

https://dspace.org/

Oral preexposure prophylaxis uptake adherence and persistence during periconception periods among women in South Africa

L T Matthews; Manjeetha Jaggernath; Yolandie Kriel; P M Smith; J E Haberer ...

LIPPINCOTT WILLIAMS & WILKINS
https://hdl.handle.net/10539/41034
WOS

Downloaded from a DSpace repository. https://dspace.org/

OPEN

Oral preexposure prophylaxis uptake, adherence, and persistence during periconception periods among women in South Africa

Lynn T. Matthews[a], Manjeetha Jaggernath[b], Yolandie Kriel[b], Patricia M. Smith[a], Jessica E. Haberer[c], Jared M. Baeten[d,e], Craig W. Hendrix[f], Norma C. Ware[g,h], Pravi Moodley[i], Melendhran Pillay[j], Kara Bennett[k], John Bassler[l], Christina Psaros[m], Kathleen E. Hurwitz[k], David R. Bangsberg[n] and Jennifer A. Smit[b]

Objective: We developed the Healthy Families-PrEP intervention to support HIV-prevention during periconception and pregnancy. We evaluated preexposure prophylaxis (PrEP) use with three objective measures.

Design: This single-arm intervention study enrolled women in KwaZulu-Natal, South Africa, who were HIV-uninfected, not pregnant, in a relationship with a partner with HIV or unknown-serostatus, and with pregnancy plans. PrEP was offered as part of a comprehensive HIV prevention intervention. Participants were followed for 12 months.

Methods: We evaluated periconception PrEP uptake and adherence using quarterly plasma tenofovir concentrations. We modeled factors associated with PrEP uptake and high plasma tenofovir (past day dosing). Patterns of use were analyzed using electronic pillcap data. Dried blood spots to measure intracellular tenofovir product (past 2 months dosing) were analyzed for a subset of women.

Results: Three hundred thirty women with median age 24 (IQR: 22–27) years enrolled. Partner HIV-serostatus was unknown by 96% ($N = 316$); 60% (195) initiated PrEP. High plasma tenofovir concentrations were seen in 35, 25, 22, and 20% of samples at 3, 6, 9, and 12 months, respectively. Similar adherence was measured by pillcap and dried blood spots. In adjusted models, lower income, alcohol use, and higher HIV stigma were associated with high plasma tenofovir. Eleven HIV-seroconversions were observed (incidence rate: 4.04/100 person-years [95% confidence interval: 2.24–7.30]). None had detectable plasma tenofovir.

[a]Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama, USA, [b]Maternal Adolescent and Child Health Research Unit (MRU), Department of Obstetrics and Gynaecology, University of the Witwatersrand, Faculty of Health Sciences, Durban, South Africa, [c]Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, [d]Department of Global Health, [e]Division of Allergy and Infectious Diseases, University of Washington, Seattle, Washington, [f]Department of Medicine (Clinical Pharmacology), Johns Hopkins University, School of Medicine, Baltimore, Maryland, [g]Department of Global Health & Social Medicine, Harvard Medical School, [h]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, [i]University of KwaZulu-Natal, School of Laboratory Medicine and Medical Sciences, National Health Laboratory Service, [j]Department of Virology, National Health Laboratory Service, Durban, South Africa, [k]Target RWE, Durham, North Carolina, [l]Department of Biostatistics, School of Public Health, University of Alabama at Birmingham, Birmingham, Alabama, [m]Department of Psychiatry, Behavioural Medicine Program, Massachusetts General Hospital, Boston, Massachusetts, USA, and [n]Vinh University College of Health Sciences, Hanoi, Vietnam.

Correspondence to Lynn T. Matthews, 1900 University Blvd, THT215E, Birmingham, AL 35294, USA.

Tel: +1 (205) 934 8148; e-mail: lynnmatthews@uabmc.edu

Received: 18 January 2024; revised: 1 April 2024; accepted: 8 April 2024.

DOI:10.1097/QAD.0000000000003925

ISSN 0269-9370 Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Conclusion: The Healthy Families-PrEP intervention supported women in PrEP use. We observed high interest in periconception PrEP and over one-third adhered to PrEP in the first quarter; one-fifth were adherent over a year. High HIV incidence highlights the importance of strategies to reduce HIV incidence among periconception women.

Clinical Trial Number: NCT03194308

Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

AIDS 2024, **38**:1342–1354

Keywords: adherence, HIV-Prevention, periconception, perinatal, pre-exposure prophylaxis, South Africa

Introduction

South Africa is home to nearly 7.5 million people with HIV (PWH); in 2021, an estimated 130 000 women and 10 000 children acquired HIV [1]. In HIV-endemic settings, many women conceive a baby with a partner with HIV or whose serostatus is unknown [2]. For women who cannot rely on partners to test, engage in care, and suppress HIV-RNA through antiretroviral treatment, condomless sex leaves them vulnerable to HIV and thus increases perinatal transmission risks.

Daily, oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for preexposure prophylaxis (PrEP) reduces HIV-acquisition risk, is well tolerated for use among pregnant and breastfeeding people, and is recommended by the WHO, U.S. Centers for Disease Control and Prevention, and South Africa Department of Health for pregnant and breastfeeding people vulnerable to HIV infection [3–5]. However, many South Africans, including pregnant and breastfeeding people, struggle with adherence [6,7].

Goals to have a healthy baby and remain HIV-free may motivate HIV prevention during periconception and pregnancy [8]. Informed by these observations and our formative work, we developed and tested the Healthy Families-PrEP (HF-PrEP) intervention to support PrEP use during periconception and pregnancy periods [9]. This manuscript describes PrEP use among women planning for pregnancy in South Africa and participating in the intervention. We aimed to discover whether women could be supported to effectively use oral PrEP as a component of comprehensive HIV-prevention for women intending to conceive a child while potentially exposed to HIV.

Materials and methods

Study design and population

We conducted a single-arm longitudinal study among women without HIV in Durban, South Africa. Participants were planning for pregnancy within the next year with a partner with HIV or of unknown serostatus. Data collection occurred from 13 November 2017 to 21 July 2021. Additional eligibility criteria included female sex; age 18–35 years; not on long-acting contraception; and likely to be fertile [10]. Women with pregnancy or HIV at screening were not eligible. Fieldwork teams recruited women from local healthcare clinics, gathering spots near the research site, and through word-of-mouth promotion. Enrolled participants were offered HIV prevention counseling including TDF/FTC PrEP with quarterly adherence support and followed for 12 months. Objective adherence data were collected from plasma, whole blood, and electronic pillcaps [9]. This manuscript is restricted to periconception (the period from enrollment until study exit or incident pregnancy); pregnant women were censored for this analysis at the date of the first positive pregnancy test.

Study activities

HIV prevention counselling (Healthy Families-PrEP)

We developed a counselling intervention, "Healthy Families-PrEP" (HF-PrEP), to support women in achieving reproductive goals while minimizing HIV acquisition, based on South African guidelines and our formative work [11]. Those initiating PrEP participated in quarterly adherence support sessions, adapted from Lifesteps for PrEP [12,13] (Table 1).

Preexposure prophylaxis provision and monitoring

Dispensing

Women could initiate or discontinue PrEP at any time. Participants initiating PrEP were provided with a 30-day supply of PrEP at initiation and a 90-day supply at subsequent visits.

Clinical laboratory monitoring

Women initiating PrEP completed blood testing to evaluate renal function and hepatitis B status. Women with abnormal renal function [serum creatinine $>$ 89 μmol/l and estimated glomerular filtration rate (eGFR) $<$ 60 ml/min] or active hepatitis B infection (hepatitis B surface antigen positive) were instructed to stop PrEP per WHO guidelines at that time [14].

Table 1. Healthy Families-PrEP support intervention.

Session[c]	Activities
1	Rapport building and introduction
	Safer conception education [a]
	Motivational strategies to prepare for behavior change
	Develop individualized safer conception plan
2	Review prior session content
	Safer conception plan review [a]
	Revise plan as needed
	Support to implement plan [b]
3	Review prior session content
	Safer conception plan review [a]
	Revise plan as needed
	Support to implement plan [b]

[a]Guidelines at the time recommend that HIV-uninfected women who want to conceive a child with a partner with HIV should encourage partner testing and serostatus disclosure within the partnership, encourage partner to initiate ART, delay sex without condoms until he achieves HIV RNA suppression or is on ART for six months, consider contraception to delay pregnancy until safer conception strategies are implemented, limit condomless sex to peak fertility, and/or consider sperm washing, donor sperm, and adoption as alternatives. We also counselled on the availability and benefits of PrEP for HIV prevention.
[b]Methods employed to support clients to implement plan: education, problem solving, motivational strategies, communication skills.
[c]Quarterly adherence support sessions throughout PrEP use. Comprehensive counselling was performed by trained study counsellors in a group format, with the option of one-on-one counseling sessions based on participant preference and study site logistics.

Participants completed beta-HCG urine testing, individual HIV counseling and testing (HCT), and syndromic screening for sexually transmitted infections (STIs) at each study visit. Those with pregnancy were eligible to remain in the study and referred for antenatal care. Those with STI symptoms were provided with treatment. Participants who seroconverted were exited from the study and followed to promote linkage to care. HIV-RNA samples were sent for genotyping.

Electronic pillcaps

Women accessing PrEP were provided a pill bottle with an electronic cap (Medication Electronic Monitoring System (MEMS) [AARDEX, Switzerland]) that recorded when the device was opened as a proxy for pill ingestion. Pillcap data were downloaded at each visit and reviewed with participants.

Adherence-related laboratory evaluation

Women who initiated PrEP provided blood samples at quarterly visits for whole blood and plasma. Concentrations of tenofovir metabolites were assayed in all plasma and a subset of DBS samples using methods described elsewhere [15]. The subset of DBS included all HIV seroconversion samples and a random subset of other samples such that 101 participants (52%) of ever PrEP users were included.

Questionnaires

At enrollment, a questionnaire was administered via face-to-face interview with a research assistant fluent in English and the dominant local language to assess constructs within our conceptual framework for periconception HIV prevention behavior [16]. Constructs were measured using instruments validated in this setting, described in detail elsewhere [9].

COVID-19 protocol adaptations

The South African government implemented a nationwide lockdown from March 27, 2020, through May 1, 2020. The research protocol was temporarily modified to optimize safety for participants and study staff. In-person visits were limited to essential visits with telephonic data collection for other study activities. Once restrictions were loosened, onsite clinical activities resumed per original protocol specifications.

Outcomes

The primary outcomes included PrEP uptake defined as the proportion of participants who ever collected a 30 day PrEP supply at least once within 12 months of enrollment and PrEP adherence as measured by plasma TFV at the first quarterly follow-up visit following initiation. Plasma TFV concentrations at least 40 ng/ml indicate dosing in the last 24 h (categorized as "high" adherence), between 10 and 40 ng/ml indicate dosing in the prior 3 days ("moderate" adherence), and less than 10 ng/ml indicate no dosing in the prior 7 days ("low" adherence) [17].

We also evaluated adherence using the proportion of days with a record of pill bottle opening and intraerythrocytic TFV-DP concentrations, reflecting use over the prior two months. Pillcap adherence was assessed during active PrEP follow-up (PrEP initiation through to the earlier of reported PrEP discontinuation or study exit) and capped at one opening per day. We estimated mean monthly adherence over time and the proportion of PrEP initiators with mean monthly adherence at least 80% ("high" adherence) [18]. Intraerythrocyte concentrations of TFV-DP were a secondary adherence measure for a subset of women. On the basis of limited data for pregnant or postpartum African women [19–21], we categorized intraerythrocytic concentrations of more than 600 fmol/punch, approximately at least 4 doses per week ("high" adherence), 450–600 fmol/punch as about three doses per week ("moderate" adherence), and between 16.6 and less than 450 as less than three doses per week ("low" adherence) [19,22]. We selected a slightly lower cut-off for the category of "high" based on the available data while accounting for our inability to adjust for anemia, thrombocytopenia, and BMI [23].

Pillcap data were used to evaluate at least 14-day breaks in PrEP use followed by resumption of daily use (i.e. continuation after an interruption) versus 14-day breaks in PrEP use without resumption (i.e. discontinuation). We chose 14 days to prioritize interruptions beyond common-but-transient gaps in pillcap use including pocket doses (i.e., multiple pills removed for later dosing), weekend breaks, reduced access to PrEP due to COVID-19 restrictions, and travel [24].

Drug concentration and pillcap data were censored at the last study visit date after the last pillcap opening. If a client stopped using PrEP in January 2020 and reported this at a follow-up visit in March 2020, they contributed adherence data through March and were subsequently classified as having discontinued PrEP and did not contribute ongoing adherence data.

Additional outcomes

We assessed HIV incidence (overall and by PrEP initiation status) measured as the time to first HIV-positive test from enrollment. Follow-up for incident cases was censored at the midpoint of the first positive and last negative HIV test result for infected women. Data for women who did not acquire HIV was censored at the time of the last available negative test.

For all participants who seroconverted, Sanger Sequencing-based HIV resistance genotyping was completed as described by Manasa *et al.* [25]. The Stanford University HIV drug resistance database (version 9.0) was used to assess the presence of HIV drug resistance mutations and antiretroviral susceptibilities [26,27]. We defined drug resistance as having any major drug resistance mutation (DRM) to nucleoside reverse transcriptase inhibitor (NRTI), nonnucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitors.

Study clinicians monitored adverse events using NIH DHHS guidelines [28] at all scheduled study visits; adverse events were reviewed by the DSMB at annual meetings.

Sample size

We proposed to enroll 350 women [9]. Due to the COVID-19 pandemic, enrollment was capped at 330 in March 2020; the last participant enrolled on January 31, 2020.

Statistical analysis

We describe adherence longitudinally with electronic pillcaps, TFV plasma, and TFV-DP in dried blood spots. However, our models to predict adherence were conducted at 3 months given high rates of exit due to seroconversion, pregnancy, losses to follow-up, and less stable and less representative numbers at 6, 9, and 12 months. We used modified Poisson regression with generalized estimating equations to assess predictors of PrEP initiation and high adherence (defined as TFV $\geq$40 ng/ml) at the first quarterly visit following PrEP initiation. Baseline predictors identified based on our periconception HIV risk conceptual framework [35] included age, education, household income, number of prior pregnancies, number of sexual partners, condom use, tobacco and alcohol use, HIV stigma [16], perceived HIV risk [29], sexual relationship power [30], dyadic trust [31], social support [32], and depression [33]. Multivariable-adjusted risk ratios were constructed using a change-in-estimate approach [34] in which relative to a fully adjusted model (i.e., all known or hypothesized confounding factors identified by subject matter knowledge of the underlying causal structure included), we removed, one by one, each factor and recorded the estimated coefficient for the predictor-outcome association. If the removal of the factor changed the coefficient by at least 10%, it was retained. Missing data are considered missing at random and complete case analyses are reported.

All statistical analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, North Carolina, USA) and R Statistical Software (v4.1.2; R Core Team 2021).

Ethics and dissemination

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

Role of the funding source

Study funders did not have a role in study design, data collection, analysis, interpretation of data, or writing of this report.

Results

Screening and enrollment

We approached 673 women for screening, of whom 621 completed the screening questionnaire, and 330 met eligibility criteria and enrolled. Figure 1 summarizes reasons for ineligibility. Among 330 enrolled women, four (1%) did not complete safer conception counseling. Thus, this manuscript reports on data collected from 326 fully enrolled participants. At enrollment, median (25^{th}, 75^{th} percentile) age was 24 (22, 27) years with 279 (86%) reporting a high school education or beyond and 145 (45%) reporting no prior pregnancies. Most women ($n = 287$; 88%) reported one sexual partner, and most ($n = 313$; 97%) did not know the HIV-serostatus of their desired pregnancy partner. Most ($n = 205$, 70%) reported that at least one of their sexual partners probably had other partners (Table 2).

Overall, 189 (58%) women completed all planned follow-up visits (Fig. 1). The most common reasons for discontinuing periconception follow-up were pregnancy ($n = 56$), loss to follow-up ($n = 46$), relocation outside the catchment area ($n = 24$), and withdrawal of consent ($n = 16$). Figure 2 illustrates that 312 women (96%)

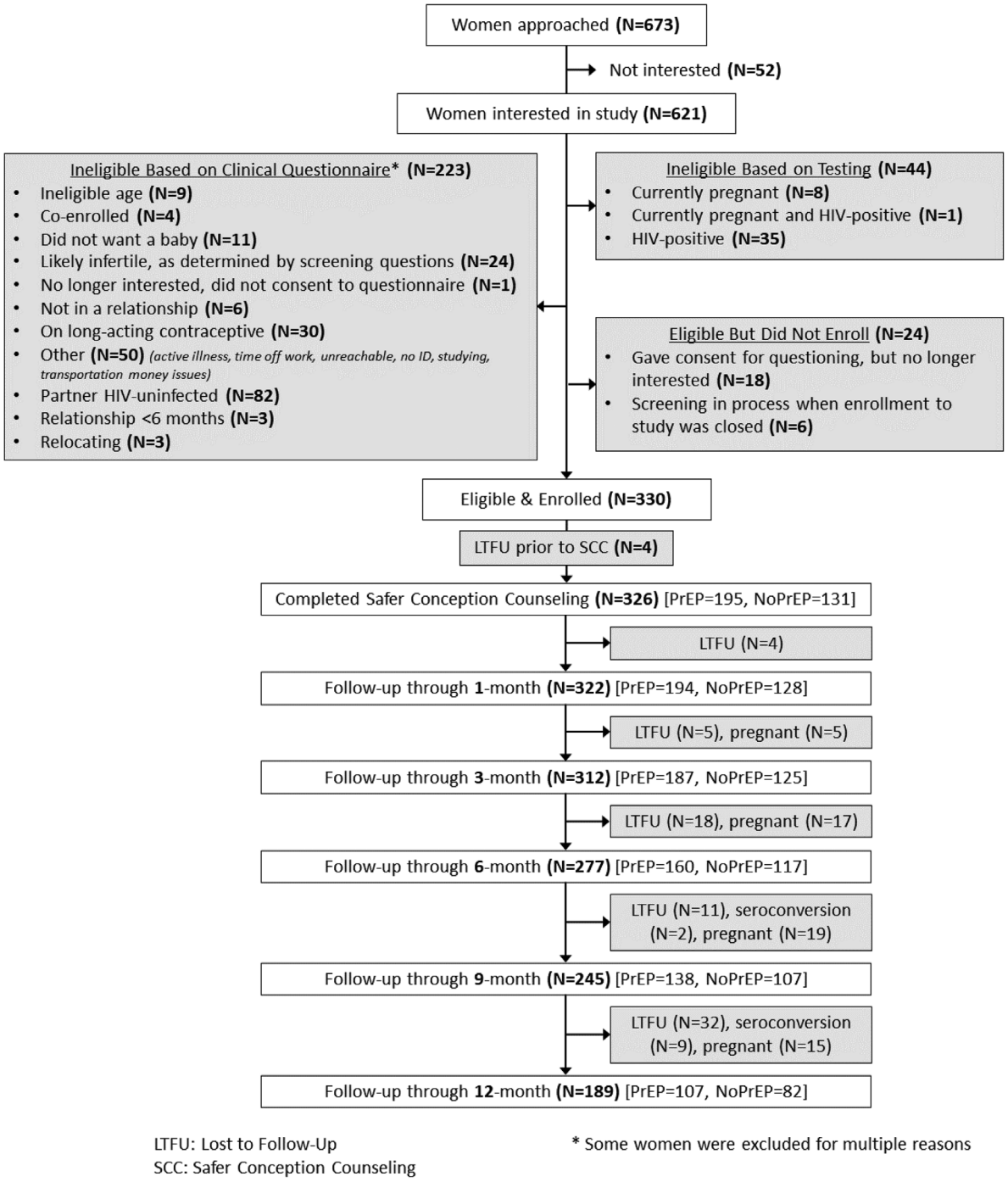


Fig. 1. Consort diagram. Flow of participants during screening, enrollment, and follow-up.

completed the 3-month follow-up visit and, therefore, all three primary Healthy Families-PrEP counseling sessions (Table 1). Eleven women acquired HIV during follow-up.

Preexposure prophylaxis initiation

A total of 195 (60%) women initiated PrEP with most ($n = 162$; 83%) starting within 2 months of enrollment; 97% initiated within 6 months of enrollment. In multivariable-adjusted models, participants with higher income, greater educational attainment, and higher HIV risk perception were less likely to initiate PrEP during follow-up (Table 3) (Supplemental File 2 provides unadjusted associations, http://links.lww.com/QAD/D217).

Preexposure prophylaxis adherence and persistence

Figure 2 highlights summary use at 3, 6, and 9 months with all three adherence measures. We found that 86–92% took at least some PrEP by pillcap, 23–36% by plasma TFV,

Table 2. Baseline characteristics, overall and by ever-initiated PrEP.

	Overall (*N* = 326)	Did not initiate PrEP (*N* = 131)	Initiated PrEP (*N* = 195)
Individual characteristics			
Age, years			
Median (IQR)	24 (22, 27)	24 (22, 26)	24 (22, 27)
Education			
Grade 7 (Standard 5) - Grade 11 (Standard 9)	47 (14.4%)	14 (10.7%)	33 (16.9%)
Grade 12 (Standard 10) and postgrade 12	279 (85.6%)	117 (89.3%)	162 (83.1%)
Income, monthly ($USD)			
< $116	75 (31.6%)	22 (23.4%)	53 (37.1%)
$116–$232	81 (34.2%)	39 (41.5%)	42 (29.4%)
> $232	81 (34.2%)	33 (35.1%)	48 (33.6%)
Missing	*89*	*37*	*52*
Total pregnancies			
0 or 1	266 (81.6%)	112 (85.5%)	154 (79.0%)
2+	60 (18.4%)	19 (14.5%)	41 (21.0%)
Currently using tobacco products			
Yes	28 (8.6%)	12 (9.2%)	16 (8.3%)
No	296 (91.4%)	119 (90.8%)	177 (91.7%)
Missing	*2*	*0*	*2*
Frequency of alcohol use in the past year			
Never	154 (47.7%)	61 (47.3%)	93 (47.9%)
Any Amount	169 (52.3%)	68 (52.7%)	101 (52.1%)
Missing	*3*	*2*	*1*
Partnership characteristics			
Partner HIV Status			
Primary partner's HIV status is known by participant	11 (3.4%)	3 (2.3%)	8 (4.1%)
Primary partner's HIV status is unknown by participant	313 (96.6%)	127 (97.7%)	186 (95.9%)
Missing	*2*	*1*	*1*
Sexual partners, past 3 months			
0 or 1	288 (88.6%)	119 (90.8%)	169 (87.1%)
2+	37 (11.4%)	12 (9.2%)	25 (12.9%)
Missing	*1*	*0*	*1*
Pregnancy partner (main or other) has other partners			
Definitely/Probably does not	90 (30.5%)	41 (33.3%)	49 (28.5%)
Definitely/Probably does	205 (69.5%)	82 (66.7%)	123 (71.5%)
Missing	*31*	*8*	*23*
Depression Score [a]			
≤ 1.75	303 (94.1%)	120 (92.3%)	183 (95.3%)
> 1.75	19 (5.9%)	10 (7.7%)	9 (4.7%)
Missing	*4*	*1*	*3*
Parenthood motivation: Social control [b]			
Median (IQR)	7 (6, 8)	7 (5, 8)	7 (6, 8)
Missing	*8*	*2*	*6*
HIV Stigma Score [c]			
Median (IQR)	2 (0, 6)	2 (0, 7)	2 (0, 5)
Missing	*15*	*8*	*7*
Perceived HIV Risk [d]			
Median (IQR)	20 (18, 22)	20 (19, 22)	20 (18, 22)
Missing	*17*	*7*	*10*
Sexual Relationship Power Scale [e]			
Median (IQR)	3 (2, 3)	3 (2, 3)	3 (2, 3)
Missing	*43*	*18*	*25*
Dyadic Trust Score [f]			
Median (IQR)	29 (26, 34)	30 (26, 34)	29 (25, 34)
Missing	*3*	*1*	*2*
Social support [g]			
Median (IQR)	4 (4, 4)	4 (4, 4)	4 (4, 4)
Missing	*1*	*0*	*1*
PrEP Optimism [h]			
Median (IQR)	5 (5, 6)	5 (5, 6)	6 (5, 7)
Missing	*5*	*2*	*3*

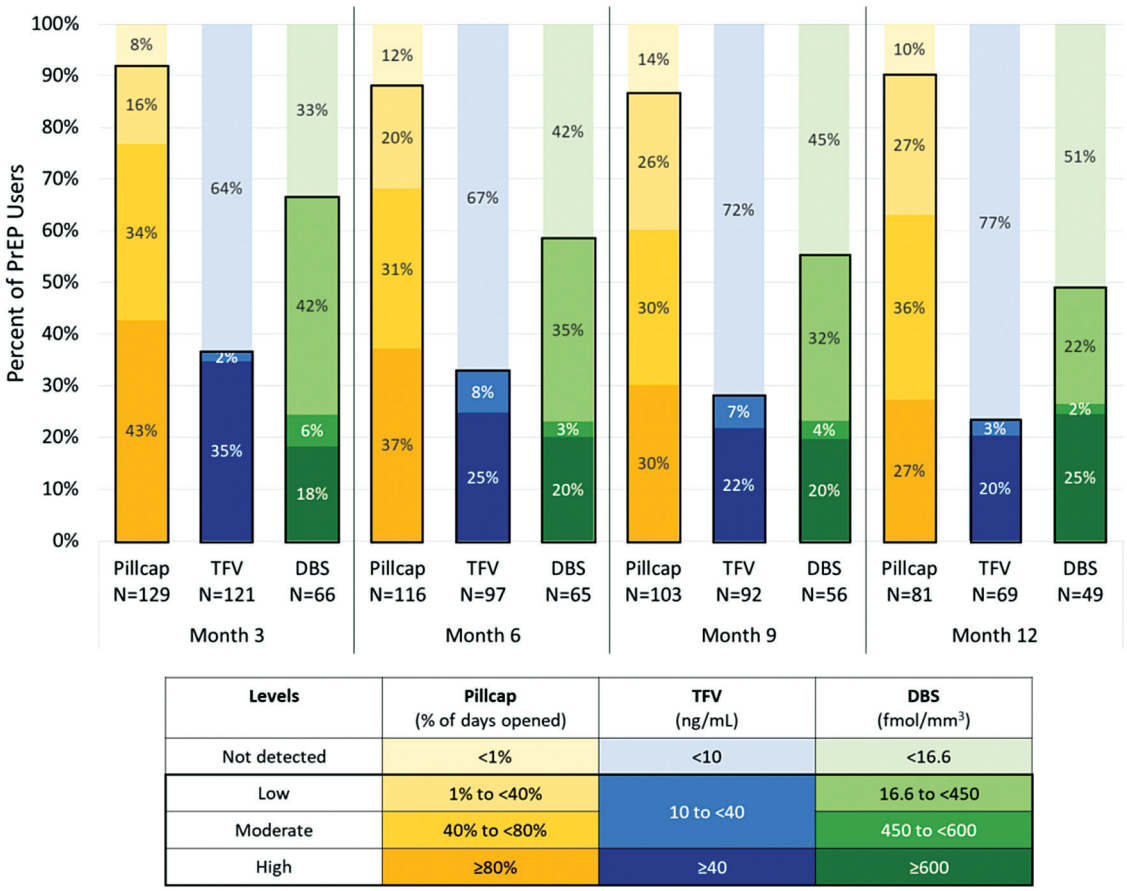
[a]Depression: Depression was measured using 10 items questions from the Hopkins Symptoms Checklist [33]. Items were scored on a 4-point Likert scale [ranging from (1) ''Not at all'' through (0) ''Extremely'']. An average score of 1.75 and above was classified as having depression.
[b]Social Control: (a) ''My environment (others, family) expect it of me''; (b) ''Others around me have children''; (c) "I want to have a baby to avoid being an outsider''.
[c]HIV stigma: HIV stigma (attributed stigma, perception how most people feel) was assessed using 17 items from the HIV Stigma Scale [65,66] with the response profile (1) Agree or (0) Disagree. A score was obtained by summing over the 17 items with higher scores indicating higher attributed stigma about HIV.

Table 2. Continued.

[d]Perceived HIV risk: Perceived HIV risk was measured using the Perceived Risk of HIV scale developed by Napper *et al.* [29]. Participants responded to the seven-item questions with Likert scale responses: (1) ''What is your gut feeling about how likely you are to get infected with HIV?'' [responses range from (1) Extremely unlikely to (4) Extremely likely], (2) ''I worry about getting infected with HIV'' [responses range from (1) Never to (4) All the time], (3) '' Picturing myself getting HIV is something I find''[responses range from (1) very hard'' to (4) ''Very easy to do''], (4) ''Getting HIV is something I am. . ..'' [responses range from 'Not concerned about' to 'Extremely concerned about'], (5) ''I am sure I will not get infected with HIV.'' [responses range from (1) ''Strongly agree'' to (4) ''Strongly disagree''], (6) ''I feel I am unlikely to get infected with HIV.'' [responses range from (0) ''Strongly agree'' through (5) ''Strongly disagree''], (7) ''I feel vulnerable to HIV infection.'' [responses range from (5) ''Strongly agree'' through (0) ''Strongly disagree'']. Items were summed with higher scores indicating higher perceived HIV risk.
[e]Sexual relationship power: Sexual relationship power was measured using the Sexual relationship Power Scale [67], which includes 23 questions and two subscales: relationship control [15 questions with response options ranging from (5) ''Strongly agree'' through (0) ''Strongly disagree''] and decision-making dominance subscale [eight questions with response options ''Your partner,'' ''Both of you equally,'' or ''You'']. Items were summed and overall score was derived. A higher score indicate more power in relationship in the area of relationship control and decision-making dominance.
[f]Dyadic trust: Dyadic trust was measured using the Dyadic Trust Scale [31], which includes eight-item questions with a 5-point Likert scale response options [ranging from (4) Agree through (0) Disagree]. An average score was derived with a higher score indicating higher trust.
[g]Social support: Social support was measured using 10 items from the Duke-UNC Functional Social Support Questionnaire [32]. Items were scored on a 4-point Likert scale [ranging from (1) As much as I would like through (4) Never]. An overall score was derived with higher scores indicating higher social support.
[h]PrEP optimism: PrEP optimism was assessed based on three-item questions adapted from the Partners PrEP adherence sub-Study [68]: (1) ''PrEP reduces risk of getting HIV,'' (2) ''PrEP makes it easier to relax about sex without condoms,'' and (3) ''PrEP makes me worry less.'' Responses to each item questions were given scores of 0 (for ''strongly disagree''), 1 (for ''disagree''), 2 (for ''agree''), 3 (for ''strongly agree''), and summed with higher scores indicating greater PrEP optimism.

and 49–67% by TFV-DP at 3, 6, 9, and 12 months of follow-up. In addition, 27–43% were highly adherent taking at least 80% of doses by pillcap, 20–35% with high plasma tenofovir, and 18–25% with high TFV-DP. Adherence waned over time by all measures.

Among 180 women who initiated PrEP and had pillcap data, median duration of persistent PrEP use was 219 days (range: 1–545). Serial short gaps in use were common; the median proportion of time on PrEP for PrEP users was 63% (IQR 43%, 83%). Seventy-eight (43%) women



Levels	Pillcap (% of days opened)	TFV (ng/mL)	DBS (fmol/mm^3)
Not detected	<1%	<10	<16.6
Low	1% to <40%	10 to <40	16.6 to <450
Moderate	40% to <80%		450 to <600
High	≥80%	≥40	≥600

Fig. 2. Periconception PrEP use over 12 months by electronic pillcap (proportion of days pillcap opened summarized over prior quarter), plasma TFV (past day use), intraerythrocytic TFV-DP (past 8 weeks use).

Table 3. Multivariable-adjusted risk ratios and 95% confidence intervals for (a) initiation of PrEP during follow-up and (b) plasma TFV (>40 ng/ml) at 3 months following PrEP initiation.

Covariate	Outcome: Ever initiated PrEP during follow-up [a]		Outcome: Plasma TFV>40 ng/ml at 3 months [b]	
	aRR (95% CI)	*P*	aRR (95% CI)	*P*
Age (years)	1.01 (0.97–1.04)	0.74	1.03 (0.96–1.10)	0.46
Education				
Grade 7 (Standard 5) - Grade 11 (Standard 9)	REF	–	REF	–
Grade 12 (Standard 10) and postgrade 12	0.74 (0.58–0.94)	**0.02**	1.77 (0.68–4.65)	0.24
Income, monthly ($USD)		**0.01** [c]		**0.04** [c]
< $116	REF		REF	
$116–$232	0.66 (0.50–0.86)		0.74 (0.37–1.46)	
> $232	0.78 (0.62–0.99)		0.44 (0.20–0.98)	
Total pregnancies				
0 or 1	REF	–	REF	–
2+	1.18 (0.93–1.50)	0.18	0.91 (0.35–2.37)	0.85
Currently using tobacco products [d]				
No	REF	–		
Yes	0.79 (0.49–1.28)	0.34		
Frequency of alcohol use in the past year				
Never	REF	–	REF	–
Any amount	0.97 (0.81–1.18)	0.78	2.18 (1.20–3.99)	**0.01**
Sexual partners, past 3 months				
0 or 1	REF	–	REF	–
2+	1.24 (0.96–1.60)	0.10	0.59 (0.17–2.04)	0.40
Pregnancy partner (main or other) has other partners				
Definitely/Probably is not	REF	–	REF	–
Definitely/Probably is	1.05 (0.84–1.32)	0.66	0.79 (0.39–1.60)	0.52
Depression Score [d]				
≤ 1.75	REF	–		
> 1.75	0.71 (0.32–1.60)	0.41		
Parenthood motivation: Social control	0.99 (0.92–1.07)	0.86	1.10 (0.92–1.31)	0.30
HIV Stigma Score	1.00 (0.97–1.02)	0.83	1.16 (1.07–1.26)	**<0.01**
Perceived HIV Risk	0.97 (0.94–0.99)	**0.046**	1.06 (0.96–1.18)	0.23
Sexual Relationship Power Scale	1.04 (0.77–1.41)	0.79	0.87 (0.35–2.15)	0.76
Dyadic Trust Score	1.00 (0.98–1.02)	0.69	1.00 (0.93–1.07)	0.94
Social support	0.89 (0.53–1.48)	0.65	3.29 (0.45–24.18)	0.24
PrEP Optimism	1.00 (0.93–1.07)	0.97	1.12 (0.93–1.35)	0.23

See supplemental file 3, http://links.lww.com/QAD/D218 for each minimally adjusted model of factors associated with initiating PrEP. See supplemental file 4, http://links.lww.com/QAD/D219 for fully adjusted multivariable analysis of factors associated with ever-PrEP use and 3-month plasma >40 ng/ml.
[a]PrEP initiation analyses conducted among $n = 326$ participants who completed all enrollment activities.
[b]Plasma TFV analyses conducted among $n = 134$ PrEP initiators who provided a sample at the 3-month follow-up visit.
[c]P-value computed based on a chi-square distribution with 2 degrees of freedom.
[d]Multivariable-adjusted analyses for tobacco use and depression score were not conducted due to insufficient sample size.
P-values < 0.05 are in bold.

had at least one adherence interruption of 14 days or more (Fig. 3); median time to first 14-day interruption was 77 (IQR 31–127) days with median time to restart was 22 (IQR 17–40) days. Median time to PrEP discontinuation without restarting was 200 (IQR 85–326) days (Fig. 4).

In multivariable-adjusted models, women with lower income, any alcohol use, and higher levels of attributed community HIV stigma were more likely to have high plasma TFV concentration (Table 3) (Supplemental File 2 provides unadjusted associations, http://links.lww.com/QAD/D217).

HIV incidence

Eleven incident infections occurred among 315 participants with a repeat HIV test result, contributing 272 years of follow-up. HIV incidence was 4.04 per 100 person-year [95% confidence interval (95% CI) 2.24–7.30]. Five of these seroconversions occurred among 122 participants who did not initiate PrEP with 108 years of follow-up for an HIV incidence of 4.62 (95% CI: 1.92–11.10). The remaining six seroconversions occurred among 193 women who initiated PrEP with 164 years of follow-up with an HIV incidence of 3.66 (95% CI: 1.64–8.15). Four of the six had undetected plasma TFV at the visit where they were diagnosed with HIV. The remaining two had undetected plasma TFV at the visit prior to diagnosis with HIV. Three women who had TFV-DP tested had concentrations below limits of detection. Two additional women had either undetected of a low concentration (21.3 fmol/punch) at a visit prior to HIV-seroconversion. Among the six women who initiated PrEP and seroconverted, three had NNRTI resistance mutations (V106 M, K103N, E138A), all unrelated to exposure study product (TDF/FTC).

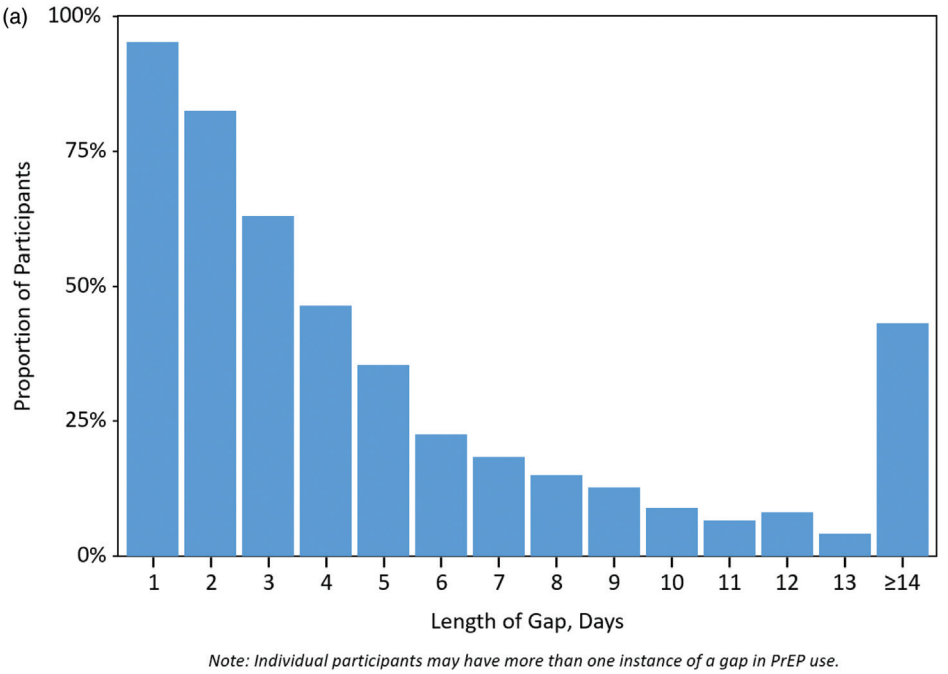


Fig. 3. Proportion of $N = 180$ periconception participants who started PrEP and used the electronic pillcap who had adherence gaps of 1 through ≥14 days.

Adverse events

We observed 60 adverse events (among 44 participants) of which 23 events (among 20 participants) were considered serious. None of the serious adverse events were deemed to be related to study procedures, including PrEP use (See Supplemental file 1 for all adverse events, http://links.lww.com/QAD/D216). No clients were advised to stop PrEP due to renal dysfunction. One unvaccinated person with HBV at baseline stopped PrEP shortly after initiation.

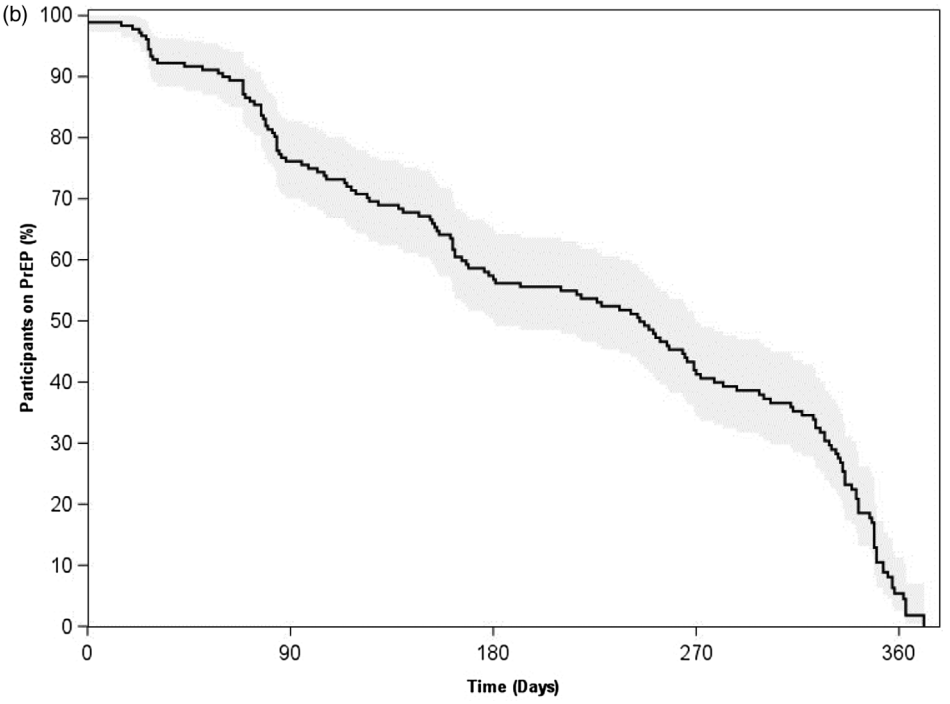


Fig. 4. Time to PrEP discontinuation (black) and 95% CI (grey), where PrEP discontinuation is defined as the first 14-day interruption in treatment without resumption (based on pillcap data) among $N = 180$ periconception participants who initiated PrEP.

Discussion

We conducted a longitudinal study offering an HIV prevention intervention, Healthy Families-PrEP, to women planning for pregnancy in an urban South African setting with one of the highest HIV prevalence rates in the world. The majority of participants did not know their partner's status, suspected he had other partners, and were engaging in condomless sex with goals to have a child. The HF-PrEP intervention supported high PrEP uptake (60%) and high adherence over 3 months for 20–43% of participants (depending on the adherence measure used). By pillcap, most women had gaps in their PrEP use with a median time to discontinuation of 199 days. We observed high HIV incidence and the findings suggest the importance and value of programming to promote HIV prevention for women planning for pregnancy. PrEP interest is high, and many women need additional adherence support and/or alternative prevention strategies.

Our findings of high adherence compared to many other demonstration projects among cisgender women suggest the value of PrEP care for this population. In a recent analysis of more than 6000 cisgender women accessing TDF/FTC PrEP in demonstration projects, including 78% African women, only 17% were highly adherent to PrEP by intracellular tenofovir concentrations [6]. Others also observed goals to have a healthy baby and remain HIV-free can motivate HIV prevention. In a U.S. study conducted among women without HIV planning pregnancy with men with HIV, 87% took at least four PrEP doses per week, by intracellular TFV-DP [35]. In Kenya, a periconception HIV prevention study among HIV-serodifferent couples observed that 81% of partners without HIV took more than 80% of PrEP doses [36]. We implemented an intervention similar to that used in the current study in Uganda and observed TFV-DP concentrations corresponding to at least four doses among 41% of women at 6-month follow-up [37]. These data highlight the importance of integrating HIV prevention counseling, including PrEP, into preconception care to reduce HIV incidence among women and infants. In addition, as more products are approved, choice of delivery method (vaginal ring, injectable, oral) may support uptake and adherence [38]. Novel longer-acting PrEP drugs such as the dapivirine (DPV) vaginal ring and injectable cabotegravir are efficacious [39–41], approved for use in South Africa [42,43], and may serve as important PrEP options for women who struggle with daily oral medications. Indeed, emerging data suggest that PrEP choice may promote use [44,45]. Understanding safety profiles and securing approval for use in women planning for and with pregnancy will be important [46–49].

The intervention supported about a third of women to use daily oral PrEP well enough to be protected from HIV based on pharmacokinetic estimates [18–21]. On the basis of real-world PrEP use, more women had some protection by taking more than two doses per week [6]. ALthough HF-PrEP worked for many women, it did not help all participants to successfully use PrEP. We observed an association of poorer adherence associated with lower perceived community HIV stigma. Women perceiving higher community levels of stigma may have experienced increased motivations to use PrEP and avoid HIV. We also observed higher adherence with alcohol use and lower income; generally, in the literature, women with competing demands (e.g., lower income, alcohol use [50,51]) struggle with adherence. Perhaps in this context, women faced other challenges that encouraged them to engage in their HIV prevention strategy; this positive association with alcohol use was also observed among pregnant women accessing PrEP in Cape Town [52] and men accessing PrEP in rural KwaZulu-Natal [53], suggesting that alcohol use should not be a contra-indication to PrEP care. In a nested qualitative substudy, women in our cohort described challenges getting to study visits (including for refills), succeeded when they were able to disclose PrEP use to a supporter, and made decisions about PrEP use based on sexual activity [24]. Additional intervention content could add PrEP modality choice, community delivery options, leverage problem solving to support PrEP use disclosure, and adapt to provide women with the counseling they need when they need it [54].

Interpretation of our data varies by the adherence measure used and degree to which a given adherence threshold correlates with PrEP effectiveness. Differences observed across the three PrEP adherence measures in this cohort highlight the value of incorporating multiple measures and expose gaps in our understandings of tenofovir pharmacokinetics for cis-gender women. High adherence by electronic device waned whereas the proportion with high concentrations by plasma and whole blood measures were relatively stable, suggesting that motivations to use the pillcap due to social desirability bias may have been present and waned over time [55]. However, our limited understandings of how to interpret pharmacokinetics for cis-gender black women may also underestimate adherence [56]. We rely on the pillcap data to evaluate stops and starts, which are common and important to understanding PrEP use. On the basis of our paired pillcap and drug concentration data, the pillcaps may be insensitive for capturing gaps.

Importantly, we observed high HIV incidence in this population of women planning for pregnancy. HIV acquisition during pregnancy and breastfeeding contributes to about one-third of childhood HIV incidence [57]. In this study, the first to our knowledge to measure periconception HIV acquisition risk longitudinally in an HIV-endemic setting, we observed an HIV incidence of 4.04 per 100 person-years (95% CI: 2.24–7.30), highlighting the importance of developing effective prevention programs for this population. This finding highlights the importance of offering PrEP to women

independent of whether their partner has been diagnosed and disclosed serostatus. One-third of men with HIV (MWH) in South Africa do not know their serostatus [58], and less than half of women are aware of their partner's serostatus [59,60]. Interventions to promote knowledge of partner serostatus remain important, but should not undermine opportunities to provide PrEP to women who may not know their partner's serostatus but live in an HIV-endemic area or otherwise feel vulnerable to HIV [48]. Educating men about HIV-prevention options for their pregnancy partners may also support uptake [61]. Reassuringly, genotyping of the virus among those with seroconversion revealed mutations that are not associated with exposure to NRTIs (e.g., tenofovir, emtricitabine) and thus are likely to represent transmitted resistance [62].

This project was conducted prior to approval of TDF/FTC as PrEP for women planning for or with pregnancy in South Africa, thus subject to regulations for investigational drug. Accordingly, we collected detailed information on adverse events. We observed a reassuring safety profile consistent with many PrEP studies [63,64].

Strengths of this study include incorporation of multiple adherence measures over time among a rarely studied population of women vulnerable to acquiring HIV. Limitations include that this was a research study, thus adherence may have been higher than among the general population. The project was conducted when TDF/FTC was not recommended for people planning for pregnancy in South Africa, which may have compromised use.

Conclusion

Our findings support the importance of HIV prevention for women planning for pregnancy in HIV endemic settings. Female-controlled prevention strategies are critical, and oral PrEP is an important component of safer conception care which women choose to use. Our adapted intervention helped support about a quarter of women to use PrEP well with closer to 50% using PrEP well enough to secure some protection.

Acknowledgements

Lynn T. Matthews – involved in all aspects.

Manjeetha Jaggernath – protocol development, data collection, data cleaning, analysis interpretation.

Yolandie Kriel – protocol development, data collection, data cleaning, analysis interpretation, manuscript writing.

Patricia Smith – data collection, management, writing.

Jessica E. Haberer – protocol development, adherence measurement interpretation.

Jared Baeten, Craig Hendrix – protocol development.

Norma C. Ware – protocol development (qualitative).

Pravi Moodley, Melendhran Pillay – data generation, analysis, writing.

Kara Bennett, John Bassler – analysis.

Christina Psaros – protocol development, adherence counseling support.

Kathleen Wirth Hurwitz – protocol development, analysis.

David R. Bangsberg – protocol development.

Jennifer A. Smit – all aspects.

The authors would like to thank our participants, the National Institutes of Mental Health and Gilead Sciences for their support of operations, and all other team members who made this project possible.

The data that supports the findings of this study are available in the supplementary material of this article.

This work was supported by the National Institutes of Mental Health [www.nimh.nih.gov; Awards: NIMHK23MH095655 and NIMHR01MH108412; PI: LTM]. Gilead Sciences (www.gilead.com) provided Truvada (TDF/FTC) as PrEP and supported operations. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of interest

Dr Matthews received operational support from Gilead Sciences.

Dr Haberer has been a consultant for Merck and owns stock in Natera.

Dr Hurwitz and Ms. Bennett 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.

Dr Baeten is an employee of Gilead Sciences, outside of the present work.

Dr Hendrix has received research funding from Gilead Sciences and Merck and is founder and a nonfiduciary manager of Prionde Biopharma, LLC, outside of the present work. There are no conflicts of interest for the remaining authors.

References

1. UNAIDS. Country fact sheets: South Africa (2021) 2022 [cited 8 September 2022]. https://www.unaids.org/en/regionscountries/countries/southafrica.
2. Matthews LT, Crankshaw T, Giddy J, Kaida A, Smit JA, Ware NC, Bangsberg DR. **Reproductive decision-making and periconception practices among HIV-positive men and women attending HIV services in Durban, South Africa.** *AIDS Behav* 2013; **17**:461–470.
3. Department of Health, Republic of South Africa. Guidelines for the provision of pre-exposure prophylaxis (PrEP) to persons at substantial risk of HIV infection. 2020.
4. Medicine Controls Council. Press release: Medicines Control Council approves fixed-dose combination of tenofovir disoproxyl fumarate and emtricitabine for preexposure prophylaxis of HIV 2015 [cited 25 March 2023]. https://www.sahpra.org.za/wp-content/uploads/2020/01/6614b94510.11_Media_release_ARV_FDC_PrEP_Nov15_v1.pdf.
5. World Health Organization. Technical brief: PREVENTING HIV DURING PREGNANCY AND BREASTFEEDING IN THE CONTEXT OF PREP. Geneva, Switzerland: WHO; 2017.
6. Marrazzo J, Tao L, Becker M, Leech AA, Taylor AW, Ussery F, *et al*. **HIV preexposure prophylaxis with emtricitabine and tenofovir disoproxil fumarate among cisgender women.** *JAMA* 2024; **331**:930–937.
7. Joseph Davey D, Nyemba DC, Castillo-Mancilla J, Wiesner L, Norman J, Mvududu R, *et al*. **Adherence challenges with daily oral preexposure prophylaxis during pregnancy and the postpartum period in South African women: a cohort study.** *J Int AIDS Soc* 2022; **25**:e26044.
8. Matthews LT, Beyeza-Kashesya J, Cooke I, Davies N, Heffron R, Kaida A, *et al*. **Consensus statement: supporting safer conception and pregnancy for men and women living with and affected by HIV.** *AIDS Behav* 2018; **22**:1713–1724.
9. Matthews LT, Jaggernath M, Kriel Y, Smith PM, O'Neil K, Haberer JE, *et al*. **Protocol for a longitudinal study to evaluate the use of tenofovir-based PrEP for safer conception and pregnancy among women in South Africa.** *BMJ Open* 2019; **9**:e027227.
10. Bunting L, Boivin J. **Development and preliminary validation of the fertility status awareness tool: FertiSTAT.** *Hum Reprod* 2010; **25**:1722–1733.
11. Department of Health Republic of South Africa. National contraception and fertility planning policy and service delivery guidelines. Pretoria: Department of Health Republic of South Africa; 2012.
12. Mayer KH, Safren SA, Elsesser SA, Psaros C, Tinsley JP, Marzinke M, *et al*. **Optimizing pre-exposure antiretroviral prophylaxis adherence in men who have sex with men: results of a pilot randomized controlled trial of "Life-Steps for PrEP".** *AIDS Behav* 2017; **21**:1350–1360.
13. Psaros C, Mayer KH, Mimiaga MJ, Puccinelli MJ, Taylor SW, Elsesser SA, Safren SA. Life-steps for PrEP. [Unpublished intervention manual]. (in press).
14. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a Public Health Approach; Second Edition 2016. Geneva, Switzerland: World Health Organization; 2016.
15. Phillips TK, Sinxadi P, Abrams EJ, Zerbe A, Orrell C, Hu NC, *et al*. **A comparison of plasma efavirenz and tenofovir, dried blood spot tenofovir-diphosphate, and self-reported adherence to predict virologic suppression among South African women.** *J Acquir Immune Defic Syndr* 2019; **81**:311–318.
16. Crankshaw TL, Matthews LT, Giddy J, Kaida A, Ware NC, Smit JA, Bangsberg DR. **A conceptual framework for understanding HIV risk behavior in the context of supporting fertility goals among HIV-serodiscordant couples.** *Reprod Health Matters* 2012; **20 (39 Suppl)**:50–60.
17. Hendrix CW, Andrade A, Bumpus NN, Kashuba AD, Marzinke MA, Moore A, *et al*. **Dose frequency ranging pharmacokinetic study of tenofovir-emtricitabine after directly observed dosing in healthy volunteers to establish adherence benchmarks (HPTN 066).** *AIDS Res Hum Retroviruses* 2016; **32**:32–43.
18. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, *et al*. **Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa.** *PLoS Med* 2013; **10**:e1001511.
19. Stranix-Chibanda L, Anderson PL, Kacanek D, Hosek S, Huang S, Nematadzira TG, *et al*. **Tenofovir diphosphate concentrations in dried blood spots from pregnant and postpartum adolescent and young women receiving daily observed preexposure prophylaxis in Sub-Saharan Africa.** *Clin Infect Dis* 2021; **73**:e1893–e1900.
20. Anderson PL, Liu AY, Castillo-Mancilla JR, Gardner EM, Seifert SM, McHugh C, *et al*. **Intracellular tenofovir-diphosphate and emtricitabine-triphosphate in dried blood spots following directly observed therapy.** *Antimicrob Agents Chemother* 2018; **62**:e01710-17.
21. Pyra M, Anderson P, Haberer JE, Heffron R, Celum C, Asiimwe S, *et al*. **Tenofovir-diphosphate as a marker of HIV preexposure prophylaxis use among East African men and women.** *Front Pharmacol* 2019; **10**:401.
22. Spinelli MA, Haberer JE, Chai PR, Castillo-Mancilla J, Anderson PL, Gandhi M. **Approaches to objectively measure antiretroviral medication adherence and drive adherence interventions.** *Curr HIV/AIDS Rep* 2020; **17**:301–314.
23. Ibrahim ME, Castillo-Mancilla JR, Yager J, Brooks KM, Bushman L, Saba L, *et al*. **Individualized adherence benchmarks for HIV pre-exposure prophylaxis.** *AIDS Res Hum Retroviruses* 2021; **37**:421–428.
24. Wyatt MA, Pisarski EE, Kriel Y, Smith PM, Mathenjwa M, Jaggernath M, *et al*. **Influences on PrEP uptake and adherence among South African women during periconception and pregnancy: a qualitative analysis.** *AIDS Behav* 2023; **27**:208–217.
25. Manasa J, Danaviah S, Pillay S, Padayachee P, Mthiyane H, Mkhize C, *et al*. An affordable HIV-1 drug resistance monitoring method for resource limited settings. JoVE. 2014; 85:e51242.
26. Rhee SY, Gonzales MJ, Kantor R, Betts BJ, Ravela J, Shafer RW. **Human immunodeficiency virus reverse transcriptase and protease sequence database.** *Nucleic Acids Res* 2003; **31**:298–303.
27. Shafer RW. **Rationale and uses of a public HIV drug-resistance database.** *J Infect Dis* 2006; **194 Suppl 1 (Suppl 1)**:S51–S58.
28. Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Services. UDoHaH. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events: Corrected Version 2.1. July 2017 [cited 30 April 2023]. https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf.
29. Napper LE, Fisher DG, Reynolds GL. **Development of the perceived risk of HIV scale.** *AIDS Behav* 2012; **16**:1075–1083.
30. Pulerwitz J, Gortmaker SL, DeJong W. **Measuring sexual relationship power in HIV/STD research.** *Sex Roles* 2000; **42**:637–660.
31. Larzelere RE, Huston TL. **The dyadic trust scale: toward understanding interpersonal trust in close relationships.** *J Marriage Fam* 1980; **42**:595–604.
32. Broadhead WE, Gehlbach SH, de Gruy FV, Kaplan BH. **The Duke-UNC Functional Social Support Questionnaire. Measurement of social support in family medicine patients.** *Med Care* 1988; **26**:709–723.
33. Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. **The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory.** *Behav Sci* 1974; **19**:1–15.
34. Greenland S, Pearce N. **Statistical foundations for model-based adjustments.** *Annu Rev Public Health* 2015; **36**:89–108.
35. Leech AA, Biancarelli D, Aaron E, Miller ES, Coleman JS, Anderson PL, *et al*. **HIV pre-exposure prophylaxis for conception among HIV serodiscordant couples in the United States: a cohort study.** *AIDS Patient Care STDS* 2020; **34**:295–302.
36. Heffron R, Ngure K, Velloza J, Kiptinness C, Quame-Amalgo J, Oluch L, *et al*. **Implementation of a comprehensive safer conception intervention for HIV-serodiscordant couples in Kenya: uptake, use and effectiveness.** *J Int AIDS Soc* 2019; **22**:e25261.
37. Matthews LT, Atukunda EC, Owembabazi M, Kalyebera KP, Psaros C, Chitneni P, *et al*. **High PrEP uptake and objective longitudinal adherence among HIV-exposed women with personal or partner plans for pregnancy in rural Uganda: a cohort study.** *PLoS Med* 2023; **20**:e1004088.
38. Ngure K, Nair G, Szydlo DW, Brown ER, Akello C, Macdonald P, *et al*. Choice and adherence to dapivirine ring or oral PrEP by young African women in REACH: 67% prefer ring vs 31% oral PrEP. CROI; February 23, 2022; Virtual2022.

39. Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D, *et al*. **Cabotegravir for the prevention of HIV-1 in women: results from HPTN 084, a phase 3, randomised clinical trial.** *Lancet* 2022; **399**:1779–1789.
40. Nel A, van Niekerk N, Kapiga S, Bekker LG, Gama C, Gill K, *et al*. **Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women.** *N Engl J Med* 2016; **375**:2133–2143.
41. Baeten JM, Palanee-Phillips T, Brown ER, Schwartz K, Soto-Torres LE, Govender V, *et al*. **Use of a vaginal ring containing dapivirine for HIV-1 prevention in women.** *N Engl J Med* 2016; **375**:2121–2132.
42. SAHPRA. Health Product Register: Dapiring [cited 27 March 2023]. https://medapps.sahpra.org.za:6006/Home/Details/?id=CfDJ8FLSLpTxgZVDhf4P0SUeWK3vjHjDpecnLPQ6rL-PO5XqUxXhE5_-ttoUGRA0pmuDDeIpQUroMcWOoKh-Ji3odxJZUuEVquwC48tz41hJr9gNbp9-FRdouu8EJH7meB-j9_i4w.
43. SAPHRA. Health Product Register: Product Information - APRETUDE 600 mg/3 ml [cited 27 March 2023]. https://medapps.sahpra.org.za:6006/Home/Details/?id=CfDJ8FLSLpTxgZVDhf4P0SUeWK3Ye0hD3mKRiD-XA19ELzWaM-ygCw9MJVmr5w-BNw6UIm5brorVQSz6dD-cKHgCLMU9yMHKa1v8Ttr_NZI1SFhR-ISPQ3lnNfh1CjtXbKx-cAdw.
44. Nair G, Celum C, Szydlo D, Brown ER, Akello CA, Nakalega R, *et al*. **Adherence, safety, and choice of the monthly dapivirine vaginal ring or oral emtricitabine plus tenofovir disoproxil fumarate for HIV preexposure prophylaxis among African adolescent girls and young women: a randomised, open-label, crossover trial.** *Lancet HIV* 2023; **10**:e779–e789.
45. Kamya MR, Balzer LB, Ayieko J, Kabami J, Kakande E, Chamie G, *et al.*, editors. Randomized trial of SEARCH dynamic choice HIV prevention including injectable cabotegravir (CAB-LA). CROI 2024; 3-6 March 2024; Denver, Colorado.
46. Noguchi LM, Hoesley C, Kelly C, Scheckter R, Bunge K, Nel A, *et al*. **Pharmacokinetics of dapivirine transfer into blood plasma, breast milk, and cervicovaginal fluid of lactating women using the dapivirine vaginal ring.** *Antimicrob Agents Chemother* 2019; **63**:e01930-18.
47. Owor M, Noguchi L, Horne E, Matimbira M, Ssemambo PK, Madhlopa-Mandiwa V, *et al.*, editors. DAPIVIRINE RING SAFETY AND DRUG DETECTION IN BREASTFEEDING MOTHER-INFANT PAIRS. CROI: February 19-22, 2023; 2023; Seattle, Washington.
48. Panel on Treatment of HIV During Pregnancy and Prevention of Perinatal Transmission. Recommendations for the use of antiretroviral drugs during pregnancy and interventions to reduce perinatal HIV transmission in the United States 2023 [updated 31 January 2023]. https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new?view=full.
49. Centers for Disease Control and Prevention. US Public Health Service: preexposure prophylaxis for the prevention of HIV infection in the United States—2021 update: a clinical practice guideline. 2021.
50. Gebru NM, Canidate SS, Liu Y, Schaefer SE, Pavila E, Cook RL, Leeman RF. **Substance use and adherence to HIV pre-exposure prophylaxis in studies enrolling men who have sex with men and transgender women: a systematic review.** *AIDS Behav* 2023; **27**:2131–2162.
51. Kayesu I, Mayanja Y, Nakirijja C, Machira YW, Price M, Seeley J, Siu G. **Uptake of and adherence to oral preexposure prophylaxis among adolescent girls and young women at high risk of HIV-infection in Kampala, Uganda: a qualitative study of experiences, facilitators and barriers.** *BMC Womens Health* 2022; **22**:440.
52. Miller AP, Shoptaw S, Moucheraud C, Mvududu R, Essack Z, Gorbach PM, *et al*. **Recent alcohol use is associated with increased preexposure prophylaxis (PrEP) continuation and adherence among pregnant and postpartum women in South Africa.** *J Acquir Immune Defic Syndr* 2023; **92**:204–211.
53. Castle A, Busang J, Dreyer J, Herbst C, Okesola N, Chimbindi N, *et al*. editors. Alcohol use and the preexposure prophylaxis continuum of care among men in rural South Africa. 2024 Conference on Retroviruses and Opportunistic Infections; 3–6 March 2024; Denver, Colorado.
54. Haberer JE, Bangsberg DR, Baeten JM, Curran K, Koechlin F, Amico KR, *et al*. **Defining success with HIV preexposure prophylaxis: a prevention-effective adherence paradigm.** *AIDS* 2015; **29**:1277–1285.
55. Podsadecki TJ, Vrijens BC, Tousset EP, Rode RA, Hanna GJ. **White coat compliance'' limits the reliability of therapeutic drug monitoring in HIV-1-infected patients.** *HIV Clin Trials* 2008; **9**:238–246.
56. Mugwanya K, al. e, editors. Adherence benchmarks for TFV-DP in DBS and PBMCs for African women using FTC/TDF PrEP. 2024 Conference on Retroviruses and Opportunistic Infections; 3–6 March 2024; Denver, Colorado.
57. UNAIDS. Progress towards the Start Free, Stay Free, AIDS Free targets. Geneva, Switzerland: UNAIDS; 2020.
58. Choko AT, Kumwenda MK, Johnson CC, Sakala DW, Chikalipo MC, Fielding K, *et al*. **Acceptability of woman-delivered HIV self-testing to the male partner, and additional interventions: a qualitative study of antenatal care participants in Malawi.** *J Int AIDS Soc* 2017; **20**:21610.
59. Johnson LF, Rehle TM, Jooste S, Bekker LG. **Rates of HIV testing and diagnosis in South Africa: successes and challenges.** *AIDS* 2015; **29**:1401–1409.
60. Krakowiak D, Makabong'o P, Goyette M, Kinuthia J, Osoti AO, Asila V, *et al*. **Reaching hard-to-reach men through home-based couple HIV testing among pregnant women and their male partners in western Kenya: a qualitative study.** *BMC Public Health* 2020; **20**:724.
61. Isehunwa OO, Ntinga X, Msimango LI, Smith P, van Heerden A, Matthews LT. **Opportunities to leverage reproductive goals and ideals among South African men to promote HIV testing, treatment and prevention: a qualitative study.** *Global Public Health* 2023; **18**:2173795.
62. Ntinga X, Isehunwa OO, Msimango LI, Smith PM, Matthews LT, Van Heerden A. **Perceptions of Preexposure Prophylaxis (PrEP) for HIV prevention among men living with HIV in the context of reproductive goals in South Africa: a qualitative study.** *BMC Public Health* 2024; **24**:553.
63. Chou R, Spencer H, Bougatsos C, Blazina I, Ahmed A, Selph S. **Preexposure prophylaxis for the prevention of HIV: updated evidence report and systematic review for the US Preventive Services Task Force.** *JAMA* 2023; **330**:746–763.
64. Mofenson LM, Baggaley RC, Mameletzis I. **Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding.** *AIDS* 2017; **31**:213–232.
65. Visser MJ, Kershaw T, Makin JD, Forsyth BW. **Development of parallel scales to measure HIV-related stigma.** *AIDS Behav* 2008; **12**:759–771.
66. Fu B, Qin N, Cheng L, Tang G, Cao Y, Yan C, *et al*. **Development and validation of an Infertility Stigma Scale for Chinese women.** *J Psychosom Res* 2014; **79**:69–75.
67. Pulerwitz J, Gortmaker SL, DeJong W. **Measuring sexual relationship power in HIV/STD research.** *Sex Roles* 2000; **42**:637–720.
68. Kalichman SC. **Postexposure prophylaxis for HIV infection in gay and bisexual men. Implications for the future of HIV prevention.** *Am J Prev Med* 1998; **15**:120–127.