Participants' Explanations for Nonadherence in the FEM-PrEP Clinical Trial

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Background: FEM-PrEP—a clinical trial of daily, oral emtricitabine/tenofovir disoproxil fumarate for HIV prevention among women in sub-Saharan Africa—did not show a reduction in HIV acquisition because of low adherence to the study pill. We conducted a follow-up study to identify reasons for nonadherence.

Methods: Qualitative, semistructured interviews (n = 88) and quantitative, audio computer-assisted self-interviews (n = 224) were conducted with former FEM-PrEP participants in Bondo, Kenya, and Pretoria, South Africa. Thematic analysis was used to analyze the qualitative data, and descriptive statistics were used to describe audio computer-assisted self-interviews responses. Data are presented within the 5 categories of Ickovics' and Meisler's conceptual framework on adherence: (1) the individual, (2) trial characteristics and study pill regimen, (3) patient-provider relationship, (4) clinical setting, and (5) the disease.

Results: Participants' explanations for nonadherence were primarily situated within 3 of the framework's 5 categories: (1) the individual, (2) trial characteristics and study pill regimen, and (3) the disease. Concerns about the investigational nature of the drug being tested and side effects were the prominent reasons reported for nonadherence. Participants also described being discouraged from taking the study pill by members of the community, their sexual partners, and other participants, primarily because of these same concerns. Limited acceptability of the pill's attributes influenced nonadherence for some participants as did concerns about HIV-related stigma. In addition, many participants reported that others continued in FEM-PrEP while not taking the study pill because of the trial's ancillary benefits and visit reimbursement—factors related to the clinical setting. Negative patient-provider relationships were infrequently reported as a factor that influenced nonadherence.

Conclusions: Despite substantial study staff engagement with participants and communities, concerns about the study pill and discouragement from others seemed to have influenced nonadherence considerably. Alternative study designs or procedures and enhanced community engagement paradigms may be needed in future studies.

Key Words: FEM-PrEP, pre-exposure prophylaxis, adherence, women, Africa

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INTRODUCTION

Participant adherence to a study product regimen is essential for determining drug efficacy within a clinical trial. The importance of this fundamental concept was evident in clinical trials that evaluated the antiretroviral (ARV) drug tenofovir disoproxil fumarate (TDF), with or without emtricitabine (FTC), as pre-exposure prophylaxis (PrEP) for HIV prevention[1–5]; the clinical trials with higher adherence demonstrated a reduction in HIV acquisition,[1–3] whereas trials with lower adherence did not.[4,5]

FEM-PrEP—a phase III, placebo-controlled trial to assess the safety and effectiveness of once-daily, oral FTC/TDF as PrEP among women in Kenya, South Africa, and Tanzania[4]—was one of the trials with low participant adherence to the study pill regimen. The trial closed early because of futility.[6] Posttrial drug concentration analyses demonstrated that 23% of a 150-participant subcohort rarely took FTC/TDF, if ever, and that 60% of participants took the study drug intermittently.[7]

Data collected during the clinical trial provided some but limited insight on factors that may have truly influenced nonadherence to the study pill regimen in FEM-PrEP. Only 1 factor was found to be negatively associated with adherence:

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reporting the use of oral contraceptive pills at enrollment.[7] In addition, most participants reported during the trial that they regularly took the study pill,[4] although posttrial analyses of drug concentration data demonstrated that most overreported their adherence.[8] We therefore conducted a follow-up study with former FEM-PrEP participants to identify reasons for nonadherence, believing that participants may be more willing to describe the context surrounding nonadherence many months after the trial had officially closed and when shown their drug concentration adherence data. Here, we describe participants' explanations of factors that influenced their decisions to not adhere to the daily study pill regimen and their beliefs about why other participants may not have taken the study pills.

METHODS

The FEM-PrEP Clinical Trial

FEM-PrEP was conducted among women in Bondo, Kenya, in Bloemfontein and Pretoria, South Africa, and in Arusha, Tanzania. Participants were randomly assigned to receive either FTC/TDF or placebo and asked to take their assigned study pill daily for 52 weeks. During the individual adherence counseling sessions provided by trained study counselors at each 4-week clinic visit,[9] participants identified strategies for integrating daily pill taking into their everyday lives. Participants were asked to describe any barriers they had faced in taking their study pill in the previous month, and counselors probed directly about negative peer influence, potential stigma, concerns about side effects, and partner support. Together with the counselors, participants were to identify new strategies to manage the barriers they faced. Self-report of adherence was also assessed at each clinic visit before adherence counseling and by staff different from those providing adherence counseling.

Study Populations and Data Collection

The FEM-PrEP follow-up study was conducted in 2 FEM-PrEP sites—Bondo, Kenya, and Pretoria, South Africa—with former FEM-PrEP participants who gave their permission to be recontacted for future research. We conducted qualitative, semistructured interviews (SSIs) with 88 former FEM-PrEP participants (Bondo, n = 43; Pretoria, n = 45) who were randomly assigned FTC/TDF during the trial. We also conducted quantitative, audio computer-assisted self-interviews (ACASI) with 224 participants (Bondo, n = 112; Pretoria, n = 112) who were assigned placebo or FTC/TDF during the trial.

For the SSIs, each of the 88 participants was purposively selected and placed into 1 of 3 adherence interviewing groups based on her drug concentration levels: none/scarce (n = 32), moderate (n = 31), or high (n = 25). For the trial's main adherence analyses, a composite adherence score was given to the specimen collected at each 4-week study visit, which represented a combination of plasma tenofovir and intracellular tenofovir diphosphate drug concentrations.[7] Each sample was given a score ranging from 0, representing a low number of doses or no doses at all, to 5, which was consistent with almost daily adherence. Participants could have a total of 13 analyzed specimens. However, many participants had fewer than 13 analyzed specimens available for drug concentration testing, because not all participants had completed all follow-up visits at the time of study closure.

For the follow-up study, participants were placed in the none/scarce group if most of the scores from their available specimens were 0 (Table 1). Participants were placed in the moderate group if the scores from their available specimens fluctuated across visits, remained steady around 2 to 4, or were higher when the trial began than they were as the trial continued. Participants were placed in the high group if most, if not all, of the scores from their available samples were 4 and 5. Participants who had more available specimens were prioritized for recruitment.

During the SSIs, participants viewed and had explained to them graphs displaying their individual adherence composite scores (based on available specimens) to facilitate discussions on their adherence during the trial (Fig. 1). We asked participants different questions and follow-up probes about potential barriers, based on their adherence group (ie, none/scarce, moderate). Participants in the none/scarce group were asked to describe what made taking the study pill difficult or not a good idea for them. Follow-up probes were to be asked on the potential reasons for not taking the study pills, such as believing they were not at risk of HIV; not having support from partners, parents, and others; pressure from staff; knowing that the effectiveness of FTC/TDF for HIV prevention was unknown; and being too busy. Participants in the moderate group were asked to describe reasons they took the study pill some but not all time and about times during the trial when they took the study pill less often. Follow-up probes included not taking the study pill because a sexual partner was away, having side effects, believing a partner did not have HIV, and being too busy. Before the specific probes were asked in each group, interviewers asked indirect probes (eg, "Was there anything else?") to further identify any other possible reasons for nonadherence. We also identified personalized questions for the interviewer to ask

TABLE 1. Number of Available Specimens and Composite Adherence Scores Per Adherence Group

Adherence Group	Median Number of Specimens Available (Range)	Range of Composite Adherence Scores	Range of the Mean Composite Adherence Scores for All Visits*†
None/scarce	8.5 (2–13)	0–4	0.00–0.78
Moderate	5 (2–13)	0–5	1–3.8
High	6 (1–13)	2–5	3.6–5.0

*Each participant's composite adherence scores were averaged across the 13 visits, based on their available specimens. This column displays the range of those mean scores.

†Seven participants had mean scores ranging from 3.6 to 3.9. Four of these participants were in the high group and 3 were in the moderate group. The decision about which group to place these participants in was based on a combination of the total number of specimens available and scores for each specimen.

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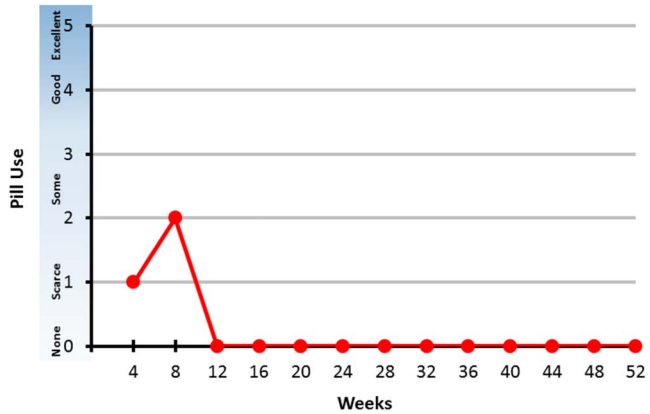

FIGURE 1. Example of an adherence composite score graph shown to participants.

a participant when appropriate (eg, when the participant had fluctuating adherence composite scores), so we could specifically probe about the context surrounding the participant's individual adherence patterns. We did not ask direct questions about barriers to adherence for participants in the high adherence group because we were interested in identifying factors that contributed to the overall low adherence in FEM-PrEP rather than the reasons participants with good adherence were unable to take the pill study on occasion; these participants were asked questions about reasons they regularly took the study pill.[10] Before asking about the participants' own adherence, we asked participants in all 3 groups about their perceptions of other participants' adherence, because this method has been shown to reduce the likelihood of socially desirable responses when discussing undesirable behaviors.[11] The SSIs were audio-recorded with permission from the participants.

For the ACASI questionnaire, the 224 participants consisted of 86 of the 88 participants who participated in the SSI on adherence and 50 participants who were assigned placebo during FEM-PrEP but who were not asked to participate in an SSI. The remaining 88 participants were former FEM-PrEP participants who participated in another aspect of the follow-up study (ie interviews about risk perceptions). During ACASI, all participants were asked to think about the days they did not take the study pill during the trial. Nineteen potential reasons followed; after each reason, participants were to answer yes or no on whether the factor was a reason for them. Participants were informed that their answers to ACASI would not be linked to their participant identification numbers or demographic information, as a method to reduce the possibility of socially desirable responses.

Additional details of the study population, of the sampling and recruitment procedures used in the follow-up study, and of the drug concentration analyses conducted in FEM-PrEP are described elsewhere.[7,10,12] All interviews were conducted at a location separate from the FEM-PrEP study clinic and by non-FEM-PrEP staff, as a method to reduce the potential for socially desirable responses.

The Kenya Medical Research Institute Ethics Review Committee (Bondo), the Pharma-Ethics Review Board (Pretoria), and the Protection of Human Subjects Committee at FHI360 in the United States reviewed and approved the research. Participants provided either verbal (Bondo) or written (Pretoria) informed consent to participate in the follow-up study, following local guidelines. The same information was provided in the verbal consent information sheet and the written consent form.

Data Analysis

Descriptive statistics were used to describe the responses from the ACASI questionnaire. Applied thematic analysis[13] was used to analyze the qualitative data from the SSIs. For a full description of data analysis, see Supplemental Digital Content 1 (http://links.lww.com/QAI/A766).

We used Ickovics' and Meisler's[14] conceptual framework on factors affecting adherence in HIV-treatment clinical trials to place the FEM-PrEP findings on behavioral and contextual factors surrounding nonadherence into a broader adherence context. Factors in the framework are categorized by (1) the individual (eg, social support and beliefs about the disease); (2) trial characteristics and study pill regimen (eg, concerns toward study arm assignment, side effects of an investigational drug, dosing frequency, adverseness of known side effects); (3) patient-provider relationship (eg, tone of relationship); (4) clinical setting (eg, services and incentives); and (5) the disease (eg, stigma).

During analysis, we chose to examine data collected during the follow-up study on motivations for continuing in the trial to shed light on the fourth category of Ickovics' and Meisler's framework—clinical setting. During ACASI, we asked participants to identify why they had continued to attend their study visits. Eleven possible reasons were provided, and participants were to answer yes or no on whether the factor was a reason for them. During the SSIs, we asked participants to describe the reasons they believed other participants continued coming to the study clinic when they were not taking the study pill. The same analytical approaches described above were used to analyze these data.

RESULTS

Many women described more than 1 reason that influenced their or other participants' decisions to refrain from regularly taking the study pill or from taking it at all. Their explanations were primarily situated within 3 of the framework's 5 categories—the individual, trial characteristics and study pill regimen, and the disease. Findings related to the other 2 categories—patient-provider relationship and clinical setting—either suggested limited influence on nonadherence (patient-provider relationship) or were possibly indirectly related based on the questions asked (clinical setting). Table 2 lists factors influencing nonadherence, as reported in the ACASI questionnaire. Figure 2 displays an overall conceptual model of the most commonly reported factors that influenced nonadherence.

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TABLE 2. Factors Influencing Nonadherence, as Reported in the ACASI Questionnaire, n (%)

Category	Subcategory	Factor	Bondo (n = 112)	Pretoria (n = 112)	Overall (n = 224)
Individual	Social support, negative influence of others	Deterred by other participants' nonadherence	11 (10)	39 (35)	50 (22)
		Were told by someone not to take the study pills	13 (12)	21 (19)	34 (15)
		Family member	12 (11)	14 (13)	26 (12)
		Community member	8 (7)	12 (11)	20 (9)
		Partner	7 (6)	8 (7)	15 (7)
	Satisfaction with pill taking	Used to taking pills only when sick	8 (7)	39 (35)	47 (21)
		Disliked taking pills	4 (4)	24 (21)	28 (13)
	Beliefs about the disease/risk perception	Felt at low risk of HIV	14 (13)	48 (43)	62 (28)
	Life balance	Forgot	18 (16)	46 (41)	64 (29)
		Was traveling	26 (23)	22 (20)	48 (21)
		Had too many other things to worry about/ tend to	17 (15)	19 (17)	36 (16)
		Adherence not important	9 (8)	12 (11)	21 (9)
Trial characteristics and study pill regimen	Clinical trial context	Pill was investigational ("being tested to find out if it could prevent HIV")	29 (26)	77 (69)	106 (47)
		Perceived placebo assignment	19 (17)	42 (38)	61 (27)
	Side effects	Feared side effects	11 (10)	48 (43)	59 (26)
		Had side effects	11 (10)	21 (19)	32 (14)
	Pill attributes	Daily pill taking was too difficult	11 (10)	60 (54)	71 (32)
		Pill was too big	12 (11)	48 (43)	60 (27)
Disease		Feared others would think she had HIV	8 (7)	14 (13)	22 (10)
Patient-Provider Relationship		Poor treatment by staff	3 (3)	3 (3)	6 (3)

Individual

Social Support

The influence of social support on nonadherence is best explained as discouragement toward adherence at the community and interpersonal levels (ie, partners and peers). In ACASI, 15% of participants reported that their nonadherence was influenced by being told by others—a family member, community member, or partner—not to take the study pill and 22% were deterred by other participants' (ie, peers') nonadherence (35% in Pretoria). However, women's narratives in the SSIs described an environment of broader discouragement shaped by concerns and rumors about the study pill that were communicated by peers, partners, and the community. Numerous women (n = 31) in the SSIs reported that such discouragement led to their own nonadherence, and most women (n = 72) said they believed that discouragement from others influenced nonadherence among other FEM-PrEP participants.

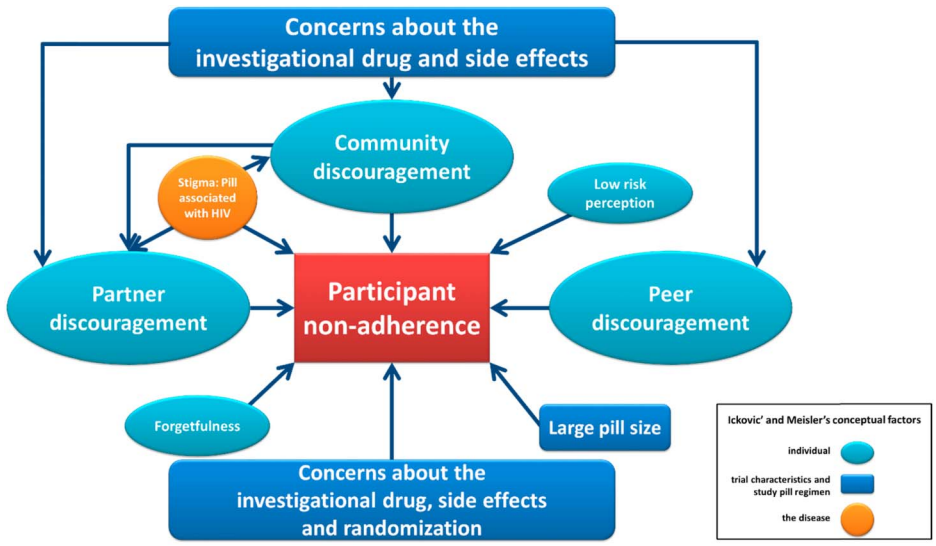

FIGURE 2. Conceptual model illustrating factors related to nonadherence in FEM-PrEP.

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Discouragement From Peers

Many women in the SSIs described situations in which influences from peers negatively affected their own study product adherence and that of other participants. Women said participants would talk with one another about their nonadherence and persuade others not to adhere. A participant from Bondo said:

> It was just influence. Because sometimes you may have started taking the pill and they (other participants) would ask you, "Are you taking the pill?" If you say "yes," they would then tell you that they do not take the pills because the pills are bad. So, this can then discourage somebody.

Narratives primarily described that participants told other FEM-PrEP participants that they had experienced side effects or that they believed the pill would cause side effects or unknown harm. A participant from Pretoria explained:

> Like when we are sitting and others will be saying, "You know that pill, I won't drink it because it is treating me this way (ie, unpleasant side effects)." And others talk of that thing, "if I also drink it, maybe it will treat me the way it is treating her."

Discouragement From Community

Participants' narratives in the SSIs illuminated influential, negative community discourse. At an individual level, women often described that such dialog, including direct persuasion (eg, others actively discouraging women from taking the study pill) but more often indirect influence (eg, hearing others talk unfavorably about the study pills), adversely affected their own adherence decisions. Negative community persuasion was also commonly described when women spoke about reasons why other participants did not take the study drug, although it was mentioned more often by participants in Bondo than by those in Pretoria. The belief that the study pills could cause harm (non-HIV related) was the most common discourse mentioned. A participant from Bondo said:

> One day I heard from women…in my house. They were saying that women are spoiling their body (health) by taking study pills that they do not know their whereabouts. To be sincere, after I had heard about this, I felt discouraged. I said to myself that "I thought I am helping other women but instead I am just spoiling my body." I got scared and stopped taking my pills after I had started taking it daily.

Women also described in the SSIs, albeit far less often, that the community discourse focused on the belief that the study pill could cause HIV. In addition, several women said that other participants were nonadherent because community members believed they had HIV, based on the participants' association with the study clinic or because the study pill is an ARV drug. Rumors (eg, participants have sex with HIV-positive men at the study clinic to demonstrate that the study pill is efficacious; concerns surrounding use of blood) were also mentioned by several women as negatively influencing others' adherence, but only among participants in Bondo.

Discouragement From Partners

Numerous women said in the SSIs that perceived or actual discouragement from partners led other participants not to take the study pill. These narratives focused primarily on the general disapproval from partners and on partners not allowing participants to take the study pills. At an individual level, several women said that a sexual partner discouraged or forbade them from taking the study pill, primarily of concern the pill would cause sickness, including HIV, or because he believed the pills were for treating HIV. A participant from Pretoria said:

> My boyfriend didn't want me to drink them. So I took them sometimes. When I was there (interviewer note: boyfriend's place) I didn't take them. I only took them sometimes when I was home. When I was with him, I didn't take them. For many women, their boyfriends didn't allow them to drink the pills from Setshaba (ie, the FEM-PrEP study site).

Women also described that partners became concerned after hearing negative rumors in the community. A participant from Bondo described:

> Sometimes, when you have joined a study, your husband knows but when someone else from the community goes and explains something different to him, he becomes wild. He even refuses to listen to you, and so you are forced to stop taking your pills. Yes, that affected so many of us women.

Many women (n = 32) also volunteered in the SSIs that participants purposefully hid their study pills from their partners of concern they would respond negatively if trial participation was discovered. Women's narratives focused on the difficulties of daily adherence when they were unable to take the study pills in private, without their partners' knowledge. A participant from Bondo explained:

> It made it hard because, let us say for example, you are all in the house, and the time for taking the pills reaches, one will be afraid of taking the pill because she fears that she might be asked why she is taking the pill.

Forgetfulness

Forgetfulness was mentioned by 29% of participants in the ACASI questionnaire and was described by many in the SSIs as a factor that influenced their own nonadherence (n = 39) or the nonadherence of others (n = 49). Numerous illustrations of forgetfulness were woven into a broader context of nonadherence in the SSIs, including not having someone to remind them, having to hide their pills and therefore not seeing them, missing their scheduled time for pill taking and not having the pill available when they later remembered, being busy or having long work days, forgetting

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to take pills with them when traveling, and not feeling sick and therefore not having internal reminders to take pills. A participant from Pretoria explained:

> …Like maybe I went to the shops. Because I am not sick, it won't click on me (ie, come to my mind) everyday. Maybe I am going to (a shop) and suddenly, "Eish! It's time to take the pills!" Then, I remember that it's not that I am sick, and I continue with my things. Then, when I come back I drink it.…but if I don't, it'd still be fine.

Perception of HIV Risk

Perceptions surrounding not feeling at risk of acquiring HIV shaped some participants' adherence decisions. In ACASI, 43% of women from Pretoria said they were nonadherent because they didn't feel at risk of HIV. In the SSIs, several narratives from women in both Bondo and Pretoria (n = 13) described that their nonadherence was influenced by not having sex because their partner was not around or because they currently did not have a sexual partner, by their partner not having HIV, or by a general feeling of not being at risk. A participant from Bondo said:

> Let me say, for someone like me whose husband is always in Nairobi—it is not a must that I take the pills everyday. It is only when my husband is around that is when I am forced to take my pills. I think some people were doing that.

Trial Characteristics and Study Pill Regimen

Placebo-Controlled Clinical Trial Context

In ACASI, being asked to take an investigational drug was the most frequently acknowledged reason by women at both sites for their own nonadherence (overall: 47%; Pretoria: 69%; Bondo: 26%). Similarly, many women (n = 69) in the SSIs described that other participants did not take the study pill because of the uncertainties related to the context of a placebo-controlled clinical trial. Such concerns were also raised when women (n = 16) discussed reasons for their own nonadherence (most of whom were in the none/scarce group). Specifically, many explained that they or other participants either believed FTC/TDF was ineffective or they were unsure about its effectiveness; some described that they or other participants had anxieties related to the unknown risks of the investigational drug. A woman from Pretoria said:

> They (study staff) told us that they are not saying it prevents, they want to see. So, you will tell yourself that either I risk with my life because they want to see. They are not saying it is working. They want to see if it could work. So you see somewhere that you are risking with your life.

Apprehension toward the study product blinding and randomization was also expressed in the SSIs. Simply not knowing which pill they were assigned and perceiving that they were assigned the placebo were often described by women in the SSIs as contributing factors to nonadherence for themselves and for other participants; 27% reported in the ACASI questionnaire that their nonadherence was because they perceived they were assigned the placebo. A woman from Bondo said during her SSI:

> What I think made it hard (to take the study pill everyday), is just that how they were explaining to us, that there are 2 pills, Truvada and placebo. We were told that one of them does not work totally (at all) and one of them is being tried to see if it works. On my side, this is what stopped me from taking—because I did not know which one I was taking. Sometimes my mind thought that I could keep on taking but I was just taking the placebo and that does not work.

Features of the Pill and Regimen

Anxiety toward the known or perceived side effects of FTC/TDF was acknowledged among some women in ACASI as a reason for nonadherence: the fear of experiencing side effects was reported to have affected women's own nonadherence (26%) more than actually experiencing an adverse reaction perceived to be caused by the pill (14%). Experiencing or worrying about side effects was a very common narrative in the SSIs to explain why other participants did not adhere (n = 54). A woman from Pretoria described why she and others did not take the study pill:

> My problem was—I didn't know what the pill will do to me. What if it hurts me, this pill? What if it makes me sick? I was thinking a lot about this…There is nothing that (study staff) could have done. I did have doubts, even though they did tell us about the side effects. They did explain that it is like this. But those pills, they were not in our minds…What was in our mind is what we talked about as a group. That what if this pill treated us this way, I won't drink it. So all of us said we won't drink it.

Furthermore, some women (n = 20) in the SSIs said that they did not personally adhere at times to the daily study pill regimen, or they stopped taking the study pill, because they experienced side effects. A participant from Pretoria described:

> Because it's a drug, sometimes it gave you a severe headache and you decide to stop drinking it for some time… (Interviewer note: Participant points at her drug concentration graph where adherence had declined). That's the time when I was getting a headache. And then I stopped (taking it), but I continued to come to the study.

The daily regimen and pill size were also acknowledged as reasons for nonadherence, particularly by women in Pretoria. In ACASI, daily pill taking was reported to be difficult among 54% of women in Pretoria but only 10% of participants in Bondo. Moreover, a greater percentage of

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women in Pretoria (43%) than in Bondo (11%) reported that the large size of the pill affected their adherence. In the SSIs, many women (n = 73) in both sites said the large pill size made it challenging for some participants; several (n = 14) participants (more often in the none/scarce group) volunteered that the size of the pill contributed to their own nonadherence. Many also emphasized the difficulty that other women had in swallowing the pill. Finally, 35% of participants from Pretoria reported in ACASI that they didn't take the study pill because they were used to taking pills only when sick. Similarly, women in the SSIs (n = 40) described that taking pills when healthy was illogical—"healthy people are not supposed to be given pills"—and said that other participants were nonadherent because they were not sick, making drugs unnecessary.

Patient-Provider Relationship

In ACASI, 3% of women reported that poor treatment by staff led to nonadherence. Similarly, in the SSIs, negative patient-provider relationships were not identified as a factor that led to nonadherence; only 1 participant said that a negative experience with 1 study staff member may have influenced some women to not take the study pill.

Clinical Setting

Ninety-three percent of women reported in ACASI that they continued in FEM-PrEP because of the health-related benefits the trial provided (Table 3); this was the most common reason acknowledged for continued participation. In the SSIs, many women (n = 76) said that the health-related services provided by FEM-PrEP motivated participants to continue with their study visits while not taking the study pill. Narratives focused on the benefits of receiving regular testing for HIV and pregnancy; receiving free study-related and ancillary medical care and treatment, such as regular check-ups, contraceptives, pap smears (Pretoria only), and treatment for common ailments, illnesses, or treatable sexually transmitted infections; and having an opportunity to speak with a health care provider, or receive counseling by trained counselors. A participant from Pretoria said:

> At Setshaba, they were taking care of us. If you have the flu, they will give you medicine…You know what I love about Setshaba? They also test you for sexually transmitted infections. If you go to (another) clinic, they will shout at you, "What were you doing?" If you want to test, at Setshaba they don't do that.

In addition, in the SSIs, almost all women (n = 78) said receiving the reimbursement at each 4-week study visit—either the money at the Bondo site (600 Kenyan Shillings, approximately U.S. $7) or the voucher at the Pretoria site (worth Rand 150, approximately U.S. $20)—influenced other participants to continue their participation in FEM-PrEP even though they were not adherent. In ACASI, 27% reported that they continued in FEM-PrEP because of the reimbursement.

Socializing with other participants at the study clinic was another reason mentioned (n = 23) in the SSIs for why participants continued with their study visits even though they were not adhering to the study pill regimen. Participants described that study visits provided participants with an opportunity to overcome the monotony and boredom of their daily lives, and to talk and share ideas with or seek the advice of other participants, with whom some had become friends.

The Disease

Ten percent of women reported in ACASI that a fear that others might think they had HIV led to their own nonadherence. In the SSIs, some narratives described that nonadherence occurred because participants were concerned that others would think they were taking pills or going to the clinic for the treatment of HIV (n = 20), or that the study pill or the clinic would give participants HIV (n = 12); 7 women said similar concerns influenced their own nonadherence.

TABLE 3. Reasons for Continuing Participation in FEM-PrEP, as Reported in the ACASI Questionnaire, n (%)

Category	Item	Bondo (n = 112)	Pretoria (n = 112)	Overall (n = 224)
Research outcome	Honor commitment	100 (89)	106 (95)	206 (92)
	Do part in finding new methods to prevent HIV	99 (88)	101 (90)	200 (89)
	Find out if FTC/TDF is effective at reducing HIV risk	78 (70)	99 (88)	177 (79)
Health-related benefits	Get health-related benefits	103 (92)	105 (94)	208 (93)
	Counseling/talk with study staff	93 (83)	91 (81)	184 (82)
	HIV testing	84 (75)	96 (86)*	180 (81)
	Medical care	71 (63)	88 (79)*	159 (71)
	Free condoms	44 (39)	43 (38)	87 (39)
Study procedures	Tracing	46 (41)	36 (32)	82 (37)
	Get reimbursement	25 (22)	36 (32)	61 (27)
Interpersonal relationships	Talk with other participants	45 (40)	65 (58)	110 (49)
	Please study staff	35 (31)	12 (11)	47 (21)

*Missing data (n = 1).

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DISCUSSION

Numerous factors that influenced nonadherence among FEM-PrEP participants were identified. Apprehension related to the investigational nature and unknown side effects of the study drug seems to have been a substantial contributor to nonadherence. Participants were also concerned about the known side effects of the study drug. Having had side effects, and having had anxiety about the potential for experiencing side effects in the future, were described as having considerable influence on participants' decisions to not take the study pill. The beliefs about the potential for the study pill to cause harm held by other participants, partners, and community members often fueled participants' nonadherence. Although responses to the ACASI questionnaire suggest that others negatively influenced adherence among only a minority of participants overall, this result may have been because of limited disclosure of study participation to others or because of the question itself (ie, the question asked if the participant was told not to take the pill). Women's narratives in the SSIs, in contrast, provided rich illustrations of the direct and indirect influence of others on participants' nonadherence.

Other barriers to adherence were also identified. Pill attributes, such as the large pill size, were described as a barrier to adherence, particularly among women from Pretoria. Not perceiving oneself to be at risk, HIV-related stigma, and forgetfulness were also barriers. Elsewhere, we have described FEM-PrEP participants' perception of risk and its perceived impact on risk-reduction methods[15] and its association with study pill adherence.[16] These barriers, however, were either not as common or not as compelling in women's narratives about barriers to adherence as were the rich descriptions of the concerns of unknown effects of the investigational drug and its known side effects and of the discouragement received from others.

Data on the reasons why women continued in the FEM-PrEP trial may illuminate other possible reasons for nonadherence. Specifically, the trial's health-related benefits seem to have encouraged women to stay in the trial even though they were no longer interested in taking the study pill, suggesting that women value their health and want access to quality and confidential health care. Alternative study designs or procedures may be needed in future studies to provide women an opportunity to receive the benefits of a study without being enrolled, reserving enrollment and study product distribution for participants who are more likely to adhere. The reimbursement also seems to have contributed to participants' decisions to continue their participation without adhering to the study regimen. We do not, however, have data on whether women who never intended to take the study pill joined the trial solely for the reimbursement.

These findings may have implications for future clinical trials on ARV-based HIV prevention products among women, and for the rollout of PrEP. Concerns regarding the known side effects and the pill size will likely remain as challenges to adherence in routine PrEP delivery; adherence counseling can explore strategies to address and monitor these concerns among women interested in taking PrEP. Concerns regarding the investigational drug and the potential for adverse events may exist among participants and their communities in future clinical trials of ARV-based and other HIV prevention products. HIV-related stigma may exist in both contexts.

Our data suggest that partner and community engagement will be paramount in future trials. Yet, we need to learn more about how to effectively engage partners and communities in supporting trial participants, as social influences seem to have had a substantial effect on nonadherence. FEM-PrEP had an extensive community engagement program and several activities to promote partner involvement. These activities, based on Good Participatory Practice,[17] began before the clinical trial initiated and continued until the final results were disseminated. The 3 overall goals that guided the program were to: (1) introduce FEM-PrEP to and obtain feedback from a range of local community stakeholders, (2) build research literacy to promote understanding of and trust in FEM-PrEP and clinical research in general, and (3) promote ongoing dialog between FEM-PrEP researchers and local community stakeholders regarding concerns, rumors, and misconceptions related to the trial.[18] To accomplish these goals, the Bondo site, for example, conducted 614 general community education meetings—180 that took place before the initiation of FEM-PrEP and 434 that were conducted during FEM-PrEP. In addition, the Bondo team conducted 19 community advisory board meetings, 72 male-involvement meetings, 11 sessions on continuing medical education for medical providers, and 39 large stakeholder meetings.[19] The extent of the FEM-PrEP community engagement activities, coupled with the findings here on partner and community discouragement, suggest that the goals of community engagement in future trials may need to be expanded and that enhanced community engagement paradigms may need to be identified.

Community models based on research literacy and open dialog may be effective at providing education, establishing partnerships, and building trust toward research. However, they may not be designed or sufficient for relieving people's concerns and anxieties about clinical research, which comes from an accurate understanding of clinical trials (eg, that trials evaluate investigational products with potential unknown risks and that such products may also have known or unknown side effects). Current community engagement models may also be insufficient in encouraging community members and partners to provide direct and indirect support to study participants, even when there is broad consensus in the community that new HIV prevention options are needed. Formative research may be needed to learn how to identify individuals who are comfortable taking an investigational product or placebo,[20] particularly in environments that might not be supportive of clinical research. Research also may be needed to determine the most appropriate way to describe the investigational nature and potential risks of a study drug (particularly risks that are rare) in consent forms and community meetings, focusing on language that fulfills the ethical requirements for disclosing risks whereas at the same time allows for thoughtful consideration of those risks by study participants and their communities. Without careful

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disclosure of such information, rumors and misunderstandings about study products can occur, derailing the identification of new products that can ultimately benefit the larger population. Ultimately, however, individuals (and their surrounding community) may hold views on the level of risk in clinical trials that they are willing to accept, which community engagement approaches may or may not be able to influence.

Participants' responses to questions in this follow-up study may have been influenced by a preference to give socially desirable responses. Many participants in the none/scarce adherence group were reluctant at first to admit to any nonadherence, particularly participants in Bondo. On being probed further, however, all offered at least 1 reason for not taking the study pill. Yet, participants in the SSIs were generally more forthcoming and expressive in their narratives on the reasons for nonadherence (using many illustrative examples) when they spoke about other participants than when they spoke about their own nonadherence. We expected that this could occur, which is why we included questions on women's perceptions about other participants. We also designed the SSIs to identify the overall barriers to adherence rather than to identify barriers that were more common among the moderate adherers than among the participants in the none/scarce adherence group. Similarly, by design, we could only describe reasons reported in ACASI for not taking a study pill by all adherence groups combined, rather than separately by adherence group, because of the procedures we took to reduce socially desirable responses. Finally, our findings may not be representative of the reasons for nonadherence among all FEM-PrEP participants who were nonadherent. Given the gap in time between the closure of FEM-PrEP (all follow-up visits among HIV-negative participants and community activities were completed by December 2011; follow-up with participants who seroconverted ended in July 2012) and the follow-up study (initiated in March 2013), as well as our sampling strategy, we did not expect to obtain a representative sample. However, the consensus of responses about reasons other participants did not adhere provide reasonable evidence that the barriers described here were common.

To conclude, by conducting follow-up interviews with FEM-PrEP participants, we were able to identify several reasons why participants likely did not take the study pill during the FEM-PrEP clinical trial. It is worth emphasizing, however, that participants in FEM-PrEP were not given a PrEP product of proven efficacy but rather were asked to take an investigational drug or placebo daily. Thus, nonadherent participants chose not to take a study product. The distinction between a study product and efficacious PrEP is critical, and the belief that African women cannot and will not be adherent if provided with PrEP outside a clinical trial setting, because they did not take the study product in FEM-PrEP, should be avoided. For instance, a recent demonstration project of oral PrEP conducted among women in Cape Town, South Africa—where participants were told that PrEP is efficacious in HIV prevention—demonstrated high adherence, particularly among participants who were asked to take PrEP daily.[21] Now that PrEP has been proven efficacious[1–3] and demonstration projects are providing evidence that some women want and are able to use PrEP daily,[21] more women deserve access to PrEP to make their own decision on whether it is the right HIV risk-reduction choice for them.

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