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ORIGINAL PAPER

# Influences on PrEP Uptake and Adherence Among South African Women During Periconception and Pregnancy: A Qualitative Analysis

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## Abstract

Pre-exposure prophylaxis (PrEP) is highly effective for HIV prevention, yet PrEP delivery to women in periconception and pregnancy has lagged. We report qualitative research from a study evaluating PrEP use as part of safer conception care for 330 South African women. Fifty-two semi-structured interviews were conducted with 25 study participants to identify influences on PrEP adherence. Influences were: (1) changing proximity to male partners; (2) COVID-19 lockdown; (3) mobile lifestyle; (4) PrEP-related stigma; (5) disclosure of PrEP use; and (6) pregnancy and motherhood. Data also revealed important contextual information shaping adherence influences for women, including: (a) not living with partners, (b) partners as drivers of pregnancy intention, and (c) feeling at high risk for HIV. Disclosure of PrEP use, addressing stigma, strategies for traveling with pills, and counseling on prevention effective adherence are promising components of PrEP-inclusive HIV prevention interventions for South African women who are pregnant or planning pregnancy.

**Keywords** PrEP adherence · Safer conception · South Africa · Periconception · Pregnancy · HIV prevention

## Introduction

Women are at high risk of HIV acquisition during pregnancy and the postpartum period [1, 2]. Acute HIV infection in pregnancy and postpartum elevates the risk of perinatal transmission to infants [3–5]. Periconception, the period when couples are trying to conceive [6], also increases HIV acquisition risk for women, insofar as it entails sex without condoms with a partner who may be living with HIV or whose HIV status is unknown [7, 8].

Tenofovir (TFV) disoproxil fumarate/emtricitabine (TDF/FTC) as pre-exposure prophylaxis (PrEP) prevents HIV, is safe during pregnancy, and is recommended by the World Health Organization, Centers for Disease Control, and South Africa's Department of Health for women exposed to HIV during periconception, pregnancy, and postpartum periods [9–11]. While PrEP scale up in Africa is underway for many high-risk populations, delivery of PrEP to women during periconception, pregnancy and postpartum remains at an early phase. Two implementation studies in Kenya evaluated approaches for delivering PrEP to women in maternal and child clinics [12–14]. Both reported rates of PrEP uptake at around 20%, with subsequent declines in PrEP use [13, 14]. An observational study of PrEP initiation and persistence in women attending antenatal care during pregnancy and postpartum is underway in Cape Town, South Africa [15]. Available data indicate exposure to PrEP prior to and during pregnancy does not increase the risk of adverse pregnancy outcomes [16]. Few reports of PrEP delivery during periconception specifically have been added to the evidence base [17, 18].

Adherence to oral PrEP has proven to be a challenge for women in sub-Saharan Africa [19–23]. As injectables and other long-acting prevention modalities are approved,

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the urgency of improving adherence to oral PrEP may be attenuated. Still, exploring daily pill adherence behavior can inform understandings of women who may use longer-acting products. Access to long-acting PrEP likely remains years away for most and oral PrEP will continue to be an important prevention option for women who are pregnant or trying to conceive. The purpose of this paper is to identify and contextualize influences on oral PrEP adherence for a group of South African women planning pregnancy and participating in a study of safer conception strategies.

## Methods

### The ZINK Study

The Zivikele Ngaphambi Kokukhulelwa Study (ZINK Study) ("Protecting Yourself Before Pregnancy," in isiZulu) was a single arm, mixed-methods intervention study evaluating PrEP uptake and adherence among South African women during periconception and pregnancy. A qualitative component was included to provide descriptive and contextual detail on PrEP adherence influences for this understudied, high-risk population. The ZINK Study hypothesized that women with personal or partner plans for pregnancy would be motivated to initiate and adhere to PrEP given the scarcity of female-controlled options for HIV prevention, and/or the desire to have an uninfected child. The study offered PrEP as one of a number of safer conception strategies aimed at reducing risk of HIV acquisition while trying to conceive. The package of strategies was developed using South African guidelines that recommend partner testing and disclosure, ART for partners living with HIV, treatment of STIs, and use of other safer conception methods, such as timing condomless sex to periods of peak fertility. ZINK Study participants received safer conception counseling in groups led by trained study counselors. Counseling sessions took place at baseline, and at each subsequent study visit [24].

Women of reproductive age (ages 18–35) who were not pregnant, in a stable relationship (≥ 6 months duration) with a partner whose HIV serostatus was positive or unknown, and who planned to become pregnant in the next 12 months were eligible to participate in the ZINK Study. Participants were followed for a minimum of 12 months; women who became pregnant during the study were followed through their pregnancy (up to 24 months). Three-hundred-thirty women (N = 330) enrolled as participants in the ZINK Study.

The ZINK Study was carried out at the MatCH Research Unit (MRU) in eThekwini, KwaZulu-Natal, South Africa, from November 2017 to July 2021. Primary outcomes were uptake of and adherence to oral PrEP [25]. Adherence was evaluated electronically using the AARDEX Medication Event Monitoring System (MEMS), which tracks medication bottle openings to estimate adherence [26], and through quarterly plasma and dried blood spot samples tested for tenofovir [27, 28].

### Qualitative Component of The ZINK Study

The ZINK Study included a qualitative component whose purpose was to characterize influences on PrEP adherence in a subsample of 25 participants. We purposefully sampled qualitative participants to include: (a) women who had initiated PrEP and had "high" MEMS adherence, defined as opening the MEMS bottle for ≥ 80% of scheduled doses in the 2 months following PrEP initiation; (b) PrEP users with "lower" MEMS adherence, defined as opening the MEMS bottle for < 80% of scheduled doses in the 2 months following PrEP initiation; and (c) women who had declined PrEP as part of the ZINK Study. We deliberately oversampled PrEP users (N = 19) and women with lower adherence (N = 11 of 19) in order to explore adherence barriers. Selected participants were contacted by study staff and invited to take part in the qualitative component.

#### Qualitative Data Collection

Data collection for the qualitative component called for up-to-3 individual semi-structured interviews carried out by trained research assistants (RAs). Initial interviews took place within 6 months of ZINK Study enrollment; exit interviews were conducted as participants completed the follow-up period. Additional interviews were conducted when "triggered" by important life events relevant to the study, such as pregnancy, changes in partnered relationships (i.e., separation or a new partner), or a change in PrEP use (i.e., new initiation of PrEP or a significant decline in adherence). Trigger events were identified during regular study follow-up visits, and through regular reviews of the MEMS database. Selection of topics for initial and exit interviews was guided by our previous qualitative research on PrEP adherence [29, 30] and by the results of formative research carried out for the ZINK Study [31]. Topics included: (a) pregnancy plans; (b) perspectives on safer conception strategies and reasons for choices; (c) disclosure experiences; (d) reasons for PrEP uptake or decline; (e) experiences of taking PrEP; (f) reasons for specific missed doses (guided by the most recent MEMS report); (g) perceived HIV risk; and (h) the impact of study participation. Trigger event interviews first elicited the "story" of the triggering event, then explored its impact on: (a) the partnered relationship; (b) pregnancy plans; (c) use of safer conception strategies; and (d) perceived HIV risk. Interviews were carried out between July 2019 and June 2021. Interviews conducted after March 2020 also explored the impact of the COVID-19 pandemic on relationships, pregnancy plans, and PrEP use.

Interviews took place in person in a private space at the ZINK Study offices at MRU in Durban. They were conducted in isiZulu or English, and typically lasted 45–60 min. Participants provided consent for initial qualitative interviews as part of the overall ZINK Study consent process. Consent for subsequent trigger event and exit interviews was obtained separately, immediately before the interviews took place.

Interviews were audio-recorded with the permission of the interviewee. Participants were reimbursed 250 South African Rand for their time and transport costs (approximately $16 USD). Audio recordings of interviews were transcribed directly into English by bilingual professional transcribers fluent in isiZulu. Transcripts were reviewed for quality by a senior member of the qualitative research team (EP), who provided RAs with feedback on content and interview technique during weekly supervision calls.

#### Qualitative Data Analysis

To reduce the qualitative data for analysis, we constructed a matrix. A matrix approach to data reduction displays relevant content from interview transcripts in relation to designated topics in a two-dimensional display [32]. An alternative to coding for data reduction, matrix construction involves reviewing each transcript in a data set for content corresponding to a pre-designated set of topics and entering that content into the appropriate cells. For this analysis, 11 topics relevant to PrEP adherence and safer conception strategies were identified from an initial reading of the transcripts by author MW. Examples of topics are: (1) perceptions of HIV risk; (2) male partner attitudes toward PrEP/study participation; (3) taking PrEP doses; (4) stopping PrEP. Author EP reviewed each transcript to identify content corresponding to the topics. Relevant content for each transcript was summarized by topic and entered into the matrix, together with illustrative quotes.

Using summaries and quotes from the matrix, we arranged the content into broader conceptual groupings to address direct influences on PrEP adherence and contextual factors that appeared related to these influences, which helped to clarify their meaning. We then developed a descriptive category from each conceptual grouping, returning to the transcripts to add detail and illustrative examples. Category development included the following steps: (a) formulating a title to summarize the concept being presented; (b) generating descriptive text to elaborate the concept, and (c) adding interview excerpts to illustrate the concept and show how it appears in the data.

Major concepts from the results were presented to the ZINK Study team and to members of the MRU Community Advisory Board, who were given the opportunity to raise questions and provide feedback. Final versions of the categories are presented under the heading, "Influences on PrEP Adherence in the Qualitative Sample", in "Results" section. Also included in Results are several points that, while not qualifying as adherence influences, help to contextualize these influences. These appear in Results, section "Contextual Information on PrEP Adherence Influences".

#### Ethics Approval

The ZINK Study was approved by: (1) the Human Research Ethics Committee at the University of Witwatersrand (Johannesburg, South Africa); (2) the University of Alabama at Birmingham Institutional Review Board for Human Use (Birmingham, AL, USA); and (3) the Institutional Review Board of Partners Healthcare (Boston, MA, USA). The ZINK Study protocol is registered at ClinicalTrial.gov (NCT02194308) and at the South African Health Products Regulatory Agency (SAHPRA).

#### Consent to Participate

All participants provided written consent before taking part in the ZINK Study.

## Results

### Personal Characteristics of Qualitative Participants

Information on personal characteristics of qualitative participants was drawn from structured questionnaires administered as part of the ZINK Study. Median age of participants in the qualitative sample was 24 years (Range 19–33 years). Seventy-two percent (N = 18) of participants had completed at least 11–12 years of education. A quarter (24%; N = 6) were employed. Eleven (44%) reported one or more previous pregnancies; 28% (N = 7) reported one or more live births previous to ZINK Study participation. Four qualitative participants (16%) became pregnant during the study follow-up period. Most women reported having only one sexual partner (N = 21); none reported knowing the HIV status of their primary partner at study enrollment (see Table 1).

### PrEP Adherence in the Qualitative Sample

PrEP adherence was calculated for the 19 participants in the qualitative sample who initiated PrEP. PrEP use was defined as the period between PrEP initiation and the last MEMSCAP bottle opening. The median number of days of PrEP use was 315 for the high adherers (Range 100–646) and 328 for the low adherers (Range 210–485). Median adherence for the period of PrEP use for high adherers was 79%; median adherence for lower adherers was 53%.

**Table 1** Personal characteristics of qualitative participants (N = 25)

| | N (%) or median (range) |
|---|---|
| Median age | 24 (19–33) |
| Highest level of formal schooling | |
| Grade 11–12 | 18 (72%) |
| Post-grade 12 | 7 (28%) |
| Employed | 6 (24%) |
| Shares a residence with partner | 0 (0%) |
| At least one previous pregnancy | 11 (44%) |
| At least one previous live birth | 7 (28%) |
| Became pregnant during study follow-up | 4 (16%) |
| Report one sexual partner | 21 (84%) |
| Reports knowing partner's HIV status | 0 (0%) |

## Qualitative Data

The qualitative data set is made up of 52 interview transcripts from semi-structured interviews with the 25 ZINK Study qualitative component participants. The transcripts represent 25 baseline interviews, 10 exit interviews, 7 trigger event interviews, and 10 "combined" trigger event and exit interviews. The "combination" interviews were conducted in a single interview session to expedite data collection following a 6-month pause during the nationwide COVID-19 lockdown beginning in March 2020.

## Qualitative Results

### Influences on PrEP Adherence in the Qualitative Sample

Below we present the primary results of the analysis—a set of descriptive categories laying out influences on PrEP adherence. We identified six significant influences on PrEP adherence in the qualitative interview data.

1. *Changing Proximity to Partners.* PrEP users' descriptions of their PrEP use suggested a "start-and-stop" pattern of dosing. Starts and stops appeared to map onto women's changing proximity to partners. These women tried to take PrEP daily when they were with their partners. However, some decided there was no need to continue taking PrEP during periods of separation, and stopped until they reunited with their partners.

> "I came back to Durban and still we were far from each other and we would not see each other for a whole month. Then I would sometimes not take [PrEP]. I would think that since my partner is not around, why would I bother to take my pills every day? …I just thought even if I skip today or if I'm not home, I don't feel guilty that, 'Oh, I didn't take PrEP,' because I know that my partner is away…. I then decided to stop. When he is about to come back, I will continue with it…." PrEP User, High adherer, Age 25 "What made me end up not taking pills? He was [away] doing [a training program]. I stopped because I didn't have another partner. I stopped. When he comes back, I start again. I make sure I adhere to the pills because sometimes you can never trust a man." PrEP User, Lower adherer, Age 28

2. COVID-19 *Lockdown.* The global COVID-19 pandemic prompted a nationwide lockdown in South Africa beginning on March 27, 2020. Since then, restrictions associated with the lockdown, including curfews, closures, movement prohibitions, and limits on the size of social gatherings, have waxed and waned over time. Initially, with little time to plan, there was a scramble to travel to family homes outside the city before the lockdown took effect, and women left without their medication or didn't carry an adequate supply of tablets with them. When supplies of PrEP ran out, some women were far from the research study site and did not know how to replace them, interrupting adherence:

> "I was unable to get them [PrEP pills] and it was lockdown. They got finished when the lockdown had just started. After that I did not take them until today. Because I did not know I had to go to the clinic and take them. I didn't know what to do." PrEP User, High adherer, Age 21

The lockdown interfered with PrEP adherence in some ways, but made taking daily doses easier in others. For some women, the lockdown brought a quieter, more orderly life, with less travel and more time spent at home. This meant PrEP medication was always nearby, sometimes even in sight. Proximity to the medication made regular dosing easier. One woman explained it this way:

> "Since there has been lockdown, one was locked inside the house. One was always in the house every day. [PrEP] is always close by. It helped me a lot. One was doing everything in the house." PrEP User, Lower adherer, Age 26

The ZINK Study team made a concerted effort to offset pandemic-related disruptions in study activities and PrEP adherence. Staff reached out by phone or text to contact study participants and ensure they had a supply of medication before the lockdown went into effect.

Where this wasn't possible, study staff provided referral letters to help participants access refills from other sites.

> "[At] the start of lockdown, how many days was it said it was going to take? I don't remember…. But when I went home [family farm] I took only a few boxes [of PrEP]. I didn't take all the boxes. When I got home, I took them until they finished and the lockdown was extended and I couldn't come back because the roads were closed and all. Then I called the [ZINK Study] clinic and told them that my pills were running out and I could not fetch them at home. The doctor made me a referral letter to collect from the nearest hospital." PrEP User, Lower adherer, Age 21

3. *Mobile Lifestyle.* Participants in the qualitative sample led highly mobile lives. Though residing near the MRU research site, they visited their rural family homesteads frequently. Visits to the homes of family members or male partners within the city were also typical, and could last for days or weeks. Women rarely carried their MEMS bottles with them, leaving them without pills at dosing time. The impact of mobility on PrEP adherence is evidenced in the following quotes:

> "I was traveling mostly. I would sometimes leave it [PrEP] at [my flat] and go to [my home]. I would be at my other place for maybe 4 days without taking it." PrEP user, Lower adherer, Age 30
> "There is my other home down the road. Actually, it is not my home; my sister is married but staying near my home so most of the time I am going there. Perhaps 7 o'clock I will be there and then I will be like, 'Oh no, I am lazy to go home.' Maybe when I get home I would take it, or I would totally forget and end up doing something else." PrEP User, Lower adherer, Age 21

4. *Pregnancy and Motherhood.* While pregnancy intentions varied for women in the qualitative sample, all agreed on the importance of safeguarding the health of their unborn child, should they become pregnant. Some saw taking PrEP during pregnancy as a means to this end. Others worried about the potential consequences of combining PrEP with other medications they might need to take as pregnant women.

> "In my opinion, now that a baby is conceived you only take Panado [acetaminophen]. You are not allowed to take other pills. So, you…maybe you stop PrEP for a short period because you are pregnant." PrEP User, High adherer, Age 21

Once they became mothers, women referenced the challenges of adjusting to a newborn, and the destabilizing effects of motherhood on their lives, including sleep disruptions and changes in daily routines. Feeling destabilized made adhering to PrEP more difficult. One woman sketched the following scenario:

> "It was a challenge. …I take my pills at 8:00; you would find that by that time I am still sleeping. Because I would make sure that I sleep when the baby is sleeping because it wakes up at night. Sometimes I would wake up [so] tired I can't even do a thing. You would find that I end up not taking pills." PrEP User, High adherer, Age 21

5. *Fear of PrEP-related Stigma.* Some women in the qualitative sample worried that taking PrEP would cause them to be mistaken for someone who was living with HIV. They feared others seeing the pills would conclude they were antiretrovirals for HIV treatment. Another concern was that partners would interpret PrEP use as evidence of sexual activity outside the relationship. Either or both of these assumptions could result in feeling stigmatized. Fear of stigma made women reluctant to disclose their PrEP use and caused them to hide dosing from their partners (and others), making daily dosing more difficult, as seen in the following quotes:

> "I didn't tell him about the pills. I was hesitant because he will say, 'Why are you preventing HIV? Are you cheating now because we don't have HIV so why are you taking pills?' So, I decided to keep quiet. I am going to tell him. But for now, I haven't told him about it." PrEP User, Lower adherer, Age 21 "People gossip. They will say, "Hawu! She is now taking ARVs." PrEP User, Lower adherer, Age 26 "Last year I was keeping them at my friend's, since I wouldn't be able to hide them at home because it's crowded at home, you see. So, I would even be unable to take them properly." PrEP user, Lower adherer, Age 21

6. *Disclosure of PrEP Use.* While some qualitative participants concealed PrEP use from their partners, others chose to disclose. Women who disclosed their PrEP use found adherence considerably easier. Disclosure eliminated many barriers to adherence, such as having to hide pills or dosing, and opened the door to support in the form of encouragement and reminders from others, as seen in the following quotes:

> "My mother used to help me with pills sometimes. She would sometimes remind me even when I am not home, she would call and say, 'Hey it's time.' You see, she's the one who has been motivating me to drink them [PrEP]." PrEP User, High

adherer, Age 21 "He [partner] reminds me about time. He would make it a joke, but not every day. He would say, 'You take pills. You haven't taken them today.' I would say, 'You know, you've just reminded me. Let me go and take them.'" PrEP User, High adherer, Age 19

When disclosing to their partners, women tended to embed their PrEP use in the larger context of ZINK Study participation. Presenting PrEP as one of a number of safer conception strategies they were practicing tended to elicit a positive response from partners, who were predisposed to approve of any activity that promised to increase the chances of having a child.

Interviewer: "What did he say when he heard about the fact that you are participating in the study?"
Respondent: He was happy because he realized that there will be more chances that I will have a baby with him…He is happy with that because most of the times when I have been here [for ZINK follow up visits], I come back and tell him that it's like this and that. If I get new information from here, I tell him…. He appreciates that." PrEP User, Lower adherer, Age 23

Once they understood the purpose clearly, most men affirmed their partners' study participation, regardless of PrEP use. Some also expressed ongoing interest, asking about study visits, and requesting regular updates on safer conception strategies. This engagement by male partners made women feel supported.

"He supports me because he can see that it's something which I keep myself busy with …I also learn a lot here…I come back and also brief him… about what I have learnt. By my benefitting here, he also benefits from my coming here…. When we see each other, if he knows that I've been here, he asks what I found today." Non-PrEP user, Age 33

### Contextual Information on PrEP Adherence Influences

The next section of qualitative results offers contextual information on PrEP adherence influences. Contextual information is related to but conceptually distinct from the study's primary results and helps to clarify their meaning. We identified four aspects of context related to influences on PrEP adherence.

1. *Meaning of Partnered Relationship.* All women participating in the ZINK Study had been in a partnered relationship lasting at least 6 months at the time of their enrollment. However, in qualitative interviews, none of the women described living with their partners; rather they shared a residence with family members or friends. A number of the qualitative participants reported seeing their partners only infrequently. As is the case for many in South Africa [33], long-distance relationships were common. Many male partners held jobs outside the area. Contact decreased and distances separating partners increased as a result of the COVID-19 pandemic, when many women traveled for extended periods of time. Understanding these patterns helps to clarify the meaning of "changing proximity to partners" and "mobile lifestyle" as adherence influences.
2. *Attitudes Toward Conception.* Attitudes toward conception varied among women in the qualitative sample. Male partners were seen as the main drivers of fertility desire in the relationship. While some women seemed to have strong pregnancy intentions, others appeared less committed, ambivalent, or saw their interest in having a child wane over time. A number re-evaluated their pregnancy intentions in the context of safer conception counseling provided through the ZINK Study. Women described counseling as encouraging them to re-think life priorities and focus on the practical aspects of having a child. As a result, some decided to defer pregnancy and continue working and/or studying instead. The following excerpts illustrate:

   "She [counselor] asked me why I wanted to have a baby when I'm still so young. We talked and I realized that she was right. She was right about what she was saying. That's when I changed to say (laughing) … a baby currently, no. I've just come out of school. I still want to go and study." PrEP user, Lower adherer, Age 21 "Participation [in the ZINK Study] affected me …since I was in a process of wanting …to have a baby. Like it taught me that you should plan for a baby, yes, like you need to budget for a baby. That's what we talked about, that if you bring a baby into the world how you should budget for it and all that." Non-PrEP user, Age 27

3. *Perception HIV Risk.* Women in the qualitative sample overwhelmingly attributed their HIV risk to their partners' presumed risky sexual behavior and/or unknown HIV status. They described themselves as monogamous, while strongly suspecting their partners were engaging in condomless sex outside the relationship. Though participants reported regularly sharing HIV test results with their partners, the partners did not reciprocate, preferring to claim HIV-negative status "by proxy" instead ('if you are negative, I am negative.'). Few couples had ever tested together. Lack of knowledge of partner HIV status, compounded by suspicions of infidelity and the

fact that most did not use condoms during sex, left most of the women feeling at high risk for HIV:

> "I think I'm at a very high risk because I don't know the ways of my partner and if he uses protection where he goes...On my side the chances are low because there's no one else I sleep with, but on the other side you can never know what your partner is doing. So, I can get it through him." PrEP user, Lower adherer, Age 24 "I can say [the chances of acquiring HIV] are high because for one I don't know my partner's HIV status.... As I am here I don't know what he's doing with whom… Sometimes we do not use condoms ...The [chances] are high, because I don't know what he does with whom." Non-PrEP user, Age 21 "I don't even trust him. I don't want to lie. I don't trust him and I will never trust him. So, I saw that it's better that I join the [ZINK] study because I don't trust him. He has done terrible things before. So, I will never stop… these pills." PrEP user, High adherer, Age 24

4. *Reasons for PrEP Uptake/Decline.* Interest in PrEP was high among women in the qualitative sample who initiated PrEP. The women were drawn to PrEP as a way of protecting themselves against HIV infection, given that they perceived themselves to be at high risk, as described above.

> "So, those pills have helped me because… in fact I didn't know what type of life (my partner) is leading. When I took those pills, I had hope that it's not easy for HIV to come close to me." PrEP User, Lower adherer, Age 26

HIV prevention was the primary reason for initiating PrEP among the 19 PrEP users in the qualitative sample. The qualitative sample also included six women who had opted against using PrEP. Reported reasons for PrEP decline included fear of side effects or a negative interaction with alcohol, and concerns about potential adverse effects on an unborn child. A few women expressed a preference for other methods of safer conception (e.g., "timed sex," or timing condomless sex to correspond to peak fertility). Some doubted their ability to take an "optional" pill correctly and consistently, every day. Women worried their unpredictable schedules would interfere with dosing, or that they would forget. Rather than start and stop the medication repeatedly, these participants felt it was better not to start.

> "I quickly forget pills. So, I'm unable to stick to a treatment routine… With PrEP, I know that I'm not obligated to take them, so [I know] I would sometimes stop. It's better for me to start when I'm ready, than to start taking them and stop, start and stop, start and stop." Non-PrEP User, Age 25

## Discussion

Twenty-five women between the ages of 19 and 33 who described themselves as being in a stable partnered relationship with plans for pregnancy took part in the qualitative component of the ZINK Study. None of these women lived with their partners; rather they reported visiting them at their homes or meeting in the community. Visits could be infrequent, and some couples were separated by long distances. Contact between partners was further limited by the imposition of a nationwide lockdown resulting from the COVID 19 pandemic.

A number of women in the qualitative sample appeared less than committed to the idea of pregnancy as individuals. Some revealed being personally ambivalent, pointing to their partners as the drivers of pregnancy intention in the relationship. Others became less interested in conception as a result of participating in study-related counseling sessions, which encouraged them to envision and plan for the reality of having a baby. Our qualitative data suggest safer conception counseling may prompt women to consider their immediate priorities and postpone motherhood. This contrasts with results from a recent qualitative study of safer conception knowledge, practices, and preferences among health care providers and women living with HIV in Botswana. Provider participants in this study expressed concern that initiating conversations about safer conception with women would be encouraging pregnancy [34].

A "stop-and-start" pattern of adherence that appeared to co-vary with changing proximity to partners emerged for some women in the qualitative sample, who took the medication when they were seeing their partners regularly, and "paused" PrEP use during periods of separation. A similar pattern has been described in a study of almost 50,000 PrEP users in Kenya, Lesotho, and Tanzania [35]. A "stop-and-start" pattern of PrEP adherence in which dosing varies with changing levels of perceived risk (as in periodic partner separations) has been termed "prevention effective adherence" [36].

Though gaining recognition in research, the concept of prevention effective adherence has yet to make its way into most standard PrEP adherence counseling programs. Greater incorporation of prevention effectiveness messaging that includes accurate information on time to protection following PrEP initiation and on the length of time PrEP remains in the body following discontinuation (drug 'tail') could improve fit with the real-world situations of

users, improve PrEP adherence and help to maximize protection against HIV infection.

Evidence that women chose to stop and re-start PrEP depending on partner proximity suggests on-demand oral PrEP strategies, in which dosing is timed to coincide with anticipated sexual activity [37], may be a good fit for women in monogamous relationships that include regular extended separations from partners. The pharmacokinetics of daily oral PrEP are not well-suited to on-demand dosing for individuals with vaginal exposure, particularly in pregnancy, but should be considered in the design of future PrEP delivery systems [38, 39].

A conceptual framework intended to comprehensively represent HIV risk behaviors in periconception for HIV serodiscordant couples has been developed from qualitative research by South African investigator Crankshaw et al. [40]. The Crankshaw et al. framework identifies determinants of individual risk behaviors at multiple contextual levels (e.g. policy, health system, sociopolitical), and posits mediating factors grounded in the dynamics of partnered relationships. Gender-based power inequalities and the communication skills of both partners are cited as mediating factors. The positive impact of disclosure of ZINK Study participation and PrEP use by women in this sample on their adherence underscores the importance of communication skills as a mediator of HIV prevention for couples. Our results also point to trust between partners as a relationship-based mediating factor, as the data show clearly how lack of trust in male partners to refrain from sex outside the relationship drove PrEP uptake and adherence efforts.

The impact of a "mobile lifestyle" has not been discussed in most previous adherence research, yet women in this qualitative sample made it clear they frequently traveled and spent nights away from home. The women were quick to identify mobility as a barrier to PrEP adherence, readily acknowledging that they were unlikely to travel with their pills, and that this resulted in missed doses. An earlier qualitative study of adherence to antiretroviral therapy among South African women by this research group also identified mobility as an adherence barrier, characterizing it as one of a number of "de-stabilizing experiences" that made daily dosing more difficult (pregnancy was another) [41].

Few studies to date have sought to understand adherence to oral PrEP among African women during pregnancy and periconception. Several early reports address PrEP adherence among South African women participating in the VOICE and FEM-PrEP efficacy trials [20–23]. These reports identify social support (or lack of support), a desire to reduce HIV risk, concern about side effects, the challenges of a daily medication regimen, and various research related factors as influences on adherence [20, 22, 23].

More closely related to the present research is a small cluster of recent reports of PrEP use during pregnancy and postpartum for women in urban and rural settings in South Africa [42–44]. These investigations identified a number of the same concerns and influences on adherence that emerged from the present study, including the desire to remain free of HIV, fear of HIV-related stigma, the perception of being at high risk as a result of partner behavior, and disclosure of PrEP use and partner support.

To date, South Africa has experienced four waves of COVID with multiple lockdowns that have varied in restrictiveness. Due to an advanced testing and surveillance system, more than 22 million tests have been administered and approximately 3.6 million laboratory-confirmed cases identified to date, making South Africa one of the African countries hardest hit by the pandemic [45]. Little systematic research exists at present to document the impact of the pandemic on the daily lives of South Africans. However, the data reported here suggest the impact on PrEP use is complex. COVID-related lockdowns made adherence more difficult for some, resulting in missed doses and longer unintended lapses due to disruptions in the process of obtaining medication refills. At the same time, spending more time at home reduced mobility-related barriers, such as not traveling with pills. Finally, for this group of women, none of whom shared a residence with sexual partners, lockdown-imposed separations reduced the risk of transmission of HIV.

This study has a number of limitations. Our qualitative sample is small and purposefully defined, meaning that the results reported are not necessarily representative of the ZINK Study population as a whole. The ZINK Study took place in a single urban site in South Africa, so the experiences and perspectives of rural South African women and women from elsewhere in sub-Saharan Africa are not represented. The national lockdown made data collection more difficult and in particular, prevented us from completing a number of planned trigger event interviews. This undermined the detail and depth of information available in the data set and meant we were largely unable to report on change over time. Finally, the perspectives of male partners are not included except as reported by the women participants. Men's reproductive goals may increase their partners' HIV risk, while their behavior in partnered relationships may determine whether women disclose their PrEP use.

## Conclusion

Interest in PrEP was high in this qualitative sample of 25 women, who saw it as a means of preventing HIV in the context of high-risk partnered relationships, and decided to take the medication largely for that reason. Overall, women appeared to struggle with taking daily doses consistently. Some women made independent decisions to practice prevention effective adherence, temporarily discontinuing PrEP

use during periods of separation from their partners. Adherence efforts appeared to be influenced by a wide variety of behavioral, experiential, psychological, interpersonal and social structural factors.

Safer conception interventions that include PrEP for women in periconception would do well to incorporate a robust package of support initiatives to encourage adherence success. This research points to support for disclosure of PrEP use, efforts to address PrEP-related stigma, development of strategies for traveling with pills, and counseling on prevention effective adherence (including time-to-protection and 'drug tail' information) as potential core components of future interventions to promote optimal use of oral PrEP for South African women in periconception and pregnancy.

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**Author Contributions** MAW and NCW designed the qualitative study. MAW and EEP oversaw the collection of qualitative data, carried out the subsequent analysis and contributed to the writing of the manuscript. NCW wrote the first draft and subsequent revisions of the manuscript, with input from LM, YK, JS, MJ, MM and PS. All authors critically reviewed and approved the final version.

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**Data Availability** Qualitative data will not be made available due to challenges of redacting identifiers. For additional information contact Dr. Lynn Matthews (lynnmatthews@uabmc.edu).

## Declarations

**Conflict of interest** The authors have no conflict of interest to disclose.

**Ethical Approval** The ZINK Study was approved by: (1) the Human Research Ethics Committee at the University of Witwatersrand (Johannesburg, South Africa); (2) the University of Alabama at Birmingham Institutional Review Board for Human Use (Birmingham, AL, USA); and (3) the Institutional Review Board of Partners Healthcare (Boston, MA, USA). The ZINK Study protocol is registered at ClinicalTrial.gov (NCT02194308) and at the South African Health Products Regulatory Agency (SAHPRA) (MCC#20170131).

**Consent to Participate** All participants provided written consent before taking part in the ZINK Study.

**Consent for Publication** Not applicable.

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