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ORIGINAL PAPER

Point-of-Care Test for Assessing Tenofovir Adherence: Feasibility and Recommendations from Women in an Oral PrEP Program in Kenya and Their Healthcare Providers

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Abstract

Oral pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention modality when taken as recommended. Women in sub-Saharan Africa may have adherence challenges that remain undisclosed to providers. Real-time measures that identify non-adherence can allow for immediate exploration of adherence challenges, counseling and interventions. We conducted a formative qualitative study in Kenya to explore oral PrEP experiences and reactions to a point-of-care urine test (UT) identifying recent (past 4 days) non-adherence to tenofovir-based PrEP among female PrEP users (25 in-depth interviews; 4 focus groups) and health care provider (10 key informant interviews). Findings indicate that use of the UT would be highly feasible in the context of regular PrEP care, largely acceptable to clients and providers, and could improve adherence. Clients emphasized the need for transparent client-centered strategies in delivering results. This formative study informs the development of tools to implement this point-of-care UT in future interventional studies and clinical settings.

Keywords Adherence · Measurement · Urine test · PrEP · TDF/FTC

Introduction

Oral pre-exposure prophylaxis (PrEP) is an effective HIV prevention strategy for those who adhere to dosing requirements during periods of HIV exposure [1, 2]. Guidelines for women using oral PrEP in the form of tenofovir disoproxil fumarate (TDF)/emtricitabine (TDF/FTC) includes daily dosing with TDF/FTC [3, 4]. The lower than expected levels of adherence to oral PrEP reported in clinical trials and in some open label demonstration projects among women, especially those not in serodiscordant relationships, in sub-Saharan Africa [5] has generated concern about (a) the validity of self-reported adherence; [6–8] and (b) the assumption that receiving PrEP equates to 'prevention effective' [9] use of the medication [10]. Indeed, emerging evidence reveals that clients engage in PrEP programs or services for a myriad of reasons that might deter them from disclosing PrEP non-use or poor adherence to providers [10–13]. Over-estimates of medication adherence to care providers or research team members is not unique to PrEP [14], and is not necessarily intentional; many factors may contribute to over-estimation that warrant careful examination [15–17]. Alternatives to self-reported adherence include objective pharmacologic measures of PrEP adherence [18] which have proliferated for use in clinical trials or well-resourced implementation programs and offer valid assessments of drug exposure, critical to estimating efficacy.

Objective pharmacologic measures of adherence use plasma, dried blood spots, or hair as biomatrices in which to determine PrEP drug concentrations [18]. Specimens are typically shipped to highly-specialized laboratories that can

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conduct liquid chromatography/tandem mass spectrometry (LC–MS/MS) for the analysis of tenofovir (TFV), FTC or their metabolites. Expense is a limitation in wide-spread use of these measures outside of clinical trials. The time-lag between sample collection and test results can also create practical challenges in the use of test results as a clinical tool for promoting candid real-time conversations about adherence. Such challenges include having to contact people to deliver test results after the study or clinic visit, coordinate follow-up intervention approaches if results indicate non-adherence, and implementing interventions that map onto past non-adherence and past barriers that may not characterize current adherence-related challenges. Moreover, phlebotomy for blood collection can be considered invasive.

Point of care measures of drug exposure using urine as the biomatrix to determine recent (past 3 days) PrEP dosing are amassing considerable support as an inexpensive clinical tool that could identify individuals in real time who may benefit from an adherence-focused discussion or intervention [19]. Barriers of cost and the time-lag can be bypassed with such a tool. The lateral flow immunoassay urine test, packaged much like a home-pregnancy dip stick with display of presence or absence of at least 1500 ng/mL of TFV, is a point of care tool that can objectively and accurately determine recent (past 3 days) exposure to TFV [20–22]. The urine test is implemented at point of care with near immediate results and has been validated for detection of tenofovir levels in healthy volunteers receiving directly observed TDF/FTC, with high specificity (99%) and sensitivity (94%) compared to the gold-standard of LC–MS/MS [22].

Although urine tests for assessing oral PrEP adherence have received some support for use among men who have sex with men (MSM) in the US [23], acceptability, attitudes towards, and concerns about the incorporation of point-of-care urine tests into PrEP programs serving women in sub-Saharan Africa has yet to be explored. Because monitoring oral PrEP use through a point-of-care urine-based test may facilitate open conversations about and counseling/interventions focused on adherence [19], it is critical to develop best practices for both the delivery and use of results in a way that promotes adherence in a supportive and non-judgmental manner. Gaining community consultation and guidance on use of this technology is an important step to create a comprehensive implementation tool-kit to accompany the point-of-care urine test. To address this, we conducted semi-structured in-depth interviews (IDIs) and focus group discussions (FGDs) with women engaged in PrEP and key informant interviews (KIIs) with providers at the PrEP program in Thika, Kenya.

Methods

Setting

The Point of Care Urine Monitoring for Adherence (PUMA) formative study took place at the Kenya Medical Research Institute–Centre for Clinical Research (KEMRI–CCR-PHRD) site in Thika; a peri-urban area of central Kenya approximately 45 km north of Nairobi.

Procedures for IDIs and FGDs

Women participating in the oral PrEP provision program at KEMRI-CCR-PHRD Thika site were recruited to take part in this qualitative study. All women were receiving oral daily PrEP at the site's comprehensive care center. Inclusion criteria included being female, over 18 years old, and not in a serodiscordant relationship by self-report, as well as being prescribed PrEP for at least one month and willing and able to give informed consent. Per protocol, women in the PrEP program who were in known serodiscordant relationships were ineligible to participate due to an interest in assessing adherence barriers among women not in serodiscordant couples. Women were asked by clinic staff about interest in participating in the study. Interested women were contacted by a study team member. Eligible women were scheduled for an in-depth interview or for participation in a focus group discussion. Upon arrival to the scheduled study activity, staff explained the process, reviewed the written consent material and documented consent for participation, all using the participant's language of choice. After consent, basic demographics were collected and the interview or focus group commenced. Discussions were audio recorded and conducted in their preferred language including English, Kiswahili or Kikuyu. Importantly, all participants were informed that the information they shared would not be provided to their care team, to encourage more candid discussions.

Interviews and focus groups took place in a private location at the clinic site. Recordings were transcribed and translated to English for coding. Transcriptions and translations were checked for accuracy by the study team. All transcripts were de-identified prior to coding.

KIIs

We conducted KIIs with health care providers from the Thika clinic. All clinic team members who would be seeing clients in a typical visit were approached for interest in participation, including clinicians providing medical care (medical doctors or clinical officers) and counselors (adherence counselors in the pharmacy or in the clinic).

Recruiters contacted providers to assess their interest in participating in the study and scheduled a time to conduct the intervention in a private location at the clinic. All KII participants provided written consent to participate, and their interviews were audio-recorded and transcribed. All transcripts were de-identified before coding.

Data collection

All interviews and groups with women in the PrEP program were conducted by the same two trained, experienced qualitative interviewers who were not part of providing PrEP care to women in the PrEP program. Interviews and focus groups followed a similar semi-structured guide to ensure consistency across all interviews [supplemental appendix A]. Discussions began with general exploration of the context in which women initiated PrEP services and related experiences with PrEP services at the site, adherence barriers and facilitators, level and type of support for adherence provided at site, and candidness and comfort in reporting non-adherence. Participants were then shown the point of care urine test, with an explanation of its use and results display. After answering any questions participants may have had about the test, interviews and focus groups focused the discussion on reactions to the test and its potential implementation at the clinic for women receiving PrEP. Women were asked about their general thoughts, likes and dislikes about the test, levels of interest, thoughts about its utility (could it help or not help women with adherence) and potential impact on PrEP adherence or persistence, the anticipated manner in which PrEP providers or clinic staff may use the results, potential influences on patient-provider relationships, feasibility of adding the test to a standard PrEP service visit, and recommendations in terms of additional training that should be provided to staff or clinicians using the test. Interviewers could probe as needed to explore any of these areas further with participants.

General procedures for the KIIs were similar to the IDIs, with the same two interviewers implementing a semi-structured KII discussion guide that asked providers about their role in the PrEP program, the existing tools they use to monitor adherence and their perception of PrEP adherence among their clients. Interviewers demonstrated the urine test and elicited providers' perceptions of the test, the acceptability and utility of monitoring PrEP adherence in real-time during the clinic visit, and how monitoring results would influence the PrEP care experience, including patient provider relationships. In addition to these questions, providers were asked how they would use this tool in their own practice, and the training required to do this.

Analyses

The qualitative coding team consisted of six team members (AL, KN, KRA, MP, NT, PC) from multiple institutions, with diverse backgrounds in PrEP-related research and implementation and qualitative methods. A modified framework analysis approach [24] was used on the IDIs and KIIs to first sort excerpts into initial frames reflecting the question posed by the interviewer. Several questions that co-occurred and highlighted the same concept were consolidated into a single frame. A total of 25 frames were used to sort extracted discourse from the semi-structured interview guide. This initial coding was conducted predominantly by one coder with a subset of transcripts double coded to confirm accurate application of the initial framework, with 100% agreement between four coders reached in discussion of this subset. Frames were then examined for main emergent themes within each frame separately. Content that was similar across participants (e.g., mentioned by two or more) or that was uncommon but offered unique insights was flagged for inclusion as a theme. A minimum of 20% of the interviews then went through double coding. Consistent application of thematic codes was supported through these reviews, as well as weekly meetings amongst coders, frequent discussions and iterative updating of the codebook. Discrepancies were recorded and resolved through discussion. Emergent themes across frames were then considered to identify cross-cutting themes. This process was similarly applied to KII transcripts.

For focus group transcripts, excerpts were thematically analyzed with an inductive/deductive approach using the emergent themes from the individual interviews and adding new themes as needed to accurately reflect focus group content. Double coding of excerpts from focus groups was done with coders reviewing and updating descriptions. Concordance was based on earlier double coding using the same codebook in the in-depth interviews.

The identified main themes specific to the UT from the three data sources were then consolidated and synthesized through discussion by the qualitative team. Themes are presented below with example quotes and data source(s) noted.

Ethics Approval

Institutional Review Board approval for this work was granted from the Kenya Medical Research Institute–Scientific Ethical Research Unit (KEMRI-SERU) and the University of California, San Francisco (UCSF). All participants provided individual written consent.

Results

Sample

A total of 25 semi-structured IDIs and 4 focus group discussions (FGD) were conducted between May 2019 and December 2019. Women were on average 29 years of age, with 48% aged 24 years or younger. Most had one or more child (80%) and 36% were married at the time of the interview. For focus groups, the average age for the 26 participants was 23 years, with 81% at or below the age of 24. Few (4 women, 15%) of the focus group participants were married at the time of the group discussion. KIIs were conducted with 10 staff: 7 clinicians providing medical care (medical doctors and clinical officers) and 3 counselors providing medication adherence and HIV test counseling on site at pharmacy or in clinic. KII participants had an average of 4.5 years of experience providing PrEP services and 8 were female.

Themes

Data from the in-depth interviews with women participating in a PrEP program are presented first (Table 1) to characterize the overall context in which women negotiated PrEP and reporting of adherence and non-adherence. Table 2 focuses on discourse from all data sources specific to the urine test (UT), which generally mapped into areas of physical characteristics of the UT, procedures for use of UT as part of PrEP programs and PrEP care, and recommendations for delivery of results to PrEP program participants, all providing themes for consideration in use of the UT point of care tool. Themes generally shared between data from clients and providers were common, however differences in nuance or emphasis are noted and unique themes that emerged only with clients or only with providers are identified as such in Tables 1 and 2.

Context of PrEP Use

As noted in Table 1, several themes emerged in the areas of PrEP education and information provision, feelings towards PrEP, difficulties in taking PrEP, and comfort in disclosure of non-adherence. When asked about experiences at the clinic with PrEP education and support, women receiving PrEP noted feeling well educated around safety and efficacy of PrEP, although there was some variability in recall of time to protection with some estimating only a week of dosing to reach protective levels. Consistent with provider discussions emphasizing education and information sharing, women noted being well-informed about potential side-effects of PrEP and the time-limited nature of start-up syndromes. Several women recalled being told to take PrEP with food and almost all interview participants recalled being told to take PrEP daily. Although uncommon, some (two women) recalled only being instructed to take PrEP daily without further explanation. Providers indicated a consistent combining of efficacy information with adherence requirements needed to achieve high levels of efficacy.

Reflecting on difficulties with PrEP dosing, women focused on side-effects, lack of support from partners, and the general burden of taking medication each day. Most women noted positive feelings towards being on PrEP, mentioning known risk for exposure because of partner(s) living with HIV and when they or their partners have multiple sex partners. Providers echoed the barriers to adherence cited by participants and also expressed that PrEP adherence was more common among discordant couples and women who "understood their risk."

Finally, in terms of experiences with PrEP adherence and related discussions with providers, some women suggested that non-adherence is generally not disclosed because of feelings of guilt or shame over failing to 'honor' their agreement to take PrEP daily, fear of negative treatment, and concern about being discontinued. Other women shared that all women using PrEP should report non-adherence to providers as an important way to get support. Importantly, most of this discourse tended to be phrased in the third person rather than referring to one's own personal beliefs or experiences. Several of the challenges to reporting non-adherence such as fear of negative treatment were also reflected in the provider KIIs. Strategies staff noted in KIIs as standard parts of the PrEP program are also presented in Table 1. The PrEP program used electronic dose monitoring for some participants which produced a dosing graph that could be reviewed with PrEP users during follow-up visits. This, and other straightforward strategies like setting an alarm and matching dosing to regularly occurring events (e.g. meals, brushing teeth), were noted as part of adherence counseling.

Feasibility, Likability and Cautions for Urine Test Implementation

Most KII, IDI and FGD participants believed that implementing the UT as part of PrEP care would be generally feasible in terms of ease of use. Women participants in the PrEP program further suggested that, in comparison to tests involving blood, urine was more feasible, and potentially more acceptable, to collect because it is discarded (not used) by one's body whereas tests using blood have been associated with fear and concern about blood loss, proper use and disposal. Time requirements to conduct the test and deliver results was noted as a potential burden for some women, but providers suggested that there was enough time to conduct the test and discuss the results during appointments.

Table 1 Context: Women's reflections on experiences of receiving PrEP and interactions with PrEP program staff and clinicians

Theme[a]	Example quote
Education—PrEP Efficacy	*She told me that when you take this medicine it will protect you from getting HIV from someone who is already infected*—IDI 24 years old *We tell them that the only way PrEP has been shown to work is if it is taken daily and consistently. It gives you 98–99%…close to 100% protection*.—KII Clinician
Education—One-week to Efficacy	*…….I was told that for PrEP to work you have to take it for 7 consecutive days and then you go taking daily and if you skip it will not help*.—IDI 19 years old *At initiation, we tell women that they have to use protection the first 7 days or abstain from sex because after those 7 days we are sure that the drug levels have reached the surface area and can give protection*.— KII Clinician
Education—Advice about Side-effects and Start-up [IDI/FGD Only]	*They advise us and encourage us especially when we get side effects. They tell us that the side effects are only for a while*.—FGD with women > 25 years of age
Education—Food requirement	*He told me first thing in the morning before I take the medication I eat a heavy meal and that is what I did*.—IDI 34 years old *I tell them that they have to select a time whether morning or evening and to make sure they have food*. – KII Clinician
Education—Take daily	*You get protection even if you have sex with a HIV infected person but you have to take the pills every day*.—IDI 40 years old *For you to get protection you need to have sufficient drug in your body and you get that from taking the pills daily. We tell them that if they miss a pill, they should remember to take the other one at the right time to avoid huge gaps in your drug taking periods*.—KII Clinician
Education—Lack of information or education* [IDI/FGD Only]	*I wasn't told anything else besides taking the pills every day at the same time*. – IDI 20 years old
Education—Education and strategies provided as part of PrEP Program [Asked in KII Only]	Strategies to remember to take same time each day: *Counselling on setting a specific time to take the pill and associate that with an event like brushing your teeth or watching TV. Enlist support if your partner is taking ART then you can take your pills together*.—KII Medical Officer Take PrEP at the same time each day and how to choose that time: *Yes, we tell them to decide the time when they are sure they will be in a place where the PrEP is. Mostly like I told you before my cohort is school going, high school and college, so I tell them the preferred time is when they are in their hostels and their houses which is mostly in the evening or early morning. So they can be sure that they do not forget at that particular time so they can be at the point where the PrEP is*— KII Clinician *MEMSCAP and Wise pill as form of feedback on adherence: I think memscap is for us to know whether they have taken but the messages are still the same. When they came back you had graphs and you would show them how they are faring on; everyone wants to do well so hopefully that would improve adherence*.—KII Clinician
Experience with PrEP—Difficulties with side-effects	*For me it is difficult because…..but for the first week it was ok because I took for 7 days and I didn't feel weak but when I started my second week I couldn't do anything, I was just relaxing in bed. I was feeling dizzy and burning feeling and then I vomit (referring to acidity)*.—IDI 50 years old *Okay, at first they experience some challenges saying that when they come they report of side effects of PrEP that is the very first month someone would say that for two weeks he experienced nausea and fatigue*.—KII Clinician

Table 1 (continued)

Theme[a]	Example quote
Experience with PrEP—Lack of support from partners or important others [IDI/FGD Only]	*…for me it is a difficult thing because my boyfriend is not very understanding about such things; if he comes and finds such big pills that look like the ones for HIV, you will find yourself arguing about their use and explaining that they are not for treating HIV. But on the other hand their help to you is important making it slightly easier but (sighs) you are caught in between.*—FGD with women < 25 years of age
Experience with PrEP—General pill burden	*sometimes you tell yourself you would rather stay without a partner if having one means you have to take medicine all the time*—IDI 40 years old *For others it is hard to have to take a pill every day and have to remember*—KII Clinician
Desire for PrEP—Recognition of risk and value of protection [IDI/FGD Only]	*I thought it was important to protect myself because I don't know where my partners have been.* [With PrEP] *I know I am safe and I am not afraid.* – FGD with women > 25 years of age
Disclosure of non-adherence - Guilt over 'breaking agreement' [IDI/FGD Only]	[They] *may fear to tell the doctor because they had agreed to take the medicine as agreed* [to] *do… they fear telling the doctor they have tripped up. …* IDI 19 years old
Disclosure of non-adherence—Fear of negative treatment	*It depends with the provider because some are understanding but some are very rude and would shout at you … You just choose to keep quiet to avoid that.*—FGD with women > 25 years of age *…others if they missed the doses it is as if you are going to maybe tell them there is going to be a problem, that they are not taking their medication so they can feel uncomfortable to tell you about the missed doses so they cover up (don't tell you)*—KII Counselor *Some of them feel you want to judge them when you talk about PrEP adherence*—KII Medical Officer
Disclosure of non-adherence—Fear of discontinuation or removal from program [IDI/FGD Only]	*sometimes people fear saying they missed because they might not? be given more and told to start all over again*—FGD with women ≤ 25 years of age
Disclosure of non-adherence - An important part of care [IDI/FGD Only]	*…do not feel bad about telling the doctor about a missed dose. They will help you.*—FGD with women ≤ 25 years of age

*Infrequent in IDIs but noteworthy

[a]Themes specific to IDI and FGDs are noted as IDI/FGD Only; themes specific to KIIs are noted as KII Only. All other themes were present across women receiving PrEP (IDIs and FGDs) and providers of PrEP care (KIIs)

Likability for the UT from the perspective of women in the PrEP program was generally high for self, due to the potential for increasing motivation to adhere to PrEP, fostering accountability, establishing a shared reality in terms of adherence with providers, and general sense that it would be helpful. As indicated in Table 2, however, participants suggested that the test would be preferred by those who were adherent; Women and key informants believed that the UT would be liked by women who would get positive results (had dosed consistently) and disliked by those who did not use PrEP. Providers noted that their PrEP clients would value an objective measure that shows that PrEP is "working" to prevent infection. Nearly all providers noted that they valued the objectivity of the measure and they felt that knowing participant's adherence would allow them to better care for their clients. Relatedly, provider KII discussions suggested UT results would be used to facilitate adherence counseling via two mechanisms: (1) the objective nature of the test would allow providers to know the client's true adherence and enable them to engage in a dialogue with clients about the barriers to adherence and strategize ways to overcome such challenges; and (2) clients would be more open and honest with providers up front because they knew they would be tested with this objective measure (instead of previously where they were not honest about their adherence or providers had to spend a long time trying to get them to disclose their adherence).

Women also noted a number of cautions to consider. Presented as 'cautions' in Table 2, these included fears that negative UT results could be used to discontinue one's access to PrEP, feeling the UT would only help adherent women (particularly if results of non-adherence would bring negative consequences), and the potential for the use of the UT to foster external motivation (taking PrEP to avoid negative interactions with providers) or white-coat dosing in general. Selective return for follow-up (not

Table 2 Feasibility, likability and cautions

Theme[a]	Example quote
Feasibility—Urine preferable to blood test(s)/Non-invasive	*No* [UT is not harmful] *because it is just urine not like a blood that you fear losing even while on your periods. I eat fruits and green vegetable just to try and recover the blood I lose. Urine has no value*.—FGD with women > 25 years of age *It's simple and non-invasive so it will not be a challenge for you to administer this test. If it was blood or something invasive, patients or participants would think twice before doing it. So for its simplicity it's a very good idea. Generally, it is a good idea.*—KII Clinician *For the time they have been coming there is a routine to be checked for pregnancy they can be comfortable as with the same urine sample provided it can also be used here it cannot be a big problem because it will seem like a normal process*—KII Counselor
Feasibility—Enough Time/Rapid Results	*Yes there is enough time because it a rapid test and it is almost instant*—Clinical Officer *You can bring in the client, greet them and get to know her well-being. Then you request the client to get the urine sample and run the test and by the time you are running the test you are getting to know whether the client has adhering well…It is not a problem, five minutes is little time because for HIV you wait for twenty minutes*—KII Clinician
Feasibility—Not enough time* [IDI/FGD Only]	*Each time we come for refills, a test is done. I don't think they would be comfortable because they would like to just get a HIV test, pick their PrEP and leave. Some people are keen on their time and responsibilities, they would feel it takes long*.—FGD2 with women > 25 years of age *It will not help everyone because there are people who will refuse to have the test done and say they have no time while others will agree. People are different and some will agree and get help, a few will refuse. Most women fail because they say they have no time*.—IDI 32 years of age
Likability—Internal Motivation	*It will make me adhere to the medicine more…Because it will protect me against HIV*—IDI 22 years of age *For me I would be happy, I am okey with it … Because it would give me motivation to continue taking the drugs* – IDI 40 years of age *For those who have doubts whether PrEP is working, it may offer them comfort or relief to know they can test for it and it is in your body. It might provide some motivation to continue taking.*— KII Clinician
Likability—Accountability (self-motivating)	*I will make sure I take PrEP daily so that when I get the test done, I get positive results. My adherence would be much higher.*—IDI 40 years of age *It will motivate others to take medication because they know that at the end it, it will be black and white if they have used or not*—KII Counselor
Likability—Shared reality	*You will know I have been taking PrEP and I know I have been taking PrEP so it becomes proof so that I can get more PrEP.—FGD with women ≤ 25 years of age* *I like it because I will fear to try lying to the doctor, so when I get there and he asks whether I have been taking the PrEP I will not be able to deny that—FGD with women ≤ 25 years of age* *The truth will be out and the doctor will be able to attend to you in a better way because sometimes we can lie that we have been using it and yet we haven't been using it*—IDI 31 years of age *Personally I think it will [help] in a very big way because knowing that they will be having some kind of test as I have said they will have to open up and say I have been having issues and we are able to deal with the problems as they arise this will help us and the participants understand each other … I think to anybody else as a provider it will be as useful*- KII Counselor

Table 2 (continued)

Theme[a]	Example quote
Likability—Helpfulness	*When I come over I should be tested, everyone who comes here should be tested. This will help people.*—IDI 19 years of age *It will help a lot of women because many who are at risk they need to use PrEP and they will be taking it because when they come back the test will tell whether they have been taking PrEP or not—FGD with women ≤ 25 years of age* [The test] *would really help them (providers) in monitoring clients and their drug intake … It's a quick way of knowing if they are taking their meds and also it will help on how to advise them how to take their meds if they are missing out on medication-* KII Clinician
Likability—Objective measure [KII Only]	*I have liked the aspect that it is able to tell whether you have taken PrEP for the last three days and a client doesn't need to lie, in fact it will make them more honest-* KII Clinician
Caution—Dislike if results show non-adherence	*There are those that will like it and those that will not. The ones who will not are those that do not take their drugs and those that will want to be tested are those that take their drugs properly.*—IDI 18 years of age *Some can be interested and some will not because maybe if the test shows they have not been using that there is a consequence for that*—KII Counselor
Caution—Dislike if used to discontinue women's access to PrEP [IDI/FGD Only]	*On my side like I have told you, I would not like it because you may call me and I have not taken medicine for the past three days and maybe next time you refuse to give me drugs and I really need to use them. It is the side effects that make me skip them.*—IDI 19 years of age
Caution—External (fear-based) motivation* [IDI/FGD Only]	*One has to take PrEP because they know the provider will find out.—FGD with women > 25 years of age* *I will take the drugs well so that the provider does not scold me when I test.—FGD with women ≤ 25 years of age*
Caution—White-coat dosing	*It will help. …50% will benefit. Those who do not adhere to PrEP and wait until a few days prior [to their visit] to start taking [will not benefit].*—IDI 49 years of age *I think there could be harm just like I said it would be a hide and seek game. Maybe your three month appointment will be due next week and you have not been taking PrEP but you have been exposing yourself to potential risks you will start taking them so that you can please the doctor so I think it will force people to be taking them in the last few days—FGD with women > 25 years of age* *It shows that the patient has been taking the drug for the last three days, so the only challenge I have with the kit is for example…I will give the participants a specific day [for their next visit], but they may say, "during this week I will take my drugs before I go to him." I will not have a good picture of what is happening before this time for they maybe be throwing the drugs since they know at the end of the day there will be a pill count or even decide to take the drugs for these three days before coming*—KII Counselor
Caution—Selective return visits* [IDI/FGD Only]	*…personally I would not want to be tested when I know that I have taken. So I would not waste time coming when I know I haven't taken but would come if I had taken.*—IDI 19 years of age *…if you come for PrEP and don't use it, it is better if you do not come at all.—FGD with women ≤ 25 years of age*

*Theme emerged uniquely among discourse with former/current PrEP users (IDIs and/or FGDs)

[a]Themes specific to IDI and FGDs are noted as IDI/FGD Only; themes specific to KIIs are noted as KII Only. All other themes were present across women receiving PrEP (IDIs and FGDs) and providers of PrEP care (KIIs)

returning to care unless recent dosing would ensure positive UT results) was also noted. KII content suggested that few providers (n = 2) would support using test results as a requirement for ongoing access to PrEP or as a reason to discontinue someone on PrEP. Consistent with the results from IDIs and FGDs, providers and staff did share concerns over the potential of "white coat" dosing (where adherence increases transiently prior to a visit).

Recommendations

As presented in Table 3, content highlighting cautions and specific recommendations for implementing a UT as part of PrEP care from all participants (women and providers/staff) could be organized into general thematic areas including: physical characteristics of the UT (including lines that provide the results), procedures for use of UT as part of PrEP programs and PrEP care (including when and how to use the UT), and recommendations for delivery of results to PrEP program participants (including training and material that should be provided to those implementing the UT).

Physical Characteristics of the UT

KIIs provided information about the potential for the test to be confused with other urine dip point of care tests, like pregnancy tests. Providers worried that women in the PrEP program would be concerned that the urine would be used to conduct other tests without their consent, such as pregnancy testing. Further, the results display for the current iteration of the UT uses two lines to indicate non-adherence, which is inconsistent with pregnancy or HIV rapid tests where two lines denote a positive result. Concerns in KIIs included potential for misinterpretation of results. Careful consideration for education and counseling on what the UT does and does not test for, and interpretation of results, was recommended. Some providers offered suggestions for altering the display (e.g., different colored lines) or overlaying additional interpretation aids on the current display (e.g., smiley and not smiley faces). Ideally, changing the results format to have two lines indicate the presence of TDV/FTC would address concerns. Importantly, these concerns came from the provider KIIs and were not noted by women in the IDIs or FGDs.

Procedures-related recommendations included strong support for transparency in the purpose and use of UT, introducing its implementation prior to actual testing, and framing the UT as part of standard of care visits. Although some women suggested unannounced testing to reduce the potential for women to dose just prior to their visit, most women were in favor of letting people know about the test at one visit and then using the test the following-visit. Presenting testing as a standard part of a PrEP care visit, done for all PrEP program clients at each visit, was recommended in the KIIs, although some providers suggested that it may be preferable *not* to inform PrEP clients about the 3-day window of the UT, to prevent white-coat dosing. Additional procedural recommendations from women that were less common, but relevant in developing implementation strategies, included a desire to have the same staff member conduct the test and discuss results and that women should be able to observe the testing process to reduce concerns about handling urine or its disposal and assure that the test is using the correct person's urine sample. Related to both procedures and delivery of UT results, consistent messaging around results was noted in provider KIIs as resting in part on the program's flexibility to work productively with women not interested in PrEP. Specifically, offering a compendium of prevention options in clinics offering PrEP was recommended as an important structural factor that could optimize use of the UT to foster conversations around HIV prevention options, rather than only using it as a tool for PrEP adherence. In situations where the clinic-level directive is to optimize PrEP uptake and adherence, counselors and providers may feel unable to pivot to other prevention strategies even when the UT results are negative.

Delivery of UT results was a specific focus area in all interview and group guides. Themes emerging in this area suggested that training of staff or providers delivering the test results is important to optimize opportunities to improve adherence. Moreover, training to avoid what some expected would be negative interactions if the test showed non-adherence was commonly recommended by women participants. Providers suggested practice sessions delivering different results to prepare for UT implementation, as well as practice with providing information about the test and developing language around educating PrEP clients about the limitations in interpretation of results.

Discussion

Our exploration of a newly-developed point of care urine-based test to objectively detect recent PrEP dosing revealed a number of important insights. Although the test in itself was largely considered feasible to use, education and frequent re-education around the meaning of the result lines (two lines for non-detection) and the function of the test (not for pregnancy testing) appeared necessary to reduce potential confusion. Women participating in a PrEP program and program staff felt the test could be useful in promoting adherence, with important caveats of providing clear forewarning for use of the test, offering supportive discussions around results, and training staff and clinicians on client-centered approaches for test delivery. We did notice in some interviews that participants opened up about adherence challenges when they realized that it was possible to test for adherence using the urine test-kit. The potential for white-coat dosing and skipping or delaying PrEP follow-up visits, or refusing to return to care altogether, was raised as a concern, as was a general sense that the test would be well liked only by those who are or appear to be adherent. These findings further support the need to adequately train providers in communicating the results in a respectful and non-judgmental manner, working with women to identify

Table 3 Recommendations for optimizing implementation of the UT in PrEP care

Recommendation[a]	Example Quote(s)
Physical Features—Clearly explain that the test does not test for pregnancy despite similar physical characteristics [KII Only]	*If the test could look a bit different from these other rapid test. It may be confused for a pregnancy test whereby the patient refuses it because they feel you might be doing a pregnancy test and lying by saying it is the test for the drug*—KII Counselor *They might not be convinced we are only testing for PrEP maybe we are testing for pregnancy without their consent, because it looks like a pregnancy kit.*—KII Clinician
Physical Features—Clearly explain meaning of results display to distinguish from other tests using line-based results [KII Only]	*Yes it can be confusing at first because we are used to other methods like from the pregnancy kit shows that the two lines shows positive and one is negative so for this one people can be confuse at first*—KII Counselor *This test is for a HIV negative person who is coming for PrEP and you present with something that is exactly like the HIV test kit that they're going to use. I can see someone getting confused. You have tested them for HIV and it is negative but then you are processing that is another kit that has two lines…I'm seeing two lines on something that looks like a HIV test. I wish it would look a little different. Just make it look different from a HIV test kit.*—KII Clinician
Procedures—Explain UT and its use prior to testing [IDI/FGD Only]	*I think you should first tell the clients about everything it contains so that they can be aware of what kind of test it is. They will ask you questions like why you are testing when all they want is a refill. You should tell them the importance and anything to do with the test so that they can come on board.*—IDI 40 years of age *I recommend that when someone comes for their next visit to pick drugs they should be tested, how they are doing and if they are taking their drugs properly or not* – IDI 28 years of age
Procedures—Routinize/normalize use of UT [KII Only]	*Once you know it (UT) is part of the procedure, you know how HIV is done, once they know it's part of the procedure and it becomes the norm, I don't think it will be an issue*—KII Clinician
Procedures—Expand services so PrEP is one of several HIV prevention options, particularly for those testing negative for PrEP on UT [KII Only]	*For an individual client, you will have that one one-on-one discussion and will be more intentional in discussing adherence and discussing whether PrEP is the thing for them or not. If you came today and you're not adherent and had come last month and you're still not adherent then we can discuss whether PrEP is the thing for you or not and that's important rather than pushing pills to you as a person and you don't feel much for it. For facility-level …* [for those repeatedly testing negative] *we* [would] *then be thinking of other intervention options for these people. So overall, I think it is a useful tool to have.*—KII Clinician
Delivering Results—Offer training to those delivering the test results	*Of course they do (need training), as simplistic as it looks, you do not want providers shouting at clients, now see you do not take your medication the way it is supposed to be, of course sometimes you are tired and people have different temperaments they should be told as much as this client is non – adherent, you should be told how to bring it to them without judging them, or you are disappointed with them so training is definitely a need…What should be included? How to interpret the results, how to explain to the client how to interpret the results, how to not react whichever result you get and what to tell the client after the results depending on what the outcome is. How to go about the counselling and what you need to add for those clients who keep having negative results.*—KII Clinician *I think it is best if the doctor is taught on how to use the kit because if he gets the results and he is not able to interpret them for you he also human he doesn't know everything so he might get angry if he sees that you are outsmarting him so I think he needs training—FGD with women ≤ 25 years of age* *It is important that providers are trained to help PrEP users understand what the test is and what the possible results would be.*—KII Clinician

Table 3 (continued)

Recommendation[a]	Example Quote(s)
Delivering Results—Promote appropriate interactions around negative test results- avoid potential harm	*A doctor is human and he can get angry! And maybe even become rude to you. So when trained you will talk and come to some agreement. You know those who provide counseling are trained but if he is not trained he will get angry.*—IDI 49 years of age *Yes they actually need his training so that the can comfortably give these results without harming the participant …The type of training is that they need to be told how the gadget works and the next stage is the discussing the result so they need to be told how to and how to manage arising issues*—KII Counselor

[a]Themes specific to IDI and FGDs are noted as IDI/FGD Only; themes specific to KIIs are noted as KII Only. All other themes were present across women receiving PrEP (IDIs and FGDs) and providers of PrEP care (KIIs)

and problem solve around barriers to PrEP adherence, and/or identifying other prevention options if PrEP doesn't appear to be the right fit for the woman.

Results collected in the current research do not support roll-out of the urine test without pre-implementation consideration of the critical factors identified in the current research. Rather, the UT should be nested within a package that includes implementation tools, such as recommended messages around use of the test and interpretation of results; education material for PrEP clients, and specific processes; and supportive non-judgmental approaches for delivering test results. Of note, we used an early iteration of the UT for our formative work but a later version of this UT will be packaged by the company for easy interpretation (e.g. plus sign if PrEP detected; minus sign if no PrEP drug detected). Training of individuals who use and deliver UT test results, using practice sessions and opportunities to gain comfort with unclear or negative test results and use of patient-centered communication strategies, should be considered as part of the pre-implementation process. Additionally, teams and programs using the UT should develop structural-level procedures for negative test results in terms of working with clients to develop alternative prevention plans that do not rely on PrEP if appropriate. These and related programmatic efforts may reduce perceived 'need' to take PrEP prior to a clinic visit to appear adherent (inaccurately). During implementation, collecting ongoing feedback from PrEP clients and monitoring for potential impact on engagement in PrEP care and missed visits may offer important data for continuous quality improvement. Programmatic recommendations are presented in Fig. 1.

Findings are similar to recent work focused on perceptions of a urine adherence monitoring tool in a clinical centre in the U.S. which showed a preference towards noninvasive urine adherence monitoring for adherence over blood and other tissues [25]. Past studies after the VOICE [26] trial used pharmacokinetic results retrospectively to initiate discussions on adherence. Women who were in the trial in southern Africa were interviewed post study [10] and shown their adherence patterns. This disclosure led to candid discussions about adherence and several participants even came up with potential solutions to their challenges. This showed the impact of providing objective results to stimulate discussions and women suggested that real time drug monitoring could improve adherence. Key informants who had worked in previous studies involving use of MEMS cap (a device that recorded every time the drug bottle was opened and the resulting data was downloaded and data presented in a graphical format) felt the information was positively received by participants.

Our own theory-building work would support the utility of expansion of services for any PrEP-providing program to ensure that PrEP is not the sole focus or function of the program [10, 27]. Offering a wide variety of prevention options such that clients would not feel they must take or appear to take PrEP to remain engaged in the program is critical for sustainable HIV prevention and care services.

Limitations of our study include that our participants were receiving ongoing PrEP services at the facility and may have felt uncomfortable discussing problems with services or barriers to PrEP or the urine test. The discussions were also framed around viewing the urine test, but not actually using it. Perceptions may differ from actual experience with the test being part of standard care.

Conclusion

Adherence is necessary for PrEP to be effective. Objective measures for measuring adherence have been available for some time. However, these measures take time and are costly. In addition, most of these measures are considered invasive in nature, requiring blood, hair and other samples to be collected. Point of care urine-based monitoring for adherence is an easy-to-use non-invasive way of objectively measuring adherence in real-time. This study is the first to evaluate the feasibility of and acceptability of the urine test among women on PrEP in sub-Saharan Africa

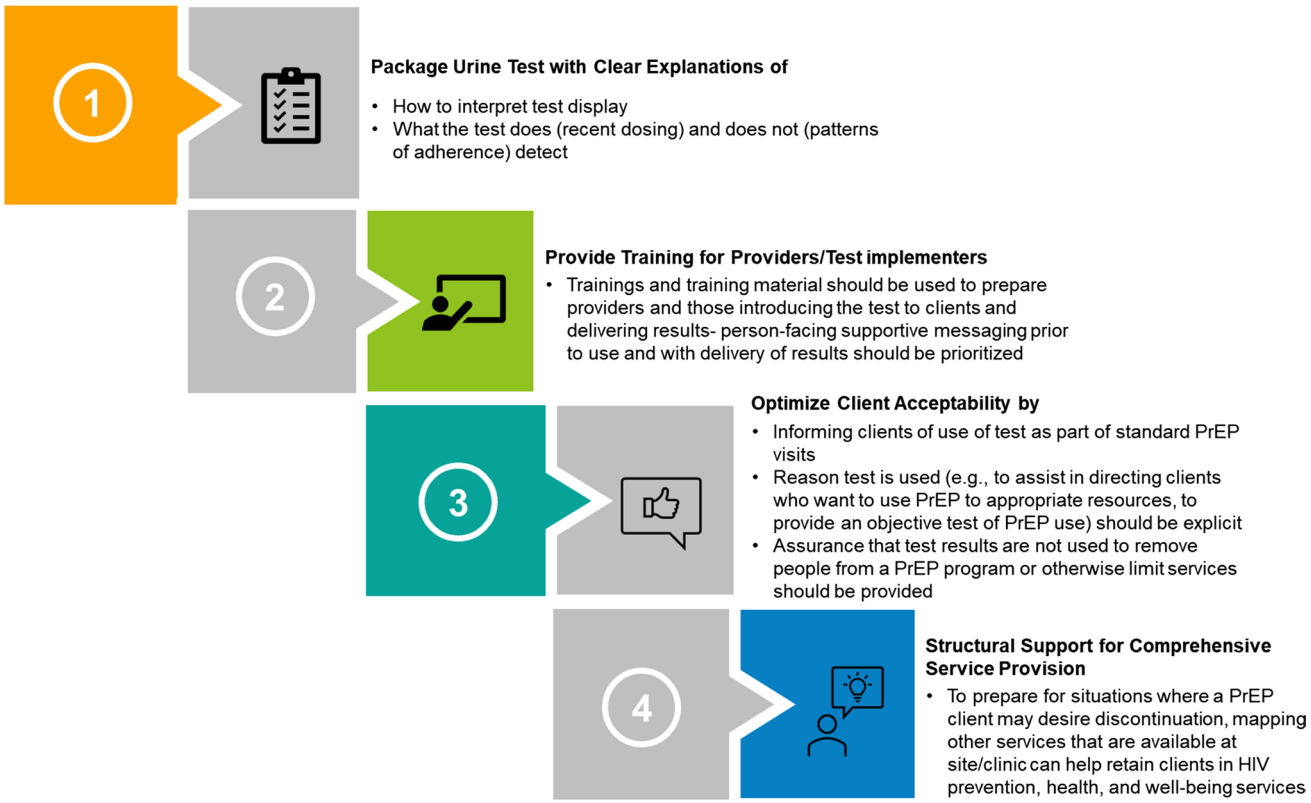

Fig. 1 Recommendations for Programs

and found the test to be both feasible to implement and acceptable to clients. For programmes, this work reveals the need for training providers to correctly conduct and interpret the urine-based adherence test and to communicate test results in a non-judgmental way with the objective of problem-solving around barriers to PrEP adherence and improving adherence counseling. An easier-to-interpret test kit for providers (showing a smiley face or plus sign for recent adherence) is being developed. The current availability of a point-of-care urine test for immediate assessment of PrEP adherence will be beneficial for PrEP implementation among women. Use of a point-of-care urine test kit will be beneficial if well implemented. This means that health providers need to be properly trained on how to use it, PrEP users need to have full information on the test (including reason for use), and finally both the provider and PrEP user have to share a common goal of finding the right HIV prevention measure for each client.

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