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ORIGINAL PAPER

High Acceptability of HIV Pre-exposure Prophylaxis but Challenges in Adherence and Use: Qualitative Insights from a Phase I Trial of Intermittent and Daily PrEP in At-Risk Populations in Kenya

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Abstract This paper used qualitative methods to explore experiences of men who have sex with men and female sex workers in Nairobi and Mtwapa, Kenya, who used oral pre-exposure prophylaxis (PrEP) for HIV prevention as part of a four-month trial of safety, acceptability and adherence. Fifty-one of 72 volunteers who took part in a randomized, placebo-controlled, blinded trial that compared daily and intermittent dosage of PrEP underwent qualitative assessments after completing the trial. Analyses identified three themes: (i) acceptability of PrEP was high, i.e. side effects were experienced early in the study but diminished over time, however characteristics of pills could improve comfort and use; (ii) social impacts such as stigma, rumors, and relationship difficulties due to being perceived as HIV positive were prevalent; (iii) adherence was challenged by complexities of daily life, in particular post-coital dosing adherence suffered from alcohol use around time of sex, mobile populations, and transactional sex work. These themes resonated across dosing regimens and gender, and while most participants favored the intermittent dosing schedule, those in the intermittent group noted particular challenges in adhering to the post-coital dose. Culturally appropriate and consistent counseling addressing these issues may be critical for PrEP effectiveness.

Keywords Men who have sex with men · HIV pre-exposure prophylaxis · PrEP · Adherence · Kenya

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Introduction

Pre-exposure prophylaxis (PrEP) refers to the use of antiretroviral medications (ARVs) by HIV-negative individuals to reduce risk of HIV infection, and to date, is one of the most promising strategies in the field of biomedical HIV prevention. Prophylactic use of ARVs in animal models has been shown repeatedly to reduce simian/HIV acquisition [1–4]. A phase III randomized controlled trial tested the efficacy of once-daily oral dose of emtricitabine–tenofovir (Truvada) versus placebo on HIV incidence among men and transgender women who have sex with men in Peru, Ecuador, South Africa, Brazil, Thailand, and the United States [5]. Results demonstrated a 44 % reduction in the incidence of HIV infection among participants who received PrEP. There were fewer infections among volunteers with higher

adherence to PrEP compared to those who had poor adherence, indicating the importance of following prescribed dosage schedules. Two other randomized controlled trials assessing the efficacy of PrEP in HIV-negative heterosexual men and women showed similar results. Partners in a PrEP study of 4,758 HIV serodiscordant couples in Kenya and Uganda showed that those who took a once-daily oral dose of tenofovir demonstrated a 62 % reduction in the incidence of HIV infection and those who took a once-daily dose of tenofovir in combination with emtricitabine demonstrated a 73 % reduction in the incidence of HIV infection [6]. Similarly the TDF2 study of 1,219 HIV-uninfected heterosexual males and females in Botswana showed that a once-daily dose of tenofovir and emtricitabine demonstrated a 63 % reduction in the incidence of HIV infection [7].

Behavioral research can help to identify factors that might determine adherence to PrEP and therefore, drug effectiveness in real-world settings. Importantly, few studies have assessed acceptability and use of PrEP, and most are based on hypothetical scenarios presented to participants [8, 9]. Factors associated with intentions to use PrEP in a sample of men who have sex with men (MSM) in the United States included the efficacy, costs, and potential side-effects of PrEP [9]. Similar findings were observed in a study of female sex workers, male-to-female transgendered persons, and MSM in Peru [10]. A study of intentions to use PrEP among African American and Caucasian women in the United States found that individuals who had engaged in high risk behavior were more likely to find PrEP acceptable than those who had not [11]. Another study among truck drivers in India demonstrated that motivation to use PrEP was associated with intentions to engage in at-risk behaviors, drug efficacy, and source of information about PrEP (that is, a physician was perceived as a more legitimate source than a public service announcement) [12]. Relationship factors were also associated with improved adherence and thus, greater effectiveness. For example partner support of PrEP use in discordant couples was understood as a function of the desire to reduce risk while preserving a partnered relationship [13]. Such intentions, however, may or may not equate to actual behavior among PrEP users.

Because PrEP represents a significant potential new addition to our arsenal of HIV prevention strategies, we need to better understand factors influencing PrEP pill-taking behavior that might determine real-world effectiveness. Little is known about acceptability and adherence to intermittent, or less than daily PrEP regimens which might be more feasible and affordable in some settings. Insight into social and behavioral factors that influence the acceptability, use of, and adherence to PrEP can inform the development of drug regimens and PrEP counseling strategies for individuals initiating a course of this prevention medication in the future. In this paper, we report on the first qualitative findings of PrEP acceptability and adherence among MSM and female sex workers who participated in a clinical trial testing safety and adherence to daily and intermittent oral PrEP regimen in Nairobi and Mtwapa, Kenya. Aims of analyses were to: (i) explore participants' perceptions of PrEP acceptability; (ii) identify challenges associated with adherence to PrEP; (iii) examine factors that might facilitate or challenge PrEP use, such as side-effects and stigma, and (iv) offer recommendations for education and counseling targeting prospective PrEP users.

Methods

Data for this study came from a randomized, placebo-controlled blinded trial (Clinical trials.gov number NCT00971230) testing the safety, acceptability and adherence to two different dosage schedules of PrEP: daily use versus intermittent use. Intermittent use involved self-administering emtricitabine–tenofovir (Truvada) twice weekly on Mondays and Fridays, and within 2 h post-coitally with a maximum of one dose per day. Qualitative approaches were used to improve understanding of the experiences in taking PrEP among at-risk populations in Kenya, a setting with a generalized HIV epidemic and an estimated national HIV prevalence of 7 %. Research was conducted between October 2009 and April 2010 in two cities in Kenya, Nairobi (the capital city) and Mtwapa (a mid-size coastal town) in Kilifi District. The study was approved by ethical review boards at the Kenya Medical Research Institute, University of Oxford and Kenyatta National Hospital, Nairobi. All participants provided written informed consent for interviews and focus group discussions.

Study Population

MSM and FSW populations from existing HIV-1 at-risk cohorts in Nairobi and Kilifi, aged between 18 and 49 years, were eligible for the PrEP trial, if they were HIV-1 uninfected and reported any of the following in the past 3 months: transactional sex work, recent sexually transmitted infection (STI), or multiple episodes of unprotected vaginal or anal sex [14]. Although most sex partners of MSM were men, sex with both men and women was also reported [15]. Overall 72 volunteers were recruited into the PrEP trial across the two sites: 31 were MSM and 5 were female sex workers from Mtwapa, while 36 were MSM from Nairobi. The average age of the trial participants was 26 years (range: 18–46 years). All participants identified as Kenyan and had primary education or higher, with three participants reporting tertiary education. Across both sites,

47 % of all PrEP participants reported drinking alcohol before sex, 67 % reported transactional sex and 64 % reported having receptive anal sex in the 28 days prior to PrEP trial enrolment [14].

The selection of volunteers for the qualitative component of the study was based on post-trial evaluation of completion and adherence rates i.e. a proportion of volunteers that took at least 80 % of the expected doses of the investigational product, a proportion of volunteers that completed the trial with moderate adherence rates (between 50 and 80 %), a proportion of volunteers with low adherence (less than 50 %), and volunteers who terminated the study early. Volunteers who could not be reached because of change in circumstances e.g. outmigration and custody, were considered lost to follow up (LFU).

Clinical Procedures

At enrollment to the PrEP trial, participants completed face-to-face interviews using standardized questionnaires to record socio-demographic information, recent sexual behavior, and health status. A standardized physical exam was performed, and specimens were collected for STI screening. All participants received HIV prevention counseling, condoms and lubricants, basic information about PrEP adherence, potential side effects, and the dosage schedule. These procedures were repeated at monthly follow-up visits. Seventy-two eligible cohort participants were randomly assigned to either active drug or an identical placebo pill in one of two dosage conditions: daily or intermittent (one tablet taken every Monday and Friday and again within 2 h after sexual intercourse on other days, with a maximum of one dose per day). Participants were instructed to follow the assigned dosage schedule for 16 weeks. Adherence was electronically monitored using electronic Medical Event Monitoring System (MEMS) caps on medication bottles. Sexual activity data were collected through daily electronic short message service (SMS). Adherence and sexual activity data were also collected by self-report using a monthly follow back calendar.

Qualitative Data Collection

Focus group discussions were held for those study participants who completed the trial. Study participants who discontinued the study prematurely or who had <50 % adherence on monthly MEMS data were asked to participate in an individual interview soon after their final visit. Participants were not identified by name and were free to decline participation in the focus group discussion or in-depth interview. Focus group discussions and semi-structured in-depth interviews took place after the final week of study participation and included topics such as likes and dislikes of the study pill, study dosing scheduling and adherence measures, and experiences with study procedures. The discussion guides were piloted with a subset of PrEP trial volunteers before commencing the study to ensure coherence and flow of questions. Most discussions were conducted in Kiswahili and some in English based on participant preference. All discussions and interviews were audio-taped, transcribed, and those conducted in Kiswahili were translated into English. Discussion facilitators were Kenyan study staff familiar with the trial aims, who had received training in qualitative interviewing skills. Focus groups were held separately for those who used intermittent versus daily PrEP, and for men and women prior to unblinding. The only participant who became HIV-infected during the PrEP trial (at the last visit) was included in a focus group discussion.

Data Analysis

Analyses of qualitative data followed the 'framework approach' described in Richie and Spencer [16], which involved systematic coding to identify and define concepts, map the concepts, create typologies, find associations between concepts, and seek explanations from the data. NVivo 8 was used for coding data. Data were coded by two independent qualitative researchers at each site to ensure that interpretations of quotes were consistent and that data quality was rigorous and transparent; differences between coding were resolved by group discussion involving other members of the research team. Recurring issues, concepts and patterns were identified using both inductive and deductive reasoning. Analyses highlighted whether findings differed by dosage schedule, adherence rates, and/or gender.

Results

Of the 72 PrEP trial participants, 51 volunteers participated in the qualitative study: 23 MSM from Nairobi and 23 from Mtwapa, and 5 female sex workers from Mtwapa. As per protocol a convenient sample of 'good adherers', 'moderate adherers', 'low adherers', and volunteers who discontinued the trial were selected for participation. Overall 10 FGDs, with a range of 2–8 participants per group, and 7 in-depth interviews were conducted. Of these, one focus group discussion and one interview was conducted with female sex workers. A similar number of group discussions [5] and individual interviews [3] were conducted with participants on intermittent and daily regimens. The participants' demographic and risk profiles were similar to the overall trial participants, as well as across dosing regimen, and type of discussion (that is, FGDs and IDIs).

Acceptability and Adherence to PrEP

Overall, acceptability of PrEP was high in this group of participants accompanied by suggestions for how best to improve the pill characteristics to make it easy to take and make more nondescript to prevent potential misperceptions among, and discrimination from family members and peers. In addition, a number of barriers and facilitators to adhering to the PrEP regimens were identified including concerns around stigma and discrimination, life styles, dosing regimens and possible side effects (although the last was noted as being easily overcome in time). Participants also mentioned that counseling and commitment to using the product enhanced their ability to adhere to the regimens despite the challenges.

Acceptability of Oral PrEP

Pill as Prevention Method Participants, regardless of dosage schedule, gender, or adherence rates indicated that oral PrEP is a feasible and acceptable form of HIV prevention. When asked, participants were in favor of PrEP being more widely available to the public should studies prove the medication efficacious in HIV prevention.

> If [PrEP] really prevents [HIV] they should be available in plenty so that they may help us.

> They should be in plenty and given to other people who did not participate in the study.

> It's easy to [use] PrEP. Because if it's to work, then would be good to reduce the infections. Although at the beginning is hard but with time you catch up. We too were not sure if we would make it, but we did so. I would encourage people to participate.

Participants were particularly in favor of promoting PrEP in at-risk populations. Because most participants were actively involved in sex work, and often faced challenges to HIV prevention including convincing paying partners to use condoms, PrEP offered them a more convenient, discrete, and controllable strategy for reducing HIV risk compared with regular condom use.

> It is a good idea for people like us who have multiple partners, because some will accept condoms and others not, so a drug like this which is good and will help to prevent infection… it is mandatory to swallow, you can't refuse to swallow.

Furthermore, participants in this highly religious setting, where Christian, Catholic, and Muslim faiths inform many cultural practices, also noted that PrEP might be more acceptable than other prevention methods due to the non-contraceptive nature of PrEP.

> Churches like the Catholic don't approve use of condom. So if such a drug is made available then it would be best and acceptable to such people because one would not be breaking any rules. So it will be very acceptable.

Physical Characteristics Although participants endorsed PrEP in principle, they offered several suggestions for improving its acceptability among potential users. One major theme for increasing acceptability focused on improving the physical characteristics of the pill that is, the size, shape, color, and taste, all of which affected comfort and ease of use. All participants noted that the pill was large, and associated some discomfort when swallowing. The angular shape of the pill may have contributed to this discomfort, with participants suggesting a rounded capsule shape. Despite these concerns, participants noted that over time, they grew accustomed to the slight discomfort of ingesting the PrEP pill.

> At first I feared the pill, that it was big like a bean. But as I continued swallowing it I got used to it.

> Well the size at first was scary, huge, but once you get used it gets easy.

> When I used to swallow, it used to scratch the throat for some time when I started. But when I got used to it, was okay.

In addition, participants expressed concern over the blue color of the pill due to detectable discoloration of the mouth, and concerns that the color might lead others to misperceive the pills as illicit drugs ('Bugizi'). There was also concern that people would think that the pills were ARVs.

> In the morning I can't take it without brushing, since it stained my tongue.

> The color should be white. When people see you using a blue …you know blue is a unique color, so when they see you taking a blue pill they start thinking that you are sick [HIV].

Opinions on the taste of the PrEP medication varied among participants. While some noted that the pill did not have a taste, others thought that the pill had a smell and taste that induced nausea. Overall, these comments indicate that these characteristics would not pose significant barriers to the use of PrEP by similar populations in Kenya at-risk of HIV infection due to its potential to prevent HIV infection, discrete and personally controllable nature, and cultural tolerance of this form of preventative behavior. Recommendations to improve the size, shape, color, and taste of the pill could facilitate wide acceptance amongst potential users.

PrEP Adherence Barriers

Side Effects Participants reported a number of side effects when using PrEP including: diarrhea, abdominal problems (gas or cramping), vomiting or nausea, headache, sleeplessness, joint pain, weight loss, dizziness, loss of taste, change in appetite, increase in body temperature, sweating, and decrease in sexual stamina. Many side effects abated over time, and participants expressed greater tolerance after the first initial weeks of discomfort and after consultations with study counselors.

> At first I was worried when I was told about the side effects, but I continued swallowing them.

> For me I may say that I liked taking them after some time. When I started taking them they actually affected me a bit. For the first week, there is that paper that we read saying that there were some things that were minor like diarrhea – so for me my first symptom I realized was diarrhea, and with time, when I continued swallowing it disappeared for good so I continued without any problems.

> When I swallowed them, I had diarrhea for three days then my head started aching. But when I called, they told me to come but after the three days I was okay. I continued swallowing and I didn't see any problem, but when I was swallowing, I was feeling hungry, now that was my problem.

Some participants, especially those on the daily schedule, mentioned being encouraged by the perceived positive side effects, including an increase in appetite:

> It helped me coz at times I was not having any appetite to eat but when I started taking the pill, I was now eating a lot…It was an advantage to me because I was able to eat more and more.

> ..Again in the morning I would be so hungry that I required eating a heavy meal.

Participants on the daily regimen also noted an increased libido:

> It was okay to me because when you go home, you feel like making love to your friend but when I stopped taking the pill, that morale faded.

Outside the context of a trial, there is a chance that PrEP users might discontinue use due to early side effects. However, participants acknowledged that the information provided at trial enrollment encouraged adherence and regular use:

> The way the study was organized by protocols and it went through steps which were good… It taught me to organize myself and it also taught me to keep time. Keeping time in swallowing drugs.

Overall the comments indicate that side effects were not so severe as to deter participants from continuing with the PrEP regime.

Intermittent Dosing Most participants, regardless of which dosage regime they were assigned to, expressed a preference for intermittent use due to a less-burdensome schedule of pill taking. While most participants preferred intermittent dosage, those in the intermittent group reported more problems with adherence, particularly with the post-coital dose which was to be taken within 2 h after sex. Firstly, falling asleep inhibited adherence:

> The difficult thing about it was, for me I used to swallow in the morning, sometimes you come from a date in the morning at 05.00am, and you go to sleep and the time passes by, and you have to swallow the drugs at 2.00pm or 3.00pm when you remember and go to swallow, but on the same day.

> Two hours should be extended to 4-6 hours since after sex one relaxes and may oversleep.

Adherence was also a challenge if participants engaged in multiple sequential sex episodes, primarily because of fear of overdosing.

> I was afraid because sometimes I could take overdose. I used to have a lot of clients over the week than Friday.

> I used to swallow on Monday and Friday … On Fridays I used to get a client. So sometimes I used to take two pills but later on I saw that it would cause me problems. I was afraid because sometimes I could take overdose.

A few participants raised the issue of privacy as a potential deterrent to taking the post-coital dose within the prescribed 2 h after sex.

> Swallowing the drug on Monday and Friday was okay to me. I used to forget sometimes after having sex let's say for like one and a half hours later that's when I remember. Or sometimes the person I had sex with is still there so I have to wait for that person to leave or I just find a way of taking the pill. But remembering the days for taking the pill was not a problem.

> The other thing is fear of the people you love. Like you're with your girlfriend and after having sex, each time you take a pill, so she will start thinking, why is he taking the pill? You know it's so "questionable".

Lifestyle Work, social schedules and substance use affected adherence, regardless of dosage schedule and gender. Many participants spoke about busy work schedules that delayed their returning home at a reasonable time leading to missed dosages.

> Coming late from work …for example I was taking the drugs at 8:00PM so I was taking them as late at 9:00 or 10.00PM, and also if I had carried the drugs I was unable to take the drug in front of a crowd of people.

Other participants described how travel, including unexpected time away from home and resultant shortages in pills, impeded adherence.

> It happened that we lost somebody and I had no time to go home but had to go on straight away.I went and there was some time I didn't swallow the drugs due to that, it was only 4 days, and we came back.

> There is a time I travelled and I only carried drugs for two days. So when I went there, I took more than two days and I could not come back for the pills. So I was forced to miss those days.

Participants also identified substance use as a barrier to adherence. For example, alcohol use was a reason for not taking pills on time or not taking them altogether:

> Sometimes you are on blackout because of having taken alcohol so there is no way one can open the MEMS cap.

> …after sex sometimes you know you get drunk and you forget. And you remember about five or six then your like should I get the pill or not. So the thing like two hours after sex…me I would prefer before sex.

Some participants mentioned the reason for not taking the pill was because they were unsure about the interactions of alcohol with the pill.

> You should check whether the pills can interact with the alcohol because sex for most people especially the youth takes place during that time of partying with beer, khat (stimulant plant) and Bhangi (Cannabis) and if it will be 2 hours after sex it will be very hard for many people. The drug should go well with beer.

Stigmatizing Effects of PrEP Participants noted the potential social risks of taking PrEP, regardless of dosage regime, gender, or adherence rates, and pointed to instances of both experienced stigma and potential situations where stigma may occur. Some participants occasionally ingested PrEP in the presence of family and peers, which prompted curiosity about the use of the pills. Other participants described either having to conceal their PrEP pill taking or to disclose the reasons for their behavior which subsequently led to stigmatization:

> So I feel we should be informed of the challenges to expect for those with family. We were informed about the challenges about the use of the drug but not the challenges to deal with the family while participating in research.

> My friends would ask whether I am using 'njugu'[colloquial term for a local ARV] so to cut the long story short I had to admit I am using 'njugu'. If it were possible it was better one taking the drugs alone when no one sees it. It was a secret and basically to many it is a burden. You wouldn't want to be known in what research one is participating. Njugu/peanuts are ARV.

Notably, many participants expressed concern that taking PrEP medication could lead others to believe they are HIV positive and on ARV medications.

> Another challenge is that the shape of the bottle is that of ARVs….others could not believe that I am not infected so it was a challenge to explain that I am not sick but in a study. Some people could not believe.

One participant attributed his spousal separation to his wife's suspicions about his HIV/AIDS status, which she questioned after seeing him taking PrEP:

> I stored [PrEP pills] in the bedroom and would swallow every morning so when my wife saw me taking drugs every morning she would question why I take drugs daily wanting to know if I am sick. In the process of explaining she was shocked and confused thus she ended up seeking more information elsewhere and got wrong information from friends. I think that is the reason my wife left me.

Other participants noted the potential for rumors to persist even if family and friends are informed about using PrEP as a prevention measure for reducing risk of HIV infection.

> Because they would not understand they will probably think I am infected thus tell others. Well, they may believe you when you tell them [about PrEP] but once they go other places they could gossip I am HIV positive.

> Fear was there, but I used to hide the drugs, and I used to swallow after making sure nobody sees me, since people used to know what the drugs were for, and they would say that you are infected, and people at home would fear you.

If suspected of being HIV-positive or having AIDS, PrEP users could be vulnerable to gossip, rumors, potential discrimination in the community and, for those engaged in sex work, loss of clients.

> People may be wondering why you are taking drugs and may think otherwise. They may think you are taking ARVs, or you have TB or you are suffering from an abnormal disease… People are different, some may spread rumors that I am taking drugs and when you pass in front of people, they will be looking at you differently. Maybe you want a girlfriend. It becomes difficult to take the drug in front of people.

Participants used a variety of strategies to counter the potential stigma of using PrEP. A common practice was to use pills secretively:

> If you are determined, you can swallow medicine even in the toilet, so that he doesn't know, and some will understand when you tell them that these are for headache, and he is satisfied.

Others lied about the reasons for taking the pills, describing them as treatment for other health issues:

> My boyfriend once opened [the medication holder] and questioned so I told him these are malaria tabs.

> I have a wife and children… They would see me swallow. I would even send my small daughter to fetch them. When she [wife] questioned, I lied that they are for asthma. She said asthma drugs are not like the study drugs. That is when I had to explain I am in study and the drugs are study drugs. Still she never believed so we had to go to VCT centre for testing and we were both negative. I continued swallowing the drugs.

A few participants viewed these questions as an opportunity to educate and inform others about HIV risk.

> People who saw me swallow thought I am sick so I would say… what about you? Do you know your status? It was so that I encouraged others to get tested in a VCT.

Indeed, these social challenges and likelihood of HIV-related stigma, particularly from family, friends, and significant others, suggest the need to understand and respond to the acceptability of PrEP not only among users but also amongst members of their social networks. These themes were particularly prominent in participants with low adherence or who discontinued the study, suggesting that these social factors may play a major role in both adherence and acceptability. Strategies for helping PrEP users inform and involve their significant others, family, and friends in pill taking and adherence might be helpful to minimize these social risks. Of note is the negative impact that perceived or experienced stigma has on a participants' ability to adhere to a given dosing regimen. The discussions and interviews highlight how participants were delayed or skipped taking pills, and did not have access to pills (as the brother took them for 'testing'), due to the fear and suspicion of family members and peers. Among high risk and often marginalized populations such as MSM and female sex workers in Africa who have unpredictable schedules and limited privacy and storage options, the fear or experience of stigma has implications on their ability to adhere to dosage regimens.

PrEP Subversion When queried about sharing of drugs, participants stated unequivocally that they did not share their PrEP medications with others who were not enrolled in the study. However, some reflected that PrEP subversion may potentially be an issue in future scale-up. One participant noted the following:

> I explained to [my family that] it's just a study and not cure so I warned them not to use my drugs. Once the study is through and drugs approved then we could share them.

Increasing Sexual Risk Behavior Risk compensation may be one potential negative side effect of PrEP. Although a few participants highlighted this issue, it was not discussed at length and very few mentioned increasing sexual risk behavior while in the study.

> Now that we have been used to swallowing the drugs, to me I feel it is prevention… It gave me confidence, even when I was with a stranger, so long as I have the pill I was 100%.

More commonly, reduced risk behavior was mentioned as a result of participating in the study.

> We were told that the study is to analyse adherence and not for prevention, so we were advised that once we enroll in study we should still carry on to protect ourselves by using condoms or other prevention. We should never have unprotected sex. That made me take precautions.

Similarly when asked if people will like the drugs once available on the market, one participant responded that PrEP would be perceived to have a 100 % protective effect:

> … because they will know the disease will have reduced and there will be no risk of infection. But

then again promiscuity will increase. Promiscuity will increase because there is a drug available.

Facilitators of PrEP Adherence

Trial-related Procedures Factors designed to facilitate adherence in this study—such as MEMScaps on the pill containers, reporting pill taking behavior, and provision of a keychain holder for carrying pills around—may not reflect real life settings. For example, one participant stated that he adhered to the prescribed dosage because of the knowledge that the research team would collect blood and hair samples to test for adherence, suggesting the likelihood for much lower adherence rates outside of a research trial context.

I was told there would take samples to prove if I had been taking the drug or not so yes I followed the advice to swallow daily so not to lie.

Role of Counseling In the light of these identified challenges, participants noted the importance of counseling on possible side effects and adherence. One participant commented on the role of counseling to forewarn users of any potential challenges associated with initial use, and expressed a local Kenya adage '*signs of rain are clouds*' to underscore the need for early caution and advice:

The time we were given the counseling for what was coming… It was preparing us so that we agree with the challenges that we would get when we start, and to me it really helped me.

More specifically, participants described how counseling prepared them for the possible challenges of self-administering the pills and helped them to anticipate minor side effects:

Most of the challenges and side effects we experienced was as told earlier and we were alert, so it was not a shock. We were well prepared so we knew what to expect. So it was very helpful.

Counseling also assisted participants in adherence by emphasizing the themes of "being honest with yourself and the research team", a message that resonated with participants:

What I found useful was the way they counseled me. The importance of taking the drugs, and the importance of being honest.

Counseling provided participants with education and prevention information to avoid risky sexual behavior, indicating a potential for behavioral effects of PrEP counseling that can extend beyond pill taking and adherence:

I was very active in anal sex but since joining study I have come to reduce. First I thought anal sex with male partner cannot give me any infections, but when I joined study I was counseled that I can surely get infected including impotency or other infection.

Counseling not only included education (that is, knowledge about the drug and the medication regimen) but also sought to establish a rapport between the participants and counselors, a strategy which facilitated adherence.

The counseling taught me to have the courage, to take the drugs without any fear, I felt it was okay to me cause it really helped me when joining….

Although participants reflected favorably on the information and counseling provided by the research, the rigorous measures taken to ensure safety might not be replicable outside the context of clinical trials research. For example, one participant reflected on having ongoing access to research study staff:

What was extremely useful is, for example, you are at home… we had been told by the counselor that if you notice anything odd such as problems with your eyes or ears we should telephone the clinic. This is one of the arrangements that impressed me, for you cannot give someone something and you are not sure whether it works or not. This requires you to be enquiring from this person about whether that this is working or not working or enquiring how he is feeling.

Altruism and Support Altruism was often stated as a factor in the decision to participate in this trial. Participants expressed the desire to help curb the spread of HIV:

There is no one who contributed to my joining this study I just decided on my own…. but if they knew I would have told them that I am trying to make some research drugs for our country Kenya.

Participation in the study and regular contact with the counselors resulted in a strong commitment to adhere and was highlighted in participants' reports of incorporating the pills into their regular routines as well as changes in the time to take the pills to match their schedules. As stated by this volunteer:

I used to remember cause of where I put my toothbrush and the alarm clock. Those two were always reminding me.

Even those participants who were on the intermittent dose spoke of using different strategies to ensure adherence such as taking the pill during the day instead of at night or when they ate a meal and so on.

While participants identified a number of factors that enabled adherence to the different regimens, most are unlikely to be replicable outside the trial context. Some participants did mention incorporating a number of strategies to ensure adherence highlighting their commitment to following the regimen. These actions might point to a commitment that could be followed outside a trial context and into their regular lives especially if there is strong motivation to prevent HIV infection. In addition, these issues can help to inform educational, outreach and clinic services for future roll-out.

In summary, the dosage schedule may be challenging due to high prevalence of unpredictable schedules and alcohol use. Intermittent dosing, particularly post-coital dosing, may not be feasible for at-risk populations with relatively high rates of transactional sex work. It is important to note that these challenges were reported despite the heavy research involvement among users throughout the trial (that is on-going counseling, MEM-Scap, and regular reminders via SMS). As such adherence outside the context of a research trial might be challenging if participants do not feel supported or accountable to others (e.g. researchers, physicians) for self-administering PrEP according to the dosing schedule.

Discussion

This paper presents some of the first qualitative data on acceptability and adherence to both daily and intermittent PrEP regimens in groups at risk of HIV infection –MSM and female sex workers in Kenya. Although this study was initiated and completed prior to any PrEP efficacy data in humans, the findings underscore the importance of behavioral adherence interventions to the success of PrEP. The adherence challenges identified in this study for both fixed intermittent dosing and post-coital dosing can help inform PrEP regimen choices for future efficacy studies. In particular, our findings clearly indicate the influence of social and individual level contexts on PrEP acceptance and adherence. Findings centered on three main themes. First, whereas acceptability of PrEP drugs was high due to the anticipated effects on HIV transmission, participants noted characteristics of the PrEP pills—such as size, color, taste—that, if altered, could further improve acceptability. Participants described side-effects that emerged shortly after initiating PrEP, but these diminished over time and did not deter them from taking the pills. Second, participants reflected on the social consequences of taking PrEP, which included relationship challenges, rumors, and experienced and perceived stigma, due to PrEP users being perceived as having AIDS or being illicit drug users. However, it bears consideration whether the roll-out of antiretrovirals for HIV prevention (as PrEP, and as earlier treatment to prevent transmission) may actually diminish stigma associated with these medications. Third, individual lifestyle issues in this at-risk cohort, such as alcohol use, work, transactional sex and travel presented significant challenges to adherence to both daily and intermittent regimens. In particular, post-coital dosing adherence appeared to be diminished by these factors.

Despite some potentially serious barriers to adherence, participants highlighted a number of creative and common place strategies to help them adhere to their assigned dosing regimen. The feasibility of doing so within the confines and conditions of everyday life as opposed to a controlled and consistent intervention such as the PrEP trial remains unclear. Because of the fluctuating nature of sex work, participants were not always able to anticipate if they would need to take pills with them when leaving home. Importantly, there remains strong stigma surrounding HIV/AIDS in Kenya as in many parts of the developing world, and being observed taking pills that have been associated with HIV/AIDS can result in discrimination. Strategies for educating the public about PrEP, ensuring regular ARV access for people living with HIV/AIDS, and for addressing HIV/AIDS stigma in the developing world more generally, are necessary concomitants of a broad public health scale-up of this approach.

Our data suggests that PrEP could be an acceptable and feasible preventive option for Kenyan MSM and female sex workers despite their unpredictable schedules and marginalized situation. Although intermittent could result in less drug exposure and less cost, the success of coitally-dependent dosing is still unclear as there remain multiple structural, social and individual issues to post-coital dosing in this population. Some of these issues may not apply to other risk groups, such as stable, cohabiting, HIV discordant couples. More work needs to be done to explore pre- and post-coital dosing which offer different advantages for different at-risk populations.

These findings also have implications for designing education and counseling materials for individuals prior to initiating PrEP. Because participants noted the fundamental importance of drug efficacy findings in determining their decision to take PrEP, potential users must be informed of drug trial results in language that can be comprehended by lay-audiences. In our data there was limited discussion by participants of partial efficacy—that is, that PrEP will not always prevent against HIV infection—which is a crucial consideration in scale-up [17].

Future PrEP users must be made aware of the limitations in PrEP efficacy, and receive counseling on behavioral risk reduction strategies for HIV prevention such as condom use and partner reduction, and on the importance of regular testing, in order to bolster the effects of the drug.

It is also essential that pre-PrEP counseling provides information on both the physical and social risks associated with pill usage. Although this study protocol provided participants with information on minor side effects and discomforts due to the drugs, participants described not having adequate forewarning about the potential social consequences of taking this drug—particularly the stigma associated with being perceived as having HIV/AIDS or being an illicit drug user. In addition to acknowledging these potential risks, pre-PrEP counseling can also provide users with skills, strategies, and support for minimizing adverse physical and social harms associated with taking oral PrEP medications. This may include suggestions for coping with side effects such as nausea or headaches, recommendations for discrete pill taking and for remembering their dose schedules, and strategies for educating and informing family and social network members about their use of PrEP. Involving partners and significant others in pre-PREP counseling and encouraging and training them to provide ongoing support to PrEP users can potentially improve adherence and clinical outcomes associated with PrEP, as has been observed in couples-focused interventions for ARV adherence among people living with AIDS [18, 13].

There are two other probable risks associated with large-scale implementation of PrEP for which we did not observe strong support in our data, but have been commented on elsewhere [17, 19]. Risk compensation—which refers to a tendency for people to increase health risk behavior if they assume they are less susceptible to illness—may be a hazard associated with PrEP scale-up. Four reasons may explain why few participants described increasing sexual risk behavior following enrollment. First, because the study was described as a safety, acceptability and adherence study, participants might have self-censored their behavioral risks due to social desirability effects. Second, individualized risk-reduction counseling may have reduced risk reporting during follow up. Third, because drug efficacy data had not yet been published at the time the current data was collected, participants were not yet certain that PrEP would protect against HIV infection and, thus, may have felt compelled to maintain low-risk behavior. Fourth, because the study was relatively short, participants might not have had enough time to relax their perceptions of susceptibility and increase at-risk behaviors. An additional consequence that might occur in large-scale implementation of PrEP is the misuse of drugs and subversion of drugs to people who were not prescribed the medication. This phenomenon has been observed with regard to sharing of ARV medication [20, 21] and other prescribed drugs [22, 23]. The controlled nature and limited duration of our pilot study may not have permitted this from occurring.

There are several limitations to this study. First, participants were sampled from an existing cohort of participants who had received multiple sessions of HIV testing and risk reduction counseling, and might not reflect the experiences in research-naïve participants or other populations lacking exposure to clinical trial research and strong HIV prevention infrastructure. Second, due to the overarching goal of this study on assessing PrEP safety, acceptability and adherence, participants might have succumbed to self-presentational biases. Third, due to the nature of qualitative methods, we cannot provide corroborating clinical data on the severity and duration of reported side effects. Fourth, the qualitative nature of the data limits the ability to generalize across similar populations and did not permit inferences about causality or temporal sequence. Fifth, due to the brief duration of the trial, we lack insight into experiences associated with long-term use of PrEP.

Conclusions

PrEP represents a core component in the future of HIV prevention. Our study of the experience of PrEP users provides support for the acceptability of PrEP in at-risk populations, however highlights a number of factors that might impede adherence and potential scale-up. Because social context and individual-level factors can substantially determine adherence and therefore drug effectiveness, PrEP cannot be considered a purely biomedical intervention. PrEP interventions must consider the synergies between the drug, the individual user's behavior, the societal context, adherence, and social harms as a result of taking PrEP outside the research setting. Behavioral and social interventions that address the contextual realities of PrEP users will be fundamental in building effective and sustainable programs and policies for wide PrEP implementation.

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Conflict of Interest Authors have no conflicts of interest.

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