	4.4%	(1.5%, 7.2%)	0.002
	Proportion offered to start or continue taking PrEP (among those who were HIV negative and at high risk who were screened)	3 (15.8%)	19	6 (9.8%)	61	4 (5.1%)	78	13 (14.0%)	93	−5.9%	(−13.8%, 2.1%)	0.148
PrEP uptake[c]	Proportion initiated PrEP today (among those offered)	1 (12.0%)	8	1 (11.0%)	9	0 (0%)	6	0 (0%)	28	–	–	–
	Proportion initiated PrEP today (among the full population)	1 (0.2%)	480	1 (0.2%)	478	0 (0%)	480	0 (0%)	481	–	–	–
PrEP continuation[c]	Already taking PrEP and will continue to take PrEP (among those offered)	1 (12.5%)	8	2 (22.2%)	9	1 (16.7%)	6	1 (3.6%)	28	–	–	–
	Already taking PrEP and will continue to take PrEP (among the full population)	5 (1.0%)	480	10 (2.1%)	478	9 (1.9%)	480	6 (1.2%)	481	–	–	–
Service time[b]	Number of minutes receiving services from health care workers	16 (10–33)	192	14 (9–27.5)	192	18 (12–36)	192	17 (11–29)	192	−0.09[a]	(−0.33, 0.14)[a]	0.435[a]
Waiting time[b]	Number of minutes spent waiting to receive services	37 (14.5–74)	192	29 (14–46.5)	192	49 (22.5–77)	192	55 (31–80)	192	0.33[a]	(0.10, 0.56)[a]	0.005[a]
Client satisfaction[b]	Satisfaction on a scale of 0–24 points; 6 questions for clients to assess their satisfaction with services received at the facility; Likert scale (worst to best: 1–5)	23.0 (20.0–23.0)	480	23.0 (20.0–24.0)	478	21.0 (19.0 −23.0)	480	23.0 (21.0–23.0)	481	0.66	(0.22, 1.09)	0.003
HCW satisfaction[b]	Average on 4-item Intervention Appropriateness Measure (IAM) scale; Likert scale (disagree to agree: 1–5)	–		–		–		19.5 (16.0, 20.0)		–	–	–
	Average on 4-item Acceptability of Intervention Measures (AIM) scale; Likert scale (disagree to agree: 1–5)	–		–		–		20.0 (16.0, 20.0)		–	–	–
Client PrEP knowledge[c]	All correct answers (6 questions based on content covered in counseling sessions)	0 (0%)	480	5 (1%)	478	5 (1%)	480	56 (11.6%)	481	9.6%	(6.5, 12.8%)	<0.001
	Number of correct answers (0–6)	0.975	480	1.234	478	1.042	480	3.019	481	1.72	(1.45, 1.99)	<0.001

[a]Not adjusted for visit type due to visit type not collected during time-and-motion activity.
[b]Primary outcome.
[c]Secondary outcome.
[d]Post hoc outcome.

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activities for data collection, it was determined that it was not feasible to extract patient adherence information; this outcome was neither collected nor compared. Women were considered eligible for HIV testing in our analytic dataset if they had not had an HIV test within the past 6 months and were not known to be living with HIV prior to the visit. For proportions with conditional denominators (PrEP uptake, PrEP offer, and HIV testing), analyses were presented first for the conditional denominator (e.g., uptake among those offered PrEP) and second for the full denominator (e.g., uptake among all women seeking services). This approach was taken to show the relative and absolute changes. The percentages for each outcome within Table 1 were calculated directly from the observed data rather than the model-predicted levels, following the proportion definitions presented in Table 1.

Participant recruitment, enrollment, and data collection

Women seeking MCH services were approached after receipt of services between May and November 2021. Clients were eligible if aged ≥15 years and able to provide oral consent. Participants completed an exit survey with trained study nurses on a tablet using REDCap after all other regular care for their visit concluded. We assessed participant demographics, HIV risk screening and counseling, PrEP knowledge, and satisfaction with services offered that particular day. Separately, we used time and motion cards designed to collect "time in" and "time out" at different service delivery locations. The study nurse would conduct oral consent with the women at the MCH entrance, document the "time of arrival" on the card, and give the woman the card to carry along. HCWs at different service delivery stations could complete the two time points (time in and time out). At intervention clinics during the post-intervention period, we approached all HCWs offering services in MCH and invited them to provide oral consent and complete a REDCap survey either alone using a computer link or with study nurses using a tablet. HCWs were given 2 weeks to complete the survey; several (typically two) follow-up attempts were made by phone; those who did not complete the survey in 3 weeks were excluded.

Data abstraction

We abstracted data without patient identifiers from PrEP registers noting the number who initiated and the number who continued PrEP aggregated by day. As these registers collected data facility-wide, it was not possible to determine where individuals initiated PrEP (e.g., MCH or another clinic) or determine who was pregnant or postpartum or a woman.

Data analysis

We summarized descriptive data using proportions, medians, and interquartile ranges, as well as means and standard deviations. We log-transformed waiting time and service time for this analysis and presented geometric means in analytic tables. We did not transform knowledge or satisfaction scores, although they were positively skewed, as transformations did not produce more normal distributions. We assessed the change associated with the implementation package using a difference-in-differences analytic approach, using a multi-level mixed-effect regression model with a random effect for the site, a binary term for intervention vs. comparison group, a binary term for pre/post time period, and an interaction term between the two. We additionally controlled for differences in the proportion of women seeking first antenatal care services through inclusion as a covariate (primary analysis) and presentation of analyses stratified by visit type (secondary analysis). We estimated the change associated with the implementation package as the interaction term and considered a change statistically significant at alpha ≤0.05. We conducted a basic optimization analysis for the PrEP steps in order to estimate the idealized scenario of the maximum number of women who might be offered PrEP and accept PrEP if PrEP counseling, PrEP risk assessment, HIV testing, and offer were optimized, without changes to the proportion accepting PrEP. We multiplied the total number of women in our sample by the proportion who had any risk indication for PrEP, the proportion who were eligible for HIV testing that day, the proportion who would have tested HIV negative (based on this dataset), and the proportion who would have accepted PrEP (based on this dataset). This yielded the maximum number who would have likely initiated PrEP in the idealized scenario of perfect penetration, fidelity, and offer and the observed proportions of uptake.

Contextual factors and temporal changes

During the 3 months of pre-intervention and 3 months during the intervention, some events occurred either at or beyond facilities that may have impacted service delivery broadly or delivery of the implementation strategy package specifically. A timeline of these events and activities is shown in Figure 1. Because the frequency of interruptions was balanced between the intervention and comparison facilities, we did not conduct sensitivity analyses accounting for these interruptions.

Results

Demographic characteristics

We enrolled a total of 1,919 participants receiving MCH services during the 3 months pre-intervention and 3 months during the intervention [960 pre-intervention (480 in comparison and 480 in intervention sites) and 959 during the intervention (478 in comparison and 481 in intervention sites)]. Among women seeking MCH services, the median age was 25 [interquartile range (IQR): 22, 30] years, 21.5% were seeking first ANC visits, while 78.5% were seeking second or subsequent ANC visits or other MCH services. In comparing the demographic details between women at intervention vs. comparison sites in the pre-intervention vs. during intervention periods, we noted no differences in age and only slight differences in the proportion seeking a first ANC visit vs. other services (comparison sites: pre-intervention, 19.0%;

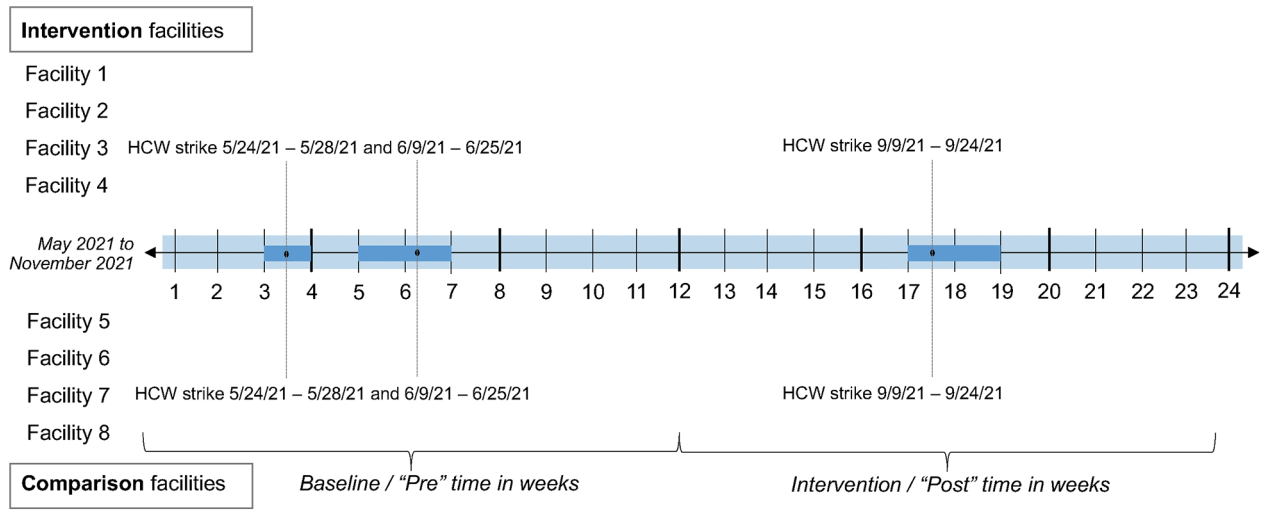

FIGURE 1
Timeline in weeks and background service delivery interruptions.

post-intervention, 18.6%. Intervention sites: pre-intervention, 26.9%; post-intervention, 21.4%) (Supplementary Table S2).

Baseline period

During the baseline period, PrEP penetration, PrEP fidelity, PrEP offer, and PrEP knowledge were low in both intervention and comparison clinics; there was substantial heterogeneity between sites in implementation outcomes (Supplementary Table S3). PrEP penetration ranged from 0%–10%, PrEP fidelity from 0%–16%, PrEP offer among eligible women from 0%–13%, and full complete PrEP knowledge from 0%–1.7%. In contrast, HIV testing was higher (ranging from 42%–95%), and satisfaction with services was high (ranging from 21 to 23 out of 24 points). Time spent waiting and receiving services ranged from 10.5–79 min and 12–25.5 min, respectively. As each clinic served as its own baseline measurement and comparison, we did not test for differences between intervention and comparison clinics in baseline implementation outcomes.

Changes associated with the implementation strategy bundle

We used difference-in-differences analysis to assess the changes associated with the implementation strategy bundle. For our primary outcomes, the implementation strategy bundle was associated with significant increases in PrEP penetration, client satisfaction, and client PrEP knowledge and was associated with a significant but small magnitude increase in waiting time and no change in service delivery time. The implementation strategy bundle was also associated with a substantial improvement in PrEP fidelity but was only trending toward significance.

The implementation strategy bundle was associated with a PrEP penetration increase of 5.4% percentage points (95% CI: 1.4, 9.3%; $p = 0.008$) in intervention vs. comparison sites and reached a high of 9.6% in intervention sites (Table 1). The change in penetration was more pronounced among clients seeking first ANC services vs. any other visit type (12.7% vs. 3.4% percentage point increase, respectively) (Supplementary Table S1). PrEP fidelity increased by 7.6% percentage points (95% CI: −0.2%, 15.4%; $p = 0.057$) more in the intervention vs. comparison sites, reaching a high of 15.5%, but only trended towards significance (Table 1). The change in fidelity was more pronounced among clients seeking first ANC services vs. any other visit type (12.5% vs. 3.5% percentage point increase, respectively) (Supplementary Table S1). Despite the increase in PrEP fidelity, there was a significant and substantial decrease in the coverage of PrEP risk screening assessment [8.8% percentage point decrease (95% CI: −15.9%, −1.8%); $p = 0.013$] between intervention and comparison sites, reaching a high of 33.1%. While both the intervention and comparison sites increased in screening assessment, the increase was larger in the comparison sites, where two comparison sites had newly added screening desks midway through the test; this difference was comparable between clients seeking first ANC services and those with any other visit type (Table 1, Figure 2, Supplementary Table S1).

The implementation strategy bundle was associated with a PrEP knowledge increase of 9.6% percentage points (95% CI: 6.5, 12.8%; $p < 0.001$) in the intervention vs. comparison sites, reaching a high of 11.6%. This corresponded to an increase in 1.72 additional questions correct out of 6 total questions. Client satisfaction increased by 0.66 points (95% CI: 0.22, 1.09; $p = 0.003$) in the intervention vs. comparison sites, reaching a high of 23.0 out of 24 points. Client waiting time increased by 0.33 min (95% CI: 0.10, 0.56; $p = 0.005$) in the intervention vs. comparison sites, reaching a median of 55 min during the post-intervention period. Neither the changes in knowledge nor satisfaction were different between clients

seeking first ANC services and those with any other visit type (Supplementary Table S1). Client service time did not substantially or significantly change [0.09-min decrease; (95% CI: −0.33, 0.14); $p = 0.435$]. Waiting and service times were not adjusted for visit type (Table 1; Figure 2).

In our secondary analyses, the implementation strategy bundle was associated with substantial and significant improvements in PrEP offer but not in HIV testing. HIV testing did not change significantly [1.5% decrease (95% CI: −12.9, 9.9%), $p = 0.800$], reaching a high of 84% in the baseline period of the intervention sites; HIV testing increased modestly in the comparison sites and decreased by a similar magnitude in the intervention sites. The difference was comparable between clients seeking first ANC services and those with any other visit type (Supplementary Table S1). PrEP offers among all women increased by 4.4% percentage points (95% CI: 1.5, 7.2%, $p = 0.002$), reaching a high of 5.8% among all women receiving services. The change in PrEP offer was more pronounced among clients seeking first ANC services vs. any other visit type (7.9% vs. 3.3% percentage point increase, respectively) (Supplementary Table S1). Among the subset of women who were HIV negative and had any high-risk factor, PrEP offer was somewhat substantially but not significantly lower [5.9% increase (95% CI: −13.8, 2.1%); $p = 0.148$] between intervention and comparison sites, reaching a high of 15.8% in the baseline period of the comparison sites (Table 1, Figure 2).

Using exit surveys, we observed that a total of two women initiated PrEP during the study period and a total of 30 women continued PrEP from prior initiations during the study period, limiting statistical comparison of PrEP initiation and continuation. Using record abstraction, we observed a total of 189 people who initiated PrEP during the study period and 357 who continued PrEP from prior initiations during the study period; it was not possible to distinguish women who initiated PrEP at MCH from all other people initiating PrEP recruited from other clinics within the facility. Overall, PrEP initiations increased in the comparison facilities more than in the intervention sites (comparison: 39–51; intervention: 43–56), while PrEP refills increased in the intervention facilities but decreased in the comparison sites (comparison: 127 –69; intervention: 79–82).

HCW perceptions of acceptability and appropriateness of the implementation strategy bundle were high; out of 20 possible points, acceptability scores had a median of 20.0 (IQR: 16.0, 20.0) and appropriateness scores had a median of 19.5 (IQR: 16.0, 20.0) (Table 2).

PrEP knowledge score component changes

Client knowledge questions included items related to PrEP for HIV prevention, frequency of PrEP taking, time to reach maximum protection, concurrent condom use, PrEP side effects, and when to discontinue PrEP. The implementation strategy bundle was associated with an increase in accurate answers regarding PrEP use for HIV prevention of 28.6% percentage points (95% CI: 20.3, 37.0%; $p < 0.001$), reaching a high of 84.8%. Clients' knowledge of the frequency of PrEP use increased by 44.3%

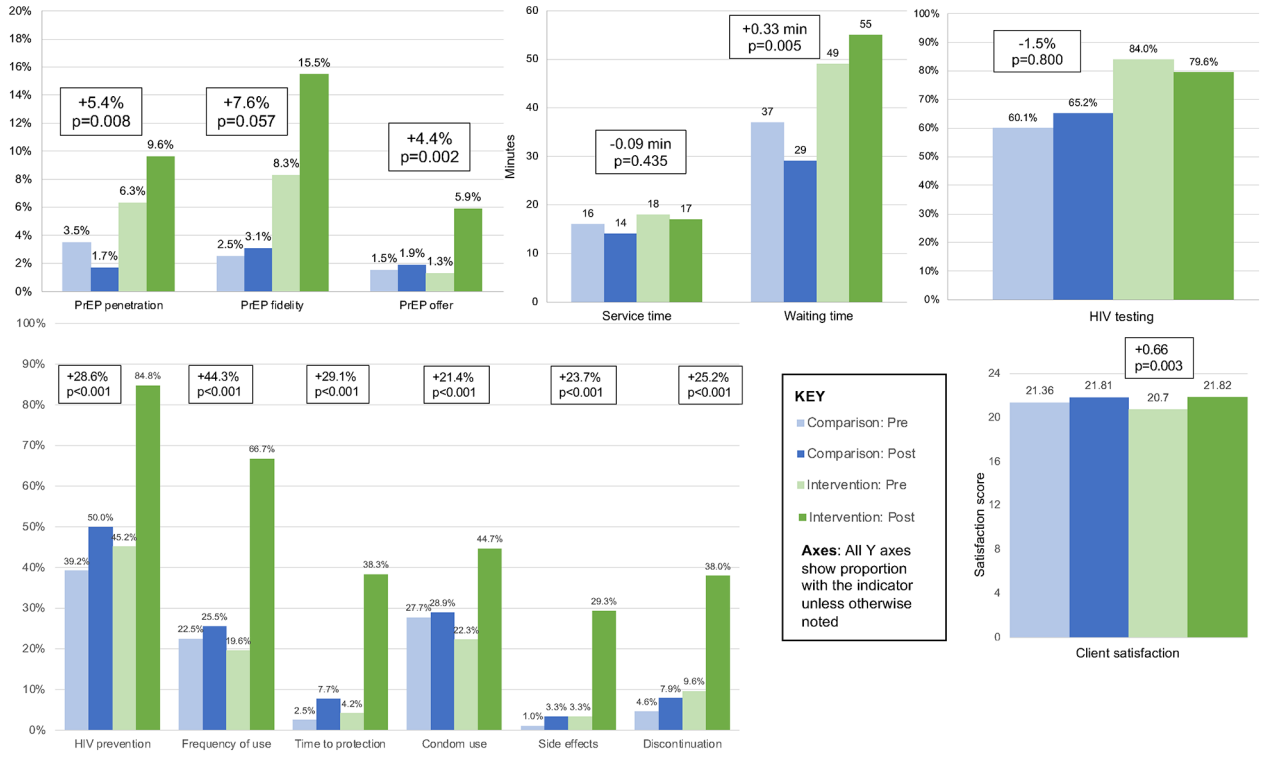

FIGURE 2
Difference in differences comparison of implementation, effectiveness, and service outcomes. Statistical test compares the difference between pre and post levels in the comparison to the intervention sites.

percentage points (95% CI: 36.6, 52.0%; $p < 0.001$), reaching a high of 66.7%. Accurate answers on the time PrEP takes to reach maximum protection increased by 29.1% percentage points (95% CI: 23.6, 34.5%; $p < 0.001$), reaching a high of 38.3%. Clients' knowledge of the concurrent use of condoms while taking PrEP increased by 21.4% percentage points (95% CI: 13.3, 29.4%; $p < 0.001$), reaching a high of 44.7%. PrEP side effects knowledge increased by 23.7% percentage points (95% CI: 19.0, 28.4%; $p < 0.001$), reaching a high of 29.3%. Knowledge of when a client can discontinue PrEP increased by 25.2% percentage points (95% CI: 19.4, 31.0%; $p < 0.001$), reaching a high of 38.0% (Table 3, Figure 2).

Hypothetical best possible performance with optimization

We calculated the hypothetical expected number of women who might be offered PrEP and accept PrEP if PrEP counseling, PrEP risk assessment, HIV testing, and offer were optimized, without changes to the proportion accepting PrEP. Among the 1,919 women who accessed care, if 77% had any risk indication for PrEP, 41% were eligible for HIV testing that day, and 99% of those tested were HIV negative—as observed within this dataset—a total of 588 women would have been offered PrEP. If 3.9% of those offered PrEP (2 initiations / 51 PrEP offers observed in this study) initiated PrEP, a total of 23 women would have initiated PrEP, approximately 12 times as many as were observed to have initiated PrEP in this study.

Discussion

In this study, we observed that an implementation strategy package with video information, HIVST, and co-location of medication dispensing enhanced PrEP delivery in terms of implementation and service outcomes and client satisfaction, while not meaningfully increasing wait time or decreasing provider-client contact time. There were significant improvements in PrEP penetration, client satisfaction, and client PrEP knowledge. There was a significant but small increase in waiting time and no change in service delivery time. There was a trend for substantial improvement in PrEP fidelity. The strategy was associated with more pronounced effects in fidelity, penetration, and PrEP offer among clients seeking first ANC services compared to other visit types.

While implementation science focused on PrEP delivery has expanded in the past several years, more of this work focuses on other priority populations than pregnant and postpartum women (34–39). Unlike some other priority populations, pregnant and

TABLE 2 Satisfaction, acceptability, appropriateness.

	Comparison sites		Intervention sites	
	Pre ($N = 480$)	Post ($N = 478$)	Pre ($N = 480$)	Post ($N = 481$)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Client satisfaction				
Quality of the service[a]	3.04 (0.60)	3.26 (0.62)	3.14 (0.62)	3.26 (0.59)
Received the kind of service the client wanted[b]	3.61 (0.68)	3.69 (0.52)	3.48 (0.62)	3.69 (0.54)
The extent to which this facility met your needs[c]	3.53 (0.70)	3.58 (0.55)	3.36 (0.64)	3.54 (0.56)
Would recommend this facility to a friend[b]	3.84 (0.45)	3.89 (0.34)	3.70 (0.55)	3.91 (0.28)
Satisfied with the amount of help received[d]	3.50 (0.73)	3.51 (0.68)	3.29 (0.70)	3.50 (0.64)
Would come back to the facility[b]	3.85 (0.43)	3.89 (0.33)	3.72 (0.52)	3.92 (0.28)
Overall (out of 24 points)	21.36 (2.83)	21.81 (2.30)	20.70 (2.74)	21.82 (2.06)
HCW perceptions of appropriateness and acceptability of implementation strategy bundle				Post ($N = 39$)
				Mean (SD)
Appropriateness (IAM)[e]				
Fitting	–	–	–	4.55 (0.64)
Suitable	–	–	–	4.60 (0.55)
Applicable	–	–	–	4.60 (0.55)
A good match	–	–	–	4.55 (0.55)
Acceptability (AIM)[f]				
Meets approval	–	–	–	4.55 (0.64)
Appealing	–	–	–	4.56 (0.55)
I like it	–	–	–	4.50 (0.60)
I welcome it	–	–	–	4.58 (0.55)

[a]Likert scale options: poor to excellent: 1–4.
[b]Likert scale options: no, definitely not to yes, definitely: 1–4.
[c]Likert scale options: none of my needs have been met to almost all of my needs have been met: 1–4.
[d]Likert scale options: not satisfied to very satisfied: 1–4.
[e]Average on 4-item Intervention Appropriateness Measure (IAM) scale; Likert scale (disagree to agree: 1–5).
[f]Average on 4-item Acceptability of Intervention Measures (AIM) scale; Likert scale (disagree to agree: 1–5).

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TABLE 3 Prep knowledge.

Indicator	Comparison sites				Intervention sites				Difference in difference [Change (intervention)—Change (comparison)] ***Adjusted for first ANC		
	Pre		Post		Pre		Post		Point estimate	95% CI	*p*-value
	n	Comparison: Pre %	*n*	Comparison: Post %	*n*	Intervention: Pre %	*n*	Intervention: Post %			
HIV prevention	188	39.2%	239	50.0%	217	45.2%	408	84.8%	28.6%	20.3%, 37.0%	<0.001
Frequency of use	108	22.5%	122	25.5%	94	19.6%	321	66.7%	44.3%	36.6%, 52.0%	<0.001
Time to protection	12	2.5%	37	7.7%	20	4.2%	184	38.3%	29.1%	23.6%, 34.5%	<0.001
Condom use	133	27.7%	138	28.9%	107	22.3%	215	44.7%	21.4%	13.3%, 29.4%	<0.001
Side effects	5	1.0%	16	3.3%	16	3.3%	141	29.3%	23.7%	19.0%, 28.4%	<0.001
Discontinuation	22	4.6%	38	7.9%	46	9.6%	183	38.0%	25.2%	19.4%, 31.0%	<0.001

postpartum women are already presenting to a status-neutral MCH care clinic where they receive sequenced integrated care for a range of health conditions. Attendance at ANC clinics is remarkably high in Kenya and many sub-Saharan African countries (40). The last step of the PrEP cascade of PrEP acceptance can be addressed through demand creation. However, the earlier steps of the PrEP cascade—PrEP counseling, risk screening, information provision, HIV testing, and PrEP offer—are well-suited to supply-side strategies. The aforementioned recent systematic review of implementation science focused on pregnant and postpartum women noted that most implementation strategies tested for this population intervened at the intrapersonal and interpersonal levels, rather than at the systems level, as the present study does. It called for testing supply-side strategies in order to improve implementation and realize the population-level benefits of PrEP for HIV prevention for pregnant women (10). We note that video education can serve both as a supply-side strategy—by shifting standard information provision from healthcare workers to automated provision—as well as a demand-generating strategy.

We observed greater improvements in knowledge scores associated with the implementation strategy package that contained video education. Video education has been tested in resource-rich and resource-limited settings; as mentioned above, a recent systematic review found that video education was as effective or more effective than counselor-delivered information (29). Standard videos are well-suited to resource-limited contexts by overcoming a variety of structural barriers; video education allows limited HCW time to be focused on individualized post-test counseling, provides standard information that can be rapidly updated faster than large cadres can receive refresher training, can present information in multiple languages, and can be delivered in group settings. In a Kenyan study testing video education for HIV testing, video education—both in an individual and group format—was associated with higher knowledge scores than counselor-delivered sessions (30). It is possible that video education provided in the waiting room in the present study allowed HCWs to provide more PrEP-related services—such as risk screening and counseling—in a fixed visit time. Waiting and service time were not substantially different between intervention and comparison clinics.

HIVST for PrEP initiation has not been widely tested, despite the widespread use of HIVST in non-facility settings and some use of HIVST at MCH clinics. A recent systematic review of HIVST for PrEP initiation and continuation found limited trial data supporting HIVST for PrEP continuation and no comparative study results testing HIVST for PrEP initiation but noted several ongoing studies (41). This presents the first data demonstrating the use of HIVST for PrEP initiation in a real-world setting. In our study, HIVST was offered only to women who had received standard HIV testing at a prior ANC visit; while this added complexity, it was deemed necessary for women to have had prior counseling experience in standard HIV testing. A prior study conducted by Oyaro et al. in Kenya also utilized HIVST for repeat maternal HIV testing in MCH clinics; just over half of women elected HIVST instead of counselor-delivered blood-based testing, citing privacy, ease, and speed as major

factors (31). Substantial logistical coordination was necessary to facilitate the use of HIVST in busy waiting rooms, ensuring confidentiality and proper test performance, as well as confirmatory reading by HCWs; privacy booths were utilized following the experience described by Oyaro et al.

Co-locating PrEP dispensing services in the MCH clinic rather than at a central facility pharmacy or an HIV care-specific pharmacy was tested to improve flow, efficiency, and acceptability for women. Prior qualitative studies in Kenya with pregnant and postpartum women highlighted that women not living with HIV did not want to receive their HIV prevention medications from an HIV care-specific pharmacy for reasons of stigma (17). Prior quantitative studies noted that integrated delivery in MCH was feasible in models with additional healthcare workers (16, 24). A study in Kenya that tested a "one-stop-shop" model—including co-location of dispensing and services, provider cross-training and task shifting, and shifting to a lower volume clinic—observed a decrease in waiting time, no change in PrEP initiations and continuation, and high acceptability of the model due to decreased stigma and increased privacy (42). In our study, we observed a small increase in waiting time, unlike the one-stop-shop model, but similarly observed higher client satisfaction and no change in provider service time.

Within this study, we were able to use exit surveys to readily measure and compare implementation outcomes but were not able to meaningfully compare clinical outcomes—such as PrEP initiation and continuation changes—due to low frequency. Conversely, we were able to use routine records to compare PrEP initiations and continuation events, but not PrEP implementation outcomes due to limited fields collected in register data. However, PrEP initiation and continuation records do not specify the location from which a client was referred or initiated, limiting the use of this data source to assess the impact of implementation strategy testing within certain clinics within a site. While revisions to PrEP and MCH registers are expected in the near future in Kenya, it will likely remain necessary to include both primary data and record abstraction to meaningfully assess the impact of implementation strategies across the PrEP cascade.

While we noted substantial improvements in implementation outcomes associated with this implementation strategy package, large gaps remained in absolute coverage for each step. Two steps that could be optimized simply, namely, PrEP penetration (being talked to about PrEP today) and PrEP offer among eligible women, remained below 10% and 16%, respectively, even in intervention clinics. Additional implementation strategies that prompt providers to offer consistent services to each client—such as checklists, inclusion in standard registers, and other "nudge" strategies—should be tested in the future to close these noted gaps in implementation and offer high-quality and consistent services to clients. Improvements were more pronounced among women seeking their first ANC visit; this visit may offer an additional opportunity to nudge for high coverage of PrEP penetration and offer. Additionally, levels of uptake of PrEP in pregnant and postpartum populations are widely variable, with staffing being a likely determinant of uptake. The PrIYA and PrIMA studies in Kenya both offered integrated PrEP in MCH in western Kenya and included additional research staff that delivered services; uptake of PrEP was 22% and 18.6% in PrIYA and PrIMA, respectively (16, 24). In contrast, the same sites that participated in the PrIYA study were assessed after study staff departed; uptake was substantially lower at 4% (22), which was similar to the 3.9% uptake noted in the present study. Approaches are needed to address the large differences in uptake of PrEP that appear to be partially related to staffing, especially as the field looks forward to national scale-up.

Our study has several limitations. While we aimed to test implementation strategies in real-world contexts, without additional research staff for delivery, certain resources, such as purchasing privacy booths and televisions, were necessary in order to activate the strategy. These were purchased using research rather than program funds, limiting external validity. Additionally, there were external factors that influenced service provision, including three HCW strikes spread over 5 weeks; the frequency and duration of these strikes were balanced between the intervention and comparison clinics and nearly balanced between the pre-intervention and post-intervention periods, having minimal impact on our difference in difference analysis approach. Were these interruptions not present, we would have expected a larger magnitude difference associated with the implementation strategy bundle. While we initially aimed to conduct a controlled interrupted time series analysis, the interruptions in data collection necessitated a switch to a difference-in-differences analytic approach, which has poorer control for baseline temporal trends. We assessed PrEP penetration by asking if "someone 'talked' to a client about PrEP today"; while this was intended to assess the number of women receiving basic information about PrEP by a counselor or by video, women who received information by video likely answered "no" more frequently. This assumption is further amplified by large observed improvements in knowledge among women in the intervention groups. We may have systematically underestimated PrEP penetration in the intervention group during the post-intervention period, which would have underestimated the magnitude of the association between the implementation strategy package and PrEP penetration. Future studies that assess PrEP penetration should assess learning information about PrEP through any facility-based interaction or experience. We were not able to collect process data on the number of women offered and accepting HIVST, the denominator of women eligible for HTS by facility-specific guidelines, nor information on whether their visits were specifically shorter, limiting our ability to further investigate the limited impact of this strategy on implementation. We allocated facilities to intervention vs. comparison conditions prior to initiating baseline data collection; therefore, we missed the opportunity to balance the distribution of PrEP outcomes between conditions, potentially contributing to a less robust parallel trends assumption for a difference in differences design. Finally, the facilities selected for this study are somewhat generalizable to the larger volume of health facilities in Siaya, Homa Bay, and Kisumu counties, but there may be a bias towards better-resourced facilities in terms of physical space.

Conclusions

An implementation strategy package with video information, HIV self-testing, and co-location of medication dispensing enhanced integrated PrEP delivery for pregnant women in MCH clinics. There were significant improvements in PrEP penetration, client satisfaction, and client PrEP knowledge. The implementation strategy package was not associated with meaningfully increased wait time or decreased provider-client contact time. This package of strategies, which did not include additional healthcare workers or research staff, merits broader implementation, alongside additional strategies to close gaps in absolute coverage.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Kenyatta National Hospital/University of Nairobi Ethics & Research Committee and the University of Washington Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because Anonymous surveys with emancipated minors (pregnant and ≥15 years) approved for oral informed consent.

Author contributions

JK and GJ-S are study PIs and conceptualized the study. FA, JD, LG, AW, JK, and GJ-S designed the study protocol and data collection. BO, FA, NN, and JS oversaw data collection conducted by GO and ES LG, SH, JS, AW, and JD were involved in data cleaning and analysis. JS and AW wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/frph.2023.1205503/full#supplementary-material

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The effect of daily oral PrEP use during pregnancy on bone mineral density among adolescent girls and young women in Uganda

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Introduction: Oral pre-exposure prophylaxis (PrEP) is recommended during pregnancy for at-risk cisgender women. Pregnancy is known to impede bone growth and tenofovir-based PrEP may also yield detrimental changes to bone health. Thus, we evaluated the effect of PrEP use during pregnancy on bone mineral density (BMD).

Methods: We used data from a cohort of women who were sexually active, HIV-negative, ages 16–25 years, initiating DMPA or choosing condoms for contraception and enrolled in the Kampala Women's Bone Study. Women were followed quarterly with rapid testing for HIV and pregnancy, PrEP dispensation, and adherence counseling. Those who became pregnant were counseled on PrEP use during pregnancy per national guidelines. BMD of the neck of the hip, total hip, and lumbar spine was measured using dual-energy x-ray absorptiometry at baseline and annually. We compared the mean percent change in BMD from baseline to month 24.

Results: Among 499 women enrolled in the study, 105 pregnancies occurred in 90 women. At enrollment, the median age was 20 years (IQR: 19–21) and 89% initiated PrEP. During pregnancy, 67% of women continued using PrEP and PrEP was dispensed in 64% of visits. BMD declined significantly in women using PrEP during pregnancy compared to women who were not pregnant nor used PrEP: relative BMD change was −2.26% (95% CI: −4.63 to 0.11, $p = 0.06$) in the femoral neck, −2.57% (95% CI: −4.48 to −0.66, $p = 0.01$) in total hip, −3.06% (95% CI: −5.49 to −0.63, $p = 0.001$) lumbar spine. There was no significant difference in BMD loss when comparing PrEP-exposed pregnant women to pregnant women who never used PrEP. Women who became pregnant were less likely to continue PrEP at subsequent study visits than women who did not become pregnant (adjOR: 0.25, 95% CI: 0.16–0.37, $p < 0.001$). Based on pill counts, there was a 62% reduction in the odds of high PrEP adherence during pregnancy (adjOR = 0.38, 95% CI: 0.27–0.58, $p < 0.001$).

Conclusion: Women who used PrEP during pregnancy experienced a similar reduction in BMD as pregnant women with no PrEP exposure, indicating that BMD loss in PrEP-using pregnant women is largely driven by pregnancy and not PrEP.

KEYWORDS

bone mineral density, oral PrEP, young women and adolescent girls, HIV prevention, Uganda

Introduction

Pregnancy is a period with an elevated risk for acquiring HIV (1–3), estimated to be >2-fold higher than non-pregnant periods (1, 4). Biological changes in hormonal levels as well as changes in sexual behavior are likely responsible for the increase in HIV susceptibility of cisgender women during pregnancy (5, 6). Pregnancy rates in sub-Saharan Africa are among the highest in the world and oral PrEP can play a critical role in reducing HIV acquisition during this period (7, 8). Oral PrEP containing tenofovir disoproxil fumarate (TDF) is safe and recommended for use during pregnancy and postpartum by women at substantial risk of acquiring HIV (9–11).

With reassuring data on the safety of PrEP with regards to birth outcomes and infant growth (10), the remaining questions are related to whether there are subclinical consequences from PrEP use during pregnancy, such as effects on bone health. Women's bone mineral density (BMD) reaches its peak between the ages of 20 and 26 years and plateaus until menopause (12, 13). However, BMD loss or premature attainment of peak BMD can occur in premenopausal women due to various reasons, including the use of depot medroxyprogesterone acetate (DMPA), pregnancy, and breastfeeding (12). Changes in BMD during pregnancy and lactation are due to mineral transfer to a fetus or infant to facilitate growth (12, 14). Additionally, the use of TDF-based oral PrEP has been postulated to be a potential factor linked to BMD loss (15, 16) because of its excretion through the renal system and the kidney-bone development pathway (17, 18). Despite the independent association of pregnancy and BMD and the subclinical impact of TDF on creatinine levels, it is not known whether PrEP use during pregnancy and/or breastfeeding could exacerbate BMD loss in young women.

In addition, how pregnancy impacts oral PrEP adherence and continuation needs to be further evaluated. A recent PrEP implementation study among pregnant women found that only 40% continued PrEP use one month after initiation (19). While protecting the fetus from HIV might provide an incentive for pregnant women to use and adhere to PrEP, experiencing side effects in conjunction with those elicited by pregnancy and fear of unknown effects on the fetus might prompt discontinuation, beyond the effects of stigma and pill burden that all PrEP users face (19–23). Prior studies have primarily examined patterns of PrEP use among women who initiated PrEP use during pregnancy; however, PrEP use patterns may differ in women who were already on PrEP at the time of pregnancy.

Using data from women enrolled in a prospective cohort study evaluating the impact of concurrent TDF-based PrEP and DMPA on bone health in Kampala, Uganda, we evaluated the impact of TDF-based PrEP use on BMD loss during pregnancy. Secondarily, we investigated the effect of pregnancy on daily oral PrEP adherence and continuation.

Methods

Study design and population

We used data from all women enrolled in the Kampala Women's Bone Study (ClinicalTrials.gov #NCT03464266), an open-label prospective cohort study aimed to address bone safety questions with concurrent TDF-based PrEP and DMPA use. Between May 2018 and March 2020, the Kampala Women's Bone Study recruited women who were at high risk for HIV and seeking DMPA or condoms as contraception in family planning clinics, youth-based centers, and higher learning institutions in Kampala, Uganda. Women who were HIV-negative, ages 16–25 years, initiating DMPA or choosing to use male condoms for contraception, without contraindications for DMPA or TDF-based PrEP, and not planning to become pregnant in the next 24 months were eligible to enroll in the study.

Data collection and outcomes

Over 24 months, women were followed quarterly with HIV prevention counseling and condom distribution, diagnostic testing for HIV (using rapid testing according to the national algorithm), urine pregnancy testing, provision of DMPA injections, offers of PrEP, PrEP adherence counseling, and provision of PrEP medication (FTC/ TDF). At enrollment and quarterly visits, interviewers administered standardized questionnaires to collect data on demographic characteristics, medical history, sexual behavior, sexual relationship power, HIV perception and salience, diet and physical activity, alcohol and drug use, and contraceptive and PrEP use. At the first visit at which the participant was found to be pregnant, data on the last menstrual period date, expected delivery date, whether the pregnancy was intended, obstetric history, and decision on PrEP continuation were collected. Women who became pregnant while using PrEP were counseled about the known and unknown risks and benefits of PrEP use during pregnancy according to the national guidelines and supported to continue or discontinue PrEP.

At enrollment and annual study visits, after confirming HCG negative urine pregnancy test results, dual-energy x-ray absorptiometry (DXA) scans were conducted to measure BMD for the lumbar spine, total hip, and neck of the hip. For women who

were pregnant, DXA scans were withheld and completed as soon after pregnancy as possible. We measured PrEP continuation using pharmacy PrEP refill data and pill count as measures of PrEP adherence and defined "continuation" based on PrEP being dispensed at the visit. Quarterly pill use was quantified by dividing the number of pills used and pills not returned by the expected number of pills to be used, and a value of ≥80% was considered high adherence. The start of pregnancy was estimated using the last menstrual period date or the estimated delivery dates. The end of pregnancy was determined using the reported date of pregnancy outcome or estimated delivery date.

Statistical analysis

Baseline participant characteristics were summarized using descriptive statistics. To evaluate the effect of PrEP use during pregnancy on BMD, we used a generalized linear model (GLM) with a Gaussian link to compare the mean percent change in BMD between baseline and the end of the two-year follow-up in women who were using PrEP during pregnancy and non-pregnant women who didn't initiate PrEP during the study. Models were adjusted for confounders identified *a priori*: age as a continuous variable, baseline body-mass index (BMI), and baseline DMPA use. In a sensitivity analysis, we repeated the analysis excluding non-full-term pregnancies. To evaluate the effect of pregnancy on PrEP continuation and PrEP adherence, we used generalized estimation equation (GEE) models with a logit-link and exchangeable correlation structure to compare the odds of PrEP continuation and PrEP adherence between women who experience pregnancy and those who did not experience pregnancy over the 24 months study follow up. The models were adjusted for potential confounders identified *a priori*: age, education, income, relationship status, and partner's HIV status. In separate models, we compared PrEP continuation during pregnancy to non-pregnant periods among women who became pregnant during the study. All analyses were done using R 4.0.

Ethical considerations

The study protocol was approved by the National HIV/AIDS Research Committee of Uganda, the Uganda National Council for Science and Technology, and the Human Subjects Division at the University of Washington. Participants ≥18 years provided written informed consent and participants <18 years provided written assent with a consenting guardian or were qualified to provide consent based on their status as an emancipated or mature minor.

Results

Participant characteristics

A total of 499 sexually active young women were enrolled in the study. At enrollment, the median age was 20 years [interquartile range (IQR):19–21], 87 were married or had a steady partner, 92% received financial support from their partners, 63% did not know their partner's HIV status, and 89% initiated PrEP. Over the 24-month study period, 90 participants became pregnant. Women who became pregnant more frequently had chosen to use condoms than DMPA at baseline as a contraceptive compared to women who did not become pregnant (61% vs. 43%, respectively). Other baseline characteristics including age, marital status, education level, sexual behavior characteristics, BMI, and BMD were similar between women who did and did not become pregnant (Table 1).

Pregnancy characteristics

Among 499 participants enrolled in the study, 396 (79%) were retained for one year, and 331 (66%) participants were followed for two years. Although we were not able to contact the majority (60%) of participants who were lost to follow-up to ascertain reasons for study discontinuation, two-thirds of the loss to follow-up occurred after March 2020, when the COVID-19 pandemic began in Uganda. During the study period, 105 pregnancies occurred, including 15 women who experienced multiple pregnancies. The median time between enrolment and the start of pregnancy was 426 days (IQR: 235–524). Among those who became pregnant, 61 (67%) women [during 72 (69%) pregnancies] used PrEP during their pregnancy (Table 2). Overall, 73% of pregnancies were unintended, 62% were the woman's first pregnancy, and 35% of pregnancies resulted in pregnancy loss. There was no difference in pregnancy outcomes by PrEP exposure groups.

Association of PrEP use, pregnancy, and bone mineral density

We examined the association between PrEP use during pregnancy with changes in mean BMD from baseline to 2 years at the neck of the hip, lumbar spine, and total spine. Among the 331 study participants who were followed for two years, 294 (89%) participants had DXA scans at baseline and the 24-month visit. The median time between the end of pregnancy and the exit DXA scan was 119 days [IQR: 55–221]. The mean percent change in BMD for pregnant women who used PrEP during pregnancy at the neck of the hip was −1.91% (95% CI: −4.28% to +0.46%), −2.20% (95% CI: −4.17% to −0.23%) at the total hip and −3.78% (95% CI: −6.28% to −1.27%) at the lumbar spine [Table 3]. Over the 24-month study period, the mean percent change in BMD was significantly greater in pregnant women using PrEP during pregnancy relative to women who were not exposed to either PrEP or pregnancy. After adjusting for age, BMI, and DMPA use prior to pregnancy, the relative mean percent change in BMD was −2.26% (95% CI: −4.63 to 0.11, $p = 0.06$) at the femoral neck, −2.57% (95% CI: −4.48 to −0.66, $p = 0.01$) at the total hip, and −3.06% (95% CI: −5.49 to −0.63, $p = 0.001$) at the lumbar spine. The decline in BMD in those pregnant but who had never been exposed to PrEP or who were pregnant but not taking PrEP during pregnancy was not

TABLE 1 Baseline characteristics of women in the study ($N = 499$).

Characteristic	No pregnancy during study, $N = 409$, N (%) or median (IQR)	At least one pregnant during study follow-up, $N = 90$, N (%) or median (IQR)	Total, $N = 499$, N (%) or median (IQR)
Age (years)	20 (19, 21)	20 (18, 21)	20 (19, 21)
Relationship status			
Single	48 (12%)	17 (19%)	65 (13%)
Married/in a steady partnership	361 (88%)	73 (81%)	434 (87%)
Lives with partner	22 (5.4%)	2 (2.2%)	24 (4.8%)
Earns own income	211 (52%)	50 (56%)	261 (52%)
Partner provides financial support	377 (92%)	80 (89%)	457 (92%)
Years of education	11 (8, 12)	11 (9, 12)	11 (8, 12)
Partners HIV status			
Positive	7 (1.7%)	2 (2.2%)	9 (1.8%)
Negative	147 (36%)	30 (33%)	177 (36%)
Unknown	254 (62%)	58 (64%)	312 (63%)
Travel time to research clinic			
<1 h	58 (14%)	18 (20%)	76 (15%)
1–2 h	335 (82%)	68 (76%)	403 (81%)
>2 h	16 (3.9%)	4 (4.4%)	20 (4.0%)
Any condomless sex, past 3 months	274 (67%)	63 (70%)	337 (68%)
Any condomless sex, past 7 days	123 (49%)	23 (47%)	146 (48%)
Had more than one partner, past 3 months	238 (58%)	41 (46%)	279 (56%)
Contraception choice			
Condoms	176 (43%)	55 (61%)	231 (46%)
DMPA	233 (57%)	35 (39%)	268 (54%)
Initiated PrEP	360 (88%)	80 (89%)	431 (86%)
Body-mass index, kg/m^2	23 (21, 25)	23 (21, 25)	22 (21, 25)
Mean BMD (g/cm^2)			
The neck of the hip	0.86 (0.11)	0.87 (0.12)	0.85 (0.11)
Lumbar spine	0.95 (0.12)	0.95 (0.12)	0.93 (0.11)
Total hip	0.94 (0.10)	0.94 (0.10)	0.93 (0.09)

significantly different compared to women who were not pregnant and had never been on PrEP, although numbers were small in both groups.

BMD declined significantly in pregnant women who used PrEP during pregnancy compared to women who used PrEP but did not become pregnant. After adjusting for age, BMI, and DMPA use, the relative mean BMD percent change was −2.47% (95% CI: −4.22 to −0.71, $p = 0.006$) at the femoral neck, −2.08% (95% CI: −3.50 to −0.66, $p = 0.004$) at the total hip, and −2.98% (95% CI: −4.78 to −1.18, $p = 0.001$) at the lumbar spine. The decline in BMD in pregnant women who were using PrEP during pregnancy was not statistically significant compared to women who experienced pregnancy but were not exposed to PrEP. The relative mean BMD percent change was −2.26% (95% CI: −6.54 to 2.01, $p = 0.30$) at the femoral neck, −2.47% (95% CI: −5.92 to 0.99, $p = 0.16$) at the total hip, and 0.67% (95% CI: −3.71 to −5.06, $p = 0.76$) at the lumbar spine. Similar results were observed in a sensitivity analysis limited to full-term pregnancies.

Prep continuation during pregnancy

Among the 90 women who became pregnant during the study, 10 (11%) did not use PrEP during the study, 19 (21%) did not continue PrEP use during pregnancy, and 61 (67%) chose to continue PrEP during their pregnancy. Among 80 women who became pregnant after initiating PrEP, PrEP was dispensed in 64% of visits during pregnancy (Table 4).

After adjusting for age, education, relationship status, income, and partner's HIV status, we found that women who became pregnant were less likely to get PrEP refill at subsequent study visits than women who did not become pregnant (adjusted OR: 0.25, 95% CI: 0.17, 0.37, $p < 0.001$). In the subset of women who became pregnant and had initiated PrEP ($N = 80$), there was a statistically significant 70% reduction in the odds of PrEP continuation during pregnancy (adjusted OR = 0.30, 95% CI 0.20–0.46 $p < 0.001$) compared to their non-pregnant periods.

Prep adherence

Over the 24-month follow-up period, there were 2,735 follow-up study visits among participants who were dispensed PrEP at a previous visit. Based on pill counts, high PrEP adherence (>80% of expected pills not returned) was reported in 69% of follow-up visits (Table 5). After adjusting for age, education, relationship status, income, and partner's HIV status, women had 62% reduced

TABLE 2 Pregnancy characteristics.

Characteristic	Overall, $N = 105$, n (%)	Used PrEP during pregnancy	
		No, $N = 33$, n (%)	Yes, $N = 72$, n (%)
Pregnancy was intended[a]			
No	77 (73%)	19 (58%)	58 (81%)
Yes	28 (27%)	14 (42%)	14 (19%)
Number of previous pregnancies			
None	65 (62%)	20 (61%)	45 (62%)
One	33 (31%)	11 (33%)	22 (31%)
More than one	7 (7%)	2 (6%)	5 (7%)
Pregnancy outcome			
Live birth	40 (38%)	12 (38%)	28 (42%)
Premature live birth	3 (3.0%)	0 (0%)	3 (4%)
Pregnancy loss	37 (35%)	12 (38%)	25 (37%)
Unknown	25 (24%)	9 (27%)	16 (22%)

[a]Ascertained through interviewer conversation with the participant.

odds of high PrEP adherence (adjOR 0.38; 95% CI 0.27–0.58, $p < 0.001$) during pregnancy compared to non-pregnant periods.

Discussion

In this study in Uganda with young women who initiated PrEP before pregnancy, we observed significant BMD loss among pregnant women using PrEP that was likely driven by pregnancy, rather than PrEP use. Our study also reported that women experiencing pregnancy were significantly less likely to use PrEP than women without a pregnancy through analyses of pregnant vs. non-pregnant women and pregnant and non-pregnant periods among women who become pregnant. Additionally, we found that women are less likely to be adherent to PrEP during pregnancy based on pill count data.

Over the two-year follow-up period, we observed a significantly greater loss in BMD among PrEP-exposed pregnant women

TABLE 3 Adjusted difference in the mean BMD at the neck of the hip, lumbar spine, and total hip .

			Comparisons to women who never pregnant and never used PrEP		Comparisons of the impact of pregnancy among women who used PrEP		Comparisons of the impact of PrEP among women who experienced pregnancy	
	$N = 294$	% Change in BMD from baseline (g/cm^2)	Adjusted difference in % change in BMD (95% CI)[a]	p-value	Adjusted difference in % change in BMD (95% CI)[a]	p-value	Adjusted difference in % change in BMD (95% CI)[a]	p-value
The neck of the hip (g/cm^2)								
Not pregnant and no PrEP use ever	31	0.12 (−1.64, 1.89)	Ref.		—		—	
Not pregnant and used PrEP	206	0.54 (−1.35, 2.44)	0.21 (−1.75, 2.16)	0.83	Ref.		—	
Pregnant, no PrEP ever	6	−0.08 (−4.47, 4.31)	0.01 (−4.33, 4.33)	0.99	—		Ref	
Pregnant, no PrEP during pregnancy	12	−1.82 (−5.17, 1.53)	−1.59 (−5.03, 1.84)	0.36	—		—	
Pregnant and PrEP use during pregnancy	39	−1.91 (−4.28, 0.46)	−2.26 (−4.63, 0.11)	0.06	−2.47 (−4.22, −0.71)	0.006	−2.26 (−6.54, 2.01)	0.30
Total hip (g/cm^2)								
Not pregnant and no PrEP use ever	31	1.01 (−0.45, 2.48)	Ref.		—		—	
Not pregnant and used PrEP	206	−0.14 (−1.72, 1.43)	−0.49 (−2.07, 1.09)	0.54	Ref.		—	
Pregnant, no PrEP ever	6	−0.08 (−3.73, 3.57)	−0.10 (−3.60, 3.39)	0.95	—		Ref.	
Pregnant, no PrEP during pregnancy	12	−0.69 (−3.44, 2.13)	−0.78 (−3.55, 2.00)	0.58	—		—	
Pregnant and PrEP during pregnancy	39	−2.20 (−4.17, −0.23)	−2.57 (−4.48, −0.66)	0.01	−2.08 (−3.50, −0.66)	0.004	−2.47 (−5.92, 0.99)	0.16
Lumbar spine (g/cm^2)								
Not pregnant and no PrEP use ever	31	3.09 (1.22, 4.96)	Ref.		—		—	
Not pregnant and used PrEP	206	−0.50 (−2.50, 1.49)	−0.08 (−2.09, 1.92)	0.95	Ref.		—-	
Pregnant, no PrEP ever	6	−4.05 (−8.68, 0.58)	−3.73 (−8.17, 0.76)	0.11	—		Ref.	
Pregnant, no PrEP during pregnancy	12	−1.75 (−5.28, 1.78)	−0.32 (−3.85, 3.20)	0.60	—		—	
Pregnant and PrEP use during pregnancy	39	−3.78 (−6.28, −1.27)	−3.06 (−5.49, −0.63)	0.01	−2.98 (−4.78, −1.18)	0.001	0.67 (−3.71, 5.06)	0.76

[a]Adjusted for age, BMI and DMPA use at enrollment.

TABLE 4 The association between PrEP continuation and pregnancy.

	PrEP was not dispensed	PrEP dispensed	Unadjusted analysis		Adjusted analysis[a]	
PrEP continuation among pregnant and non-pregnant women in the study						
	Total Visits $N = 443$, N (%)	Total Visits, $N = 3{,}038$, N (%)	OR (95% CI)	p-value	OR (95% CI)	p-value
Pregnant	49 (36%)	87 (64%)	0.32 (0.22–0.46)	<0.001	0.25 (0.17–0.37)	<0.001
Not pregnant	394 (11%)	2,951 (88%)	Ref.	Ref.	Ref.	Ref.
PrEP continuation among women who became pregnant during pregnant and non-pregnant periods						
	Total Visits, $N = 147$, N (%)	Total Visits, $N = 565$, N (%)				
Pregnant	49 (36%)	87 (64%)	0.38 (0.26–0.56)	<0.001	0.30 (0.20–0.46)	<0.001
Not pregnant	98 (18%)	447 (82%)	Ref.	Ref.	Ref.	Ref.

[a]Adjusted for age, income, education, partner's HIV status, and relationship status.

TABLE 5 Association of PrEP adherence with pregnancy.

	High PrEP adherence	Low PrEP Adherence	Unadjusted analysis		Adjusted analysis[a]	
	Total Visits $N = 1{,}878$ (N %)	Total Visits, $N = 857$ (N %)	OR (95% CI)	p-value	OR (95% CI)	p-value
Pregnant	46 (44%)	58 (56%)	0.36 (0.25–0.54)	<0.001	0.38 (0.27–0.58)	<0.001
Not pregnant	1,832 (70%)	799 (30%)	Ref.	Ref.	Ref.	Ref.

[a]Adjusted for age, income, education, partner's HIV status, and relationship status.

compared to women who did not become pregnant and were not exposed to PrEP. Isolating our analysis to estimate the effect of PrEP only, we did not see a significant difference in BMD loss when comparing PrEP-exposed pregnant women to pregnant women who never used PrEP. However, it is important to note that in both the femur and the hip, we saw a trend toward a greater reduction in BMD in women who use PrEP during pregnancy, and due to the small sample size of pregnant women who are not exposed to PrEP our estimates may be unstable. Given that previous studies have shown that TDF-based PrEP is associated with bone loss (16, 24, 25) and our study included young women who have not yet achieved peak bone mass, have high fertility rates, and are more likely to be exposed to injectable contraceptives that may compound bone loss (26), any significant BMD reduction in this group is particularly concerning and warrants further investigation. Studies are needed to determine the clinical implications of the decline in BMD associated with concurrent pregnancy and high adherence to TDF-based PrEP in young women and whether the decline is reversible after the end of pregnancy. It is also important to study the potential implications of a more prolonged decline in BMD when TDF-based oral PrEP is used during breastfeeding and the trajectory of BMD subsequent to the cessation of lactation.

Among the 80 women who initiated PrEP and became pregnant, 61(76%) chose to continue PrEP during pregnancy. However, our results indicate at subsequent visits, pregnant women were less likely to get PrEP refills compared to non-pregnant women, highlighting the importance of open discussion about the risks and benefits of PrEP use during pregnancy, the increased risk of HIV acquisition and devising strategies to support prevention-effective PrEP use in adolescent girls and young women during pregnancy. A recent study in South Africa found that the most common reason for PrEP discontinuation among pregnant women was gastrointestinal side effects, including nausea and vomiting (27). Providing women with counseling and strategies to manage nausea and vomiting could improve PrEP continuation. In addition, strategies such as regular adherence counseling, drug-level feedback, and adherence support clubs could be used to support oral PrEP adherence in young pregnant women (28–30).

Research in family planning methods has demonstrated that increasing the number of contraceptive products yielded increases in uptake and protection from unintended pregnancy (31, 32). New PrEP products, particularly longer-acting PrEP, could reduce challenges with oral PrEP persistence and adherence and may be convenient for some women to use. Newer PrEP products may also have less effect on bone density, making them a good alternative for women worried about BMD loss during pregnancy. However, safety data on the use of these products by pregnant and breastfeeding women are still forthcoming and the current product labels exclude their use by these populations.

We acknowledge that our study has several limitations. First, we used pill count as a measure of adherence which might not accurately reflect whether participants adhere to PrEP or not. Adherence measured using pill counts does not always align with TFV levels measured using pharmacologic adherence measures such as plasma and dried blood spots (DBS) (33–36). However, pharmacologic methods require skilled laboratory personnel and specialized equipment, making them difficult to access in resource-limited settings such as Uganda (37). A point-of-care TFV (POC TFV) urine test could be used for data-driven adherence counseling to support young women using PrEP (38–40). Future studies are planned to evaluate PrEP exposure using POC TFV (41). Even with these limitations, PrEP adherence was relatively poor during pregnancy in our study population, and future studies should evaluate the impact of more consistent TDF-based PrEP exposure on BMD decline during pregnancy.

Second, we used DXA scans at enrollment and exit from the study. For some women, the exit DXA scan closely followed the end of pregnancy while for others the length of time between pregnancy and the DXA scan was longer. BMD begins to rebound after pregnancy and continues to rebound after breastfeeding ceases and thus, the longer the interval between the end of pregnancy and the exit DXA scan, the greater the potential for lactation to confound the relationship between PrEP, pregnancy, and BMD since most women in Uganda aim to breastfeed for 2 years. Our data on breastfeeding were insufficient to accurately account for the effect of lactation. Additionally, our analysis did not account for the length of PrEP exposure during pregnancy. The extent of bone loss could be different between those with longer-term PrEP exposure compared to women with shorter-term PrEP exposure.

Conclusions

In conclusion, we found that BMD decline during pregnancy was not significantly greater among women who used PrEP during pregnancy compared to pregnant women with no PrEP exposure, suggesting that BMD loss in PrEP-using pregnant women is largely driven by pregnancy rather than PrEP use. Our study has also shown that women who experienced pregnancy while using PrEP were less likely to adhere to or continue using PrEP than those who did not experience pregnancy. Taken together, further assessments of the effect of quantifiable TDF-based PrEP use during pregnancy on bone health are needed. Additionally, it is important to advance research on alternative PrEP products that may have a lesser effect on bone health and could improve PrEP adherence during pregnancy.

Data availability statement

Public sharing of individual participant data was not included in the informed consent form of the project and cannot be posted in a supplemental file or a public repository because of legal and ethical restrictions. De-identified data underlying this project can be made available to interested researchers upon reasonable request by contacting the corresponding author.

Ethics statement

The study protocol was approved by the National HIV/AIDS Research Committee of Uganda, the Uganda National Council for Science and Technology, and the Human Subjects Division at the University of Washington. Participants ≥18 years provided written informed consent. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

Study conceptualization: KZ and RH. Data analysis: KZ. Writing original draft: KZ and RH. Writing review and editing: All authors. All authors participated in the critical review and have read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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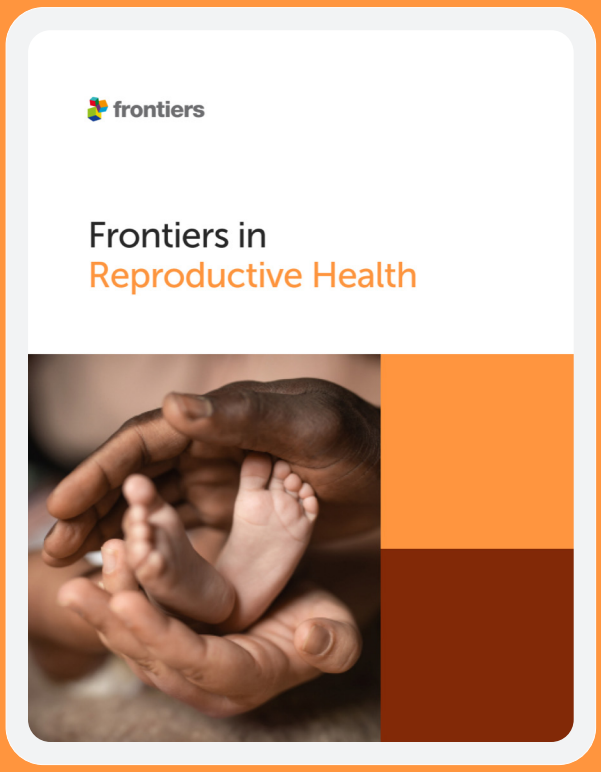

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