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Participant Experiences and Facilitators and Barriers to Pill Use Among Men Who Have Sex with Men in the iPrEx Pre-Exposure Prophylaxis Trial in San Francisco

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Abstract

In 2010, the iPrEx study demonstrated efficacy of daily emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) pre-exposure prophylaxis (PrEP) in reducing HIV acquisition among men who have sex with men. Adherence to study product was critical for PrEP efficacy, and varied considerably, with FTC/TDF detection rates highest in the United States. We conducted a qualitative study to gain insights into the experiences of iPrEx participants in San Francisco (SF) where there was high confirmed adherence, to understand individual and contextual factors influencing study product use in this community. In 2009 and 2011, we conducted focus groups and in-depth interviews in 36 and 16 SF iPrEx participants, respectively. Qualitative analyses indicate that participants joined the study out of altruism. They had a clear understanding of study product use, and pill taking was facilitated by establishing or building on an existing routine. Participants valued healthcare provided by the study and relationships with staff, whom they perceived as nonjudgmental, and found client-centered counseling to be an important part of the PrEP package. This facilitated pill taking and accurate reporting of missed doses. Adherence barriers included changes in routine, side effects/intercurrent illnesses, and stress. Future PrEP adherence interventions should leverage existing routines and establish client-centered relationships/environments to support pill taking and promote accurate reporting.

Introduction

HIV pre-exposure prophylaxis (PrEP), the use of antiretroviral medicines by uninfected individuals during periods of HIV risk, is a promising prevention strategy. Several clinical trials have demonstrated efficacy in at-risk populations, including men who have sex with men (MSM),[1] HIV-serodiscordant couples[2] and heterosexuals in Africa,[3] and injection drug users in Asia.[4] The United States Food and Drug Administration recently approved once-daily emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for the prevention of sexually acquired HIV,[5] and demonstration projects are underway to evaluate PrEP implementation.[6]

Adherence to study product is critical for PrEP efficacy.[6–9] Although the iPrEx trial demonstrated a 42% reduction in HIV acquisition among MSM provided daily oral FTC/TDF overall, greater protection (>90%) was estimated for participants with detectable drug in blood.[10] Partners PrEP demonstrated high FTC/TDF PrEP efficacy (67–75%)[11] and high rates of drug detection in heterosexual HIV-serodiscordant couples in Africa.[12] In contrast, drug detection was low in the Preexposure Prophylaxis Trial for HIV Prevention among African Women (FEM-PrEP) and Vaginal and Oral Interventions to Control the Epidemic (VOICE) studies, which were unable to show efficacy of either daily oral or topical PrEP, because of low study product adherence.[13,14]

The divergent results of PrEP trials across different populations highlight the importance of understanding individual and contextual factors that influence study product use and by extension, may affect open-label PrEP adherence. Factors

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affecting adherence may vary by social, geographical, and cultural context.[15] In iPrEx, drug detection varied significantly by geographic region: >90% in the United States (US), compared with <50% for the study overall.[16,17] The San Francisco (SF) site, where drug detection and reported adherence exceeded 90%, is an important population to analyze, given the high levels of confirmed adherence. We conducted a qualitative study among SF iPrEx participants to better understand the individual and contextual factors influencing study participation and product use.

Methods

iPrEx

iPrEx, a phase III, double-blind, randomized, placebo-controlled trial of daily oral FTC/TDF PrEP, enrolled 2499 MSM in Peru, Ecuador, Brazil, Thailand, South Africa, and the United States. Eligibility criteria have been previously described by Grant et al.[1] Participants received comprehensive HIV prevention services: HIV testing, risk-reduction counseling, condoms, and testing and treatment of sexually transmitted infections (STIs). Sexual practices and adherence were assessed by Computer Assisted Self-Interview (CASI) and interviewer-administered questionnaires, and refill and product return based adherence was also calculated. Enrollment began in SF in June 2008 and completed in December 2009; Next Step Counseling and Neutral Assessment (NSC/NA), a client-centered pill-taking support model, was implemented in January 2010, and participants were followed on study medication through August 2010. Study results were released in November 2010.

Participant sampling

Qualitative study participants were recruited from the 140 total HIV-negative MSM who enrolled at the SF Department of Public Health (SFDPH) iPrEx site. No participants who were approached refused qualitative study participation; rather, if the participant was offered participation but was ultimately not interviewed, it was because of nonresponse to attempts to contact or not being able to commit to the time slots offered. We conducted five focus groups (FG) and 16 in-depth interviews (IDI) over two time periods: during the trial (November–December 2009) and after study results had been announced (January 2011). In the first phase, participants were stratified by length of study participation (1–6, 6–12, ≥12 months) to capture a range of study participation and pill-taking experiences, then randomly selected for an IDI or one of three FG. Both FG and IDI were employed to collect complementary qualitative data; FG captured information on social norms around study participation and pill-taking, whereas IDI elicited detailed individual experiences regarding facilitators/barriers to pill-use. In the second phase, participants were randomly selected for one of two FG to capture participant perspectives after learning study results. Because the two rounds of interviews took place at different times, under different contexts – before and after study results were published and the efficacy of PrEP was known, and >1 year apart – participants who contributed in the first round were not excluded from the second.

Data collection

Both FG and IDI used an institutional review board (IRB)-approved semistructured interview guide consisting of open-ended questions designed to elicit information on study experiences and factors influencing adherence. Topics explored in the first round of interviews included (1) knowledge about the study product, (2) motivations for and experiences with study participation, (3) facilitators and barriers to pill taking, (4) pill-taking experiences and strategies, and (5) accuracy of self-reported adherence. Topics explored in the second round of interviews included (1) assessment of study-provided adherence support, (2) reflections on possible reasons for non-adherence in the study population, and (3) knowledge of iPrEx results. Written informed consent was obtained prior to data collection.

Data analysis

The FG and IDI were conducted off-site by researchers unaffiliated with iPrEx or SFDPH. The researchers conferred immediately following the FG and IDI to discuss emergent themes and identify areas requiring further investigation in the next iteration of interviews. Thus, the analytic process was initiated as soon as data collection began. The researchers refined the information collected during each subsequent interview to achieve a level of theoretical saturation.[18] Data were digitally recorded and transcribed verbatim. Researchers conducted a deductive analysis guided by the *a priori* domains of the interview guide. Inductive codes were captured when appropriate. The primary analyst coded the data; the secondary analyst reviewed the coded transcripts to verify application of *a priori* domains. Discrepancies between the analysts were resolved during analysis meetings. Researchers used Atlas.ti software to facilitate data management and organization. Using the coded transcripts, the researchers generated detailed summaries based on the original domains; these were compared and contrasted to build a set of descriptive themes.[19] Finally, the primary authors compared themes emerging from full transcripts of selected interviews with those that were identified from the coding of discrete segments of discourse in the previous steps to ensure consistency (e.g., analytic holism).[20]

Results

Fifty-two SFDPH iPrEx participants were interviewed in FG (36) or IDI (16), with 11 participating in both interview phases. Median age was 43 years (range, 22–66). The majority (66%) were white, 12% were African American, 15% were Latino/Hispanic, and 7% were Asian. Based on screening from the main iPrEx study, 48% reported unprotected receptive anal sex in the past 12 weeks. Demographic and risk characteristics of qualitative study participants were similar to the overall SF cohort (data not shown).

In order to better understand the high rates of product use in the SF cohort, we sought to identify and characterize participant experiences that produced environments that supported pill taking. We examined "adherence stories" to identify how men incorporated pill taking into their daily lives or structured their daily lives around pill taking. Factors affecting pill use fell into five categories: (1) motivations for study participation, (2) knowledge about study product, (3) experiences and skill sets established prior to enrollment, (4) experiences of daily life outside the study, and (5) experiences with study-related activities, including interactions with study staff.

Motivations for participation

Most participants joined the study altruistically, citing a desire to "give back" to the community; many discussed being touched by AIDS-related deaths of friends or family. Monitoring one's health was another motivation to join. The monetary stipend was an incentive, but not the primary motivation for participation.

> … We're here 'cause we seriously want to try to find something which is gonna work for people. We're not there only just for the money. That's nice. But there's a serious aspect to it as well. (FG-2011-02)

> We're very supportive of the gay community, we want to do our part. You know, obviously, we're not wealthy people, so we do what we can as far as donating our time and our talents and in this case, our bodies for the gay community. (Interview participant 8, age 41, white, visit week 44)

Participants felt a deep commitment to taking the pill as an important part of their study participation. Essentially, men equated participation *with* pill-taking. When told about adherence patterns at other sites, SF participants were incredulous that someone might participate in the study, but not take the study pill.

> I: … what are your thoughts on people who just- who participate in the research but don't take the study pill at all…?
> P: I think that defeats the purpose of being in the study.
> I: Defeats the purpose of being in the study? Okay.
> P: I just find that bizarre that anybody did that. (FG-2011-01)

Knowledge about study product

Participants felt well informed about how to use the study pill, what to do in the event of a missed dose, and how to mitigate potential side effects. If they had difficulty, they proactively sought advice and changed pill-taking behaviors as needed.

> They are very good about telling you…[the] side effects, so you will be fully aware that this might happen. (FG-2009-01)

> So I called my clinician and he said to start taking it at night and in 48 hours I was not as much as [sic] in pain.… (FG-2009-02)

Experiences and skill sets established prior to enrollment

We identified two kinds of experiences and skills that were antecedent to participation that appeared to contribute substantially to pill taking: having a history of daily pill taking and a predictable or routinized daily schedule.

Pre-study experiences with pill-taking. Approximately half of participants reported taking vitamins or daily medications. Prescription drugs, including those for heart conditions, blood pressure, or psychological disorders, were more consistently remembered than vitamins or supplements. Men with pre-existing pill-taking regimens found adding the study pill almost effortless.

> I don't miss my anti-depressant so it was just a simple practice…I would take Truvada and would take my Lexapro. So that was very easy. (Interview participant 2, age 44, African American, visit week 60)

Being a "person of routine". Having a routine helped men build the study pill into their lives. One participant described piling up the pills he takes every morning. As a "disciplined" person, he reportedly "never misses breakfast," and therefore rarely missed the study pill.

> It's literally a pile of 7 pills…I'm a fairly organized, disciplined, on-top-of-it kind of guy…I missed one or two the first month because I had my pile…but I wasn't in the habit of opening up the Truvada bottle yet…now it's a habit to have that in the pile. (Interview participant 7, age 48, white, visit week 8)

Outside barriers presented by daily life

Adherence barriers were both predictable and unpredictable. Participants described anticipated and avoidable adherence challenges (e.g., travel), versus unanticipated challenges (e.g., stress, change in mental health status/job/housing) more difficult to address. Many participants reported changes in routine, including a hectic schedule, or not sleeping at home, as reasons why they might miss a pill.

> The only challenge is if I'm going over to a friend's house to stay over for more than a day or going on a vacation where you kinda have to do some planning. (Interview participant 11, age 43, white, visit week 52)

> … the times that I've forgotten it it's just been fatigue, too busy, too crazy, and by the time I go to bed it's just kinda like 'Oh'. (Interview participant 8, age 40, white, visit week 40)

Some participants reported intentionally missing pills because of illnesses, surgeries, or to test whether the pills were associated with side effects. In these cases, all reported discussing these decisions with study staff. Some participants did not disclose their study participation to social or familial networks. Reasons behind this were myriad, including the observation of low levels of PrEP knowledge in the community.

> P: We have a very low profile.
> I: Low profile?
> P: Unless I happen to talk to a friend, I never hear about it at all or discuss it with anybody. I don't usually talk about it because, not an embarrassment, but there isn't much to say. (FG-2009-01)

Finally, a few African American and Latino participants reported stigma associated with the study pills, and described strategies to avoid being seen with them.

> …I take [the pill] in private 'cause I have friends that's HIV-negative and homophobic or positive-phobic and I know who those friends are so I just be real particular where I take my pills at. (Interview participant 6, age 41, African American, visit week 52)

Experiences with study-related activities and staff

Participants described staff as personable and nonjudgmental, and appreciated study benefits, including regular HIV testing and health monitoring. Participants expressed appreciation for relationships developed with counselors.

> I think just having the human contact once a month of just having a counselor…and just sort of check in and think about behaviors and things like that. I think that had a really good impact. (FG-2011-01)

> I had such a good relationship with the nurse practitioners down there…I trusted them as much as I trusted my own doctor. (FG-2011-01)

Reflections on behavior change and newfound abilities to negotiate safer sex strategies modeled in counseling sessions were common. Participants had clear recommendations for real-world PrEP implementation, including an almost unanimous opinion that counseling—both risk-reduction and adherence—will be an important part of the PrEP package.

> I actually have changed the way I have sex to a certain extent in recent months and I think after about the fifteenth reiteration of something [counselor's name] said- what he kept saying to me finally got through. (FG-2011-02)

> Yes I do believe the counseling is extremely important…You know I saw the behavior changes in myself. (FG-2011-02)

Staff worked with participants to identify and strategize around potential adherence challenges, and provided tools to facilitate pill-taking, including pillboxes and key chains. Participants' reactions to these tools were mixed. Some described them as making a difference in their adherence. Some used reminder strategies such as setting alarms on their phones; one participant downloaded a pill reminder application to his smart phone. Other participants reported adapting the pill to their mobile lifestyle by "stashing" pills in various locales (e.g., home, backpack, car, partner's house) to make sure they were accessible when needed.

Discourse suggested that some men reportedly developed routine to their daily activities, which had been previously more disorganized, in order to promote pill taking. Once a routine was established, many participants "easily" incorporated the study pill into their lives and reported rarely missing pills. One man describes how he built his routine.

> Once I started a routine, I never miss none…in the beginning I did different methods. I would put it in the little pill box and put it in my book bag and sometimes I'd forget.…I have some friends who's HIV positive that take 4 or 5 pills a day…so I asked them how they managed and they gave me tips on taking medication…I brush my teeth every morning, so I take mines before I brush my teeth, that way I know I took 'em. (Interview participant 6, age 41, African American, visit week 52)

A few participants reported some initial discomfort disclosing missed pills to staff in the first few months of participation. These discussions included mention of coming to realize that missed pills would not affect their participation and with positive rapport with staff, concerns with disclosing episodic missed pills were alleviated. Most participants reported recognition of the importance of accurately reporting pill taking and sexual activities to staff, in order to ensure quality scientific data.

> Oh no, I mention everything…by being in this study, it's not going to help them, they need empirical data and they're trusting us to be forthright and so all I can do is be forthright and um, I'm not gonna lie to myself, not going to lie to them. They need the data so, no, I'm totally 100% honest with them. (Interview participant 2, age 44, African American, visit week 60)

Discussion

This qualitative study identified factors that influenced pill use and adherence reporting among HIV-uninfected MSM at-risk for HIV acquisition in a PrEP efficacy trial in the US. Facilitators to pill taking included having clear motivation to take the pill to help answer an important scientific question; accurate information about the study pill; skills for pill-taking, either antecedent to or developed while in the study, including establishing a routine; and strong positive relationships with the study team and engaging in the counseling they offered. Barriers included changes in routine; side effects or intercurrent illnesses; stress; and rarely, stigma. These findings are generally consistent with several of the facilitators and barriers to, and strategies for adherence found in the literature on HIV treatment and other PrEP regimens.[21–27]

Unique to participating in a blinded PrEP trial, participants clearly reported commitment to the study and the scientific question as motivators to take the study pills, linking agreement to participate in the study directly to agreement to take the study product daily. US MSM have been at the forefront of HIV/AIDS research and activism since the beginning of the epidemic.[28] MSM of a certain age, in fact the age of many participants in our cohort in SF, lived through the height of the AIDS crisis. These early experiences of witnessing the intense suffering, physical and social-emotional, brought on by the HIV/AIDS epidemic, heavily influenced their motivation to participate in science, as noted in discourse here. The appeal of altruism noted in this discourse is substantiated by other qualitative work on PrEP acceptability.[29]

Participants were also motivated to participate in study activities and take the pill by the additional benefits they received, including regular health monitoring and monthly counseling with staff. Participants described relationships with staff as "essential," and several commented that the study provided "the best" healthcare they had received. These findings are consistent with qualitative data from iPrEx participants in Chiang Mai, Thailand, which found that the provision of quality healthcare and support from research staff supported PrEP adherence.[25] The importance of patient-centered care in engagement, retention, and adherence has been described in treatment settings.[30,31] Previous studies have shown that healthy MSM access healthcare less than the general male population.[32,33] Our study suggests that accessing PrEP may be a gateway for MSM to engage in regular HIV/STI testing, health monitoring, and other preventive services. The client-centered care that participants received also encouraged honest reporting of missed pills at the SF site. Although there have been discrepancies between self-reported adherence and drug detection in iPrEx overall, we observed high concordance between these measures in US iPrEx participants: 93% participants in the US reported taking doses on $\geq 50\%$ of days between visits, and concordance with drug detection was 97% in these individuals.[34]

Our data fit the information, motivation, behavioral skills (IMB) model of adherence to antiretroviral therapy,[35] which has been adapted to characterize factors associated with PrEP adherence.[36] In iPrEx, client-centered Next-Step Counseling and Neutral Assessment (NSC/NA), which builds on applying the IMB model to PrEP, was largely well-received. NSC/NA de-links adherence assessment from promotion, aiming to create safe, separate spaces for disclosure of missed pills and exploration of pill-taking strategies. Counselors explore with participants, using open-ended questions, facilitators and barriers to pill taking, tailoring each discussion to help the participant identify specific adherence needs. The counselor and participant subsequently arrive at attainable strategies for the participant to continue to take the pill, which may be as simple as returning for the next visit, and the

session ends with an agreement from the participant to try or continue the selected strategy.[36] The success of this approach highlights the importance of tailoring adherence-promotion strategies to the individual.

Current findings may be unique to our sample. Motivations for participating in a clinical trial may be different than for taking PrEP in the real world. SF has a long history of HIV-prevention trials, including HIV vaccine, herpes suppression, and pre- and post-exposure prophylaxis (PEP) studies.[37–40] Many participants joined the study to contribute to their community and HIV prevention science. Commitment to these aims motivated them to take a daily pill, knowing it could be a placebo, in the hopes of finding a new, effective prevention strategy. This motivation is quite different from motivation to take part in a clinical trial for HIV prevention in other parts of the world; for example, in the Andean region, where three iPrEx sites were located, participants identified socialization, information, and study incentives as key motivations to participate.[27] "Research literacy," defined as the cognitive and social understanding of the basic purpose, process, and value of research and research participation,[41] may also be lower in other parts of the world, compared with SF, where MSM have been "donating their bodies" since the beginning of the epidemic.[38–40] The importance of research literacy to willingness to participate in clinical trials, as well as adherence to study procedures, is a topic of interest recently.[41,42] We believe that the altruistic motivations of our participants, coupled with greater research literacy in the community, likely contributed to high adherence rates in the SF cohort. Future PrEP trials and demonstration projects should continue to evaluate participants' motivations for joining these studies and taking study products, and ensure that participants understand research goals, particularly as alternative therapies with unknown safety or efficacy are explored.

The US has anecdotally been called a "pill-popping" culture; according to a 2004 World Health Organization (WHO) report on "The World Medicine Situation," the US market share of global pharmaceutical sales was >52% in the year 2000, and high-income countries together consume >90% of the world's medicines, despite having only 15% of the world's population.[43] Individuals in the US may have more comfort and experience with taking a daily medication. Liu et al.[44] found regular medication use to be common among MSM: >50% of men participating in a national Internet survey reported currently taking medication, 90% of those daily. Many participants in this qualitative study disclosed taking medications for other health issues. The remembering and use of these medications also triggered participants to remember to take their PrEP pills. The importance of a routine to encourage consistent pill taking identified here has been described extensively.[21–27] Discourse here suggested that once participants established a routine, they could anticipate changes in routine with support from staff, and generate strategies (pillbox, phone alarm) to continue pill taking during these times. Future interventions should build on existing routines; individuals who do not have previous pill-taking experience or routines may need additional support.

Ware et al.[26] found that social support through partners and family was a key facilitator to pill taking in Partners PrEP. Some of our participants reported *not* disclosing study participation and pill taking; therefore, social support around pill taking was limited. Participants reported low levels of knowledge and discussion about PrEP in the community, which may have hindered their ability to speak to others about their PrEP use; this observation is consistent with others made at the time, regarding community knowledge of PrEP.[45–47] A few participants reported concerns about being seen with pills that may be associated with HIV, although stigma seems to be a much greater barrier to adherence in other studies and at other sites.[25,27,48] Future strategies to support MSM in discussing their participation in PrEP studies/implementation programs and their overall pill taking could include peer support interventions.[49] These interventions may include novel technology-based support strategies including SMS support groups,[50] or social media networking groups.[51]

Limitations

This research is subject to limitations. First, experiences described are of a confined geographic area, SF, which has a wealth of community health resources, including a network of publicly funded clinics and Healthy San Francisco, a program for the uninsured that guarantees universal access to health services. Therefore, findings may not generalize to areas with more limited community and health-related resources. Second, these data were collected in the setting of a double-blind randomized trial and may not be generalizable to real-world contexts. However, the similarity of many of these findings to factors influencing adherence to other treatment and prevention regimens suggest their relevance.[21–27,52] We combined data from FG with those from IDI; combining these units of analysis may have resulted in both over- and under-reporting of qualitative themes, as well as an increase in socially desirable responses. Finally, only a proportion of study volunteers in SF were interviewed, who may not be representative of the entire cohort. Because interviews were conducted outside scheduled study procedures, the views presented may over-represent those motivated to invest effort in completing additional procedures.

Conclusions

PrEP adherence in this population may be understood as a function of multiple factors, both antecedent and subsequent to PrEP initiation. Our findings guide the development of adherence-promotion strategies and recommend they (1) provide comprehensive education regarding regimen and potential side effects prior to PrEP initiation, (2) encourage personal motivations for pill-taking while also developing support structures for PrEP within the community, (3) build on existing pill-taking routines, (4) establish client-centered participant–provider relationships, and (5) create a nonjudgmental environment in which missed doses may be accurately reported. Adherence has been described as the "Achilles heel" of PrEP;[26] optimizing adherence will be critical to maximizing the public health impact of PrEP implementation.

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Author Disclosure Statement

No competing financial interests exist.

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