NOVEL TESTING STRATEGIES TO SUPPORT HIV TREATMENT AND PREVENTION: ACCEPTABILITY, PREFERENCES, AND IMPACT ON ENGAGEMENT IN CARE AND SEXUAL BEHAVIORS

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Abstract

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The primary goal of this dissertation project was to advance our understanding of the impact of novel testing strategies to support HIV treatment and prevention. Despite significant advancements in antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP), rates of suboptimal medication adherence and disengagement from care, particularly in the first year of care, remain extraordinarily high. Novel strategies are urgently needed to improve ART and PrEP adherence and retention in care, in order to reduce HIV transmission and mortality.

Point-of-care (POC) urine tenofovir testing is a newly developed tool that can provide real-time drug-level feedback for people living with HIV (PLWH) receiving ART, which could also prompt timely interventions for those experiencing adherence challenges. However, little is known about how PLWH and healthcare providers will perceive a POC urine tenofovir testing intervention and how it will impact behaviors. In Chapter 1, we conducted a qualitative study to assess the acceptability of monthly POC urine tenofovir testing in the first five months of care for PLWH and healthcare providers in South Africa. We also explored participants' perspectives on differentiated strategies for the implementation of POC

urine tenofovir testing that may be useful and appropriate for PLWH. Overall, PLWH and healthcare providers found the monthly POC urine tenofovir testing intervention to be highly acceptable, generally preferred over self-reported adherence, and motivational for improving ART adherence. Other implementation strategies in which participants believed POC urine tenofovir testing could be provided, included: testing at community-based sites where ART is refilled, random testing at clinic visits, and testing delivered by counselors or other healthcare workers. Monthly POC urine tenofovir testing in the first five months of HIV care is an acceptable and potentially effective strategy for improving ART adherence.

Novel strategies for HIV testing for people at risk of acquiring HIV may also be beneficial for improving outcomes, but it is important to understand how clients' testing preferences impact the intended outcomes. For HIV prevention, regular HIV testing is a required core component of PrEP delivery necessary to ensure a prompt transition to ART and reduce the risk of drug resistance. HIV self-testing (HIVST) may be an effective tool for supporting efficient PrEP delivery, allowing for non-clinic-based HIV testing when appropriate. A differentiated service delivery (DSD) model for PrEP that includes semiannual clinic visits, six-month PrEP dispensing, and HIVST between clinic visits resulted in non-inferior outcomes for PrEP continuation. In practice, though, PrEP clients' unique needs and preferences should be considered when choosing an appropriate and effective delivery model. In Chapter 2, we used data from the JiPime-JiPrEP trial (NCT03593629) to determine if receiving a preferred HIV testing modality to support PrEP delivery is associated with better PrEP continuation outcomes compared to receiving a non-preferred modality. Findings from Chapter 2 indicated no significant differences in PrEP continuation behaviors between participants receiving their preferred HIV testing modality and those receiving their non-preferred modality.

This DSD model of semiannual clinic visits with six-month PrEP dispensing and HIVST reduced the frequency of clinic visits without compromising PrEP continuation outcomes, but its effect on other behaviors associated with HIV risk acquisition, such as sexual behaviors, is not well known. In Chapter 3, we evaluated the effect of this DSD model of PrEP delivery supported with interim HIVST—which reduces the frequency of sexual and reproductive health and associated counseling services—on participants' sexual behaviors. We found no significant differences in sexual behaviors between participants receiving

a DSD model of PrEP that included semiannual clinic visits and HIVST and participants receiving standard-of-care. DSD models of PrEP delivery and HIV testing, including those that incorporate HIVST, that are person-centered and tailored to clients' unique needs and preferences may result in comparable outcomes to standard-of-care PrEP delivery models.

Collectively, these findings provide some of the first insights on the acceptability of monthly POC urine tenofovir testing for PLWH in South Africa, PrEP continuation behaviors for clients receiving a DSD model supported with their preferred HIV testing modality, and sexual behaviors for PrEP clients receiving a DSD PrEP delivery model supported with HIVST versus standard-of-care PrEP delivery. Evidence gleaned from this dissertation will be valuable for guiding development of person-centered models of care and testing strategies to support HIV treatment and prevention.

TABLE OF CONTENTS

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DEDICATION

To my two favorite people – Neil and Orijn – who powered me through this PhD program with their unconditional love and support.

CHAPTER 1: ACCEPTABILITY AND PERSPECTIVES ON THE IMPLEMENTATION OF MONTHLY POINT-OF-CARE URINE TENOFOVIR TESTING FOR ANTIRETROVIRAL THERAPY ADHERENCE MONITORING: QUALITATIVE FINDINGS FROM A RANDOMIZED CONTROLLED TRIAL IN SOUTH AFRICA (STREAM HIV)

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ABSTRACT

Real-time, objective adherence monitoring for antiretroviral therapy (ART), such as point-of-care urine tenofovir testing, may detect adherence issues more accurately than self-report and earlier than viral load testing. We aimed to assess the acceptability and perspectives on implementation of monthly point-of-care urine tenofovir testing among people living with HIV (PLWH) initiating ART and healthcare providers participating in the STREAM HIV trial (NCT04341779) in South Africa. We conducted in-depth interviews (IDIs) with 20 intervention participants at six-months post-enrollment and eight healthcare providers. We assessed the acceptability of (using the Theoretical Framework of Acceptability), appropriateness of, feasibility of, and willingness to use the intervention, as well as their preferred form of adherence monitoring and perspectives on differentiated implementation strategies for point-of-care urine tenofovir testing. Overall, participants found monthly point-of-care tenofovir testing to be highly acceptable, generally preferred over self-reported adherence measures, appropriate for this population, and potentially feasible to integrate with standard-of-care ART monitoring. The intervention was well-liked, perceived to be low-burden with few opportunity costs, and perceived to have several positive effects. The positive effects included consistent ART adherence, strong client-provider relationship and communications, and accurate self-reporting of adherence. Intervention participants' desire to impress and build trust with their provider motivated them to take their ART every day to achieve a positive adherence test result at each clinic visit. Point-of-care tenofovir testing holds promise as an acceptable and beneficial tool for motivating optimal adherence, improving ART adherence monitoring, and strengthening client-provider relations.

KEY WORDS

antiretroviral therapy (ART), point-of-care testing, adherence monitoring, tenofovir, randomized controlled trial, acceptability

INTRODUCTION

South Africa has made significant strides towards achieving the UNAIDS 90-90-90 targets in recent years; however, with the largest HIV epidemic in the world, South Africa still experiences significant gaps in HIV treatment coverage and viral suppression.[34] Achieving and sustaining optimal adherence is particularly challenging during the first year of treatment when people living with HIV (PLWH) are beginning to establish behaviors.[19] About half of PLWH initiating antiretroviral therapy (ART) in South Africa experience adherence challenges at least once in the first six months of treatment, and an estimated 30% of PLWH disengage from care within the first six months of treatment.[35–39] Developing and sustaining optimal adherence behaviors and preventing disengagement from care through targeted, person-centered interventions will be critical to ending the AIDS epidemic in South Africa.[40]

Early interventions targeting PLWH who are experiencing adherence challenges or other barriers to care are particularly needed to prevent adverse clinical outcomes.[40] Clinicians are reliant on subjective measures for identifying adherence challenges, such as self-reported behaviors, which may be inaccurate and unreliable for informing clinical decisions and counseling support.[41–47] Point-of-care (POC) urine tenofovir testing is a new development in therapeutic drug monitoring that can measure recent (prior 2-4 days) ART adherence in real time, allowing for prompt identification of adherence challenges and immediate interventions for adherence support.[48–52] POC urine tenofovir testing also has the potential to predict future loss to follow-up, viremia, and drug resistance[53–56] and may motivate PLWH to improve their ART adherence.[45,51,57–59] Overall, POC urine tenofovir testing may offer several benefits to PLWH and healthcare providers that could ultimately improve HIV care and clinical outcomes.

Some studies have found the POC urine tenofovir test to be generally acceptable to PLWH and healthcare providers and appropriate for monitoring ART adherence.[52,57,58,60] However, some PLWH and healthcare providers have had neutral or negative perceptions of the test, expressing uncertainty about the test's overall utility since it can only detect recent adherence and concerns about the impact of drug-level testing on client-provider relationships, particularly clients' perceptions of mistrust from their provider.[51,58,60] These findings could indicate that POC urine tenofovir testing might be suitable and acceptable for certain populations and settings, although it may not be universally applicable. Still, little is known about how a longitudinal intervention of monthly POC urine tenofovir testing will be perceived and

accepted by PLWH and healthcare providers and how it will affect the client-provider relationship and client's behaviors, such as ART adherence and retention in care. In this qualitative study, we sought to understand the acceptability of a monthly POC urine tenofovir testing intervention over the first five months of treatment among PLWH and healthcare providers in South Africa. We also collected perspectives from PLWH and healthcare providers on differentiated approaches for implementing POC urine tenofovir testing.

METHODS

Study Design

We conducted a qualitative sub-study nested within the Simplifying TREAtment and Monitoring for HIV (STREAM HIV) trial (ClinicalTrials.gov: NCT04341779) among ART clients and healthcare providers participating in the trial intervention procedures.[24] STREAM HIV is a two-arm, open-label randomized controlled trial testing the effect of a combined intervention of monthly POC urine tenofovir testing (as a proxy measure for recent ART adherence) for the first five months of HIV treatment and routine POC HIV viral load testing at six and 12 months on ART adherence, retention, and viral suppression in comparison to standard-of-care (SOC) HIV treatment services (no POC urine tenofovir testing at laboratory-based HIV viral load testing at six and 12 months).

Study Setting and Population

The STREAM HIV trial was conducted at two sites in KwaZulu-Natal, South Africa: (1) the Centre for the AIDS Programme of Research in South Africa (CAPRISA) eThekwini Clinical Research Site in urban Durban, which is connected to a public HIV clinic; and (2) the CAPRISA Vulindlela Clinical Research Site in rural uMgungundlovu District, which is connected to a public primary healthcare clinic. Both research sites are adjacent to large, public clinics which serve a high volume of PLWH receiving ART. Potential participants were also recruited from an additional urban site in Durban, the Lancers Road Clinic, and were screened and enrolled at the eThekwini site.

We enrolled two populations in this qualitative sub-study: intervention arm participants and healthcare providers who provided care to trial participants. Individuals were eligible to participate in the STREAM HIV trial if they were ≥16 years old, living with HIV, initiating a tenofovir disoproxil fumarate (TDF)-based ART, not taking any ART regimen in the prior month, and were willing and able to provide

written informed consent. Trial participants were eligible to participate in this qualitative sub-study if they were enrolled in STREAM HIV and were returning for a six-month clinic visit, had been randomly assigned to the intervention arm, and were willing and able to provide written informed consent. We purposively sampled a subset of intervention arm participants to achieve a diverse sample in terms of sex, age (≤25 years, >25 years), and adherence test results (detectable tenofovir test results at all visits, one or more undetectable tenofovir test result). Intervention participants were only included from the eThekwini site.

Healthcare providers were eligible to participate in the qualitative sub-study if they had provided care for participants in the intervention arm of the STREAM HIV trial and were willing and able to provide written informed consent. We sampled all providers who were eligible and willing to participate after about half of STREAM HIV participants had reached the six-month endpoint. We included healthcare providers from the eThekwini site and the Vulindlela site.

Study Procedures and Data Collection

The STREAM HIV trial enrolled participants and randomized them 1:1 to intervention and standard-of-care (SOC) arms. Participants assigned to the intervention arm received POC urine tenofovir testing at each monthly follow-up visit for the first five months. Urine specimens were collected by study participants in a communal bathroom in the clinic, the test was performed by a research nurse in a private exam room in the presence of the study participant (processing time of ~5 minutes), and the nurse and participant reviewed the test results together. Participants who received an undetectable tenofovir result were provided with enhanced adherence counseling. Participants who received a detectable tenofovir test result were praised for their good adherence and encouraged to continue taking their ART as prescribed. SOC arm participants received SOC adherence monitoring (i.e., self-reported ART adherence and pill counts) at each monthly follow-up visit for the first five months and enhanced adherence counseling if ART adherence was self-reported as ‘poor’. The schedule of visits and the enhanced adherence counseling procedures follow the 2019 South African Department of Health ART Clinical Guidelines for the Management of HIV and the Adherence Guidelines for HIV, TB, and NCDs.[61,62] More details about the STREAM HIV procedures can be found in the published protocol.[24] Additional study visits and procedures

occurred between months six and 18, but we will not describe them here since this qualitative sub-study was conducted at six months post-enrollment and only focused on the first five months of the intervention.

We conducted semi-structured in-depth interviews (IDIs) with participants at their six-month follow-up visit while their POC viral load test was processing. All IDIs were conducted in a private room in the participants' preferred language (English or isiZulu) and were facilitated by a trained member of the research team who was not otherwise involved in patient care. Intervention arm participants were compensated 100 South African Rand (~6 U.S. dollars) for their time; healthcare providers were interviewed during their working hours and did not receive additional compensation for their time. All IDIs were audio recorded (with consent from the participant), transcribed, translated to English if necessary, and checked for accuracy against the audio recordings by the research team. Demographic and clinical information was collected from study participants at enrollment, and demographic information was collected from healthcare providers at the time of their IDI.

Instrument Design

We developed one interview guide for study participants and one for healthcare providers. The participant interview guides were developed to capture the following domains: comprehension of the intervention; understanding of the rationale for POC urine tenofovir testing; attitudes about the intervention; experiences with the intervention; perceived effect of the intervention on self-reported adherence, client-provider relationship, ART adherence, and other behaviors; preferred ART adherence monitoring approach (POC urine tenofovir testing versus self-reporting adherence) and perspectives on other ways POC urine tenofovir testing can be implemented (i.e., who would benefit from testing, where it could be implemented, when it could be implemented, and who could administer/perform the test). Provider interview guides included the following domains: comprehension of the intervention, understanding of the rationale for POC urine tenofovir testing, attitudes about the intervention, experiences with the intervention, approach to communicating POC urine tenofovir test results to participants, barriers and facilitators to communicating test results, perception of participants' understanding of and reaction to test results, perceived feasibility of the intervention, and perspectives on other ways POC urine tenofovir testing can be implemented (i.e., who would benefit from testing, where it could be implemented, when it could be implemented, and who could administer/perform the test).

Data Analyses

We (ARB, NB) created one codebook for study participants and one for healthcare providers, which were deductively developed based on domains of interest from the interview guides. We also applied an inductive approach during the coding process to add new codes for topics that were discussed outside of the domains of interest. Each transcript was independently coded by two coders (ARB, NB), compared to identify discrepancies, and recoded when necessary. After coding consensus was achieved for each transcript, we performed thematic analyses to identify and describe emergent themes. Most themes overlapped with constructs from the Theoretical Framework of Acceptability (TFA) (affective attitude, burden, intervention coherence, effectiveness, opportunity costs); therefore, we created a thematic map of all the themes related to acceptability using this framework.[63] We also mapped themes related to implementation of POC urine tenofovir testing using the Differentiated Service Delivery elements (context, clinical characteristics, specific populations) and building blocks (who, what, when, where).[64] Additional themes were described for preferences for adherence monitoring, willingness to implement the intervention, and perceptions about the appropriateness and feasibility of the intervention. All transcripts were stored, coded, and analyzed using Dedoose software (SocioCultural Research Consultants, LLC, Los Angeles, CA, USA). We also used descriptive statistics to present demographic and baseline clinical characteristics (only intervention participants) of participants included in this qualitative study.

Ethical Considerations

The STREAM HIV trial received ethical approvals from University of Washington Human Subjects Division (STUDY00007544), the University of KwaZulu-Natal Biomedical Research Ethics Committee (BREC/00000833/2019), and the National Institutes of Health Division of AIDS Regulatory Support Center (DAIDS-ES ID #38509). All participants provided written informed consent to participate in qualitative interviews, as well as the trial.

RESULTS

We enrolled 28 participants in this qualitative sub-study of the STREAM HIV trial; 20 were PLWH enrolled in the trial intervention arm, and eight were healthcare providers (**Table 1**). Half (50%, 10/20) of intervention participants and 88% (7/8) of healthcare providers were female. Three intervention

participants (15%) had received one undetectable tenofovir test result, and 85% (17/20) had received only detectable tenofovir results. The healthcare providers included an enrolled nurse assistant, research nurses, and clinicians. The median duration of IDIs was 50 minutes (IQR 44-55 minutes) for study participants and 45 minutes (IQR 40-60 minutes) for providers.

Acceptability of monthly POC urine tenofovir testing

Overall, intervention participants and providers perceived the monthly POC urine tenofovir testing intervention as highly acceptable. We mapped each theme to relevant constructs from the TFA. We summarize emergent themes by TFA constructs in **Figure 1** and illustrate these themes with supporting quotes within each section and in **Table 2**.

Affective attitude

The majority of intervention participants liked the intervention, and several stated that seeing their test results made them feel happy. Intervention participants expressed that adherence testing made them feel supported by their providers and demonstrated that the providers cared about the wellbeing of their clients. Intervention participants liked the intervention because it held them accountable for their adherence, it facilitated open and honest adherence discussions with their provider(s), they were recognized for their good adherence, and they were included in the testing process. Providers also described observing some intervention participants as eager to use the adherence test.

> *"I liked it because I saw that it meant I'll be getting help." (Intervention participant, female, 42 years old)*

> *"It showed positive, one line. And it made me happy, and I had that closure that 'oh! I'm doing it the proper way.'" (Intervention participant, female, 25 years old)*

The remainder of intervention participants expressed neutral attitudes about the intervention.

> *"It's okay if it's part of the study to help other people, but for me personally, it does nothing. I don't gain nor lose anything due to fact that I know how my pills work." (Intervention participant, male, 43 years old)*

All of the providers had positive attitudes about the intervention.

> *"I think it's a good thing. I think it's beneficial." (Healthcare provider, female, urban site)*

Perceived effectiveness (and secondary benefits)

Overall, most participants perceived the intervention to have many positive effects and benefits for PLWH and healthcare providers. All providers and nearly all intervention participants perceived the intervention as having a positive impact on participants' overall adherence. The test was motivational to intervention participants to take their ART every day and improve their adherence.

> *"It had positive impact because it encourages me to always remember my pills not just when the next date to [the clinic] is near, I'm not doing it for [the clinic], I'm doing it for myself." (Intervention participant, female, 39 years old)*

Intervention participants often thought about their upcoming adherence test when they were at home, which served as a daily reminder to take their ART. As discussed previously, several participants believed the test was able to detect adherence over an entire month, which prompted them to take their ART as prescribed every day. A couple participants understood that the test's ability to only detect recent dosing could influence some PLWH to take a pill before an upcoming adherence test to manipulate the test results, though no participants reported attempting to manipulate the test in that way.

> *"I would say that the test played some sort of an alarm to me. By saying an alarm, I mean that, I knew if I miss a day or two of pills there will be something that will tell that I wasn't honest in taking the treatment. So that's the role that the tests played and was sort of like a motivator because I knew that it will be evident if I took them and if I didn't take them in three or four days. So I was happy that*

> *these tests made me to comply to taking my pills constantly." (Intervention participant, male, 37 years old)*

Some participants felt internally incentivized to improve their adherence and take control of their health, but the primary motivation to improve ART adherence was driven by the desire to have a 'good' adherence test result to provide evidence of their adherence, impress their provider, build trust with their provider(s), and receive recognition and praise for their effort. Intervention participants were also motivated by the fear of being exposed if their adherence test were to reveal undetectable tenofovir, which they perceived would be a disappointment to their provider. One intervention participant believed that their provider may react poorly and 'fight' with them if they were to receive an undetectable tenofovir test result. A couple of intervention participants perceived the intervention as having no effect on their adherence; no participants perceived the intervention as having a negative effect on adherence.

> *"Yes, it had an impact because it encouraged me to take the pills the way I am supposed to. The way the nurses were so welcoming, not just one of them but all of them it made it seem like we were a team so that also encouraged me to take the pills right. Not just one person, sometimes I would find a different nurse from the one that I saw previously, but they are just the same it really gave peace and spend most of the time with them." (Intervention participant, male, 37 years old)*

> *"…it will strengthen adherence, because with them, knowing that you're going to be testing, they obviously don't want to come to you, and then have a bad result. So I think it will also motivate them a little bit to say, because we're going to be testing for this, they would be a little bit more motivated to, or determined I'd say, to take their treatment so their results are good when they do come to us. So, I mean, psychologically, it may also have an effect and help with adherence." (Healthcare provider, female, urban site)*

The intervention was also perceived to be more effective than SOC for providing early evidence of adherence (before participants' first viral load test) and prompting appropriate adherence interventions.

> *"I think that [tenofovir testing is] a good way to detect whether the patient, the participant, really has, you know, some issues early. Like it's an earlier stage than having to wait for the viral load at six months, so that's like…cause from the first 5 months, you have to just hear from what the participant tells you. If they say they take their medication, then you can't dispute that. So for the POC arm, it's easier to see whether they are really missing the doses, so I think that's like early detection of defaulting and all that." (Healthcare provider, female, urban site)*

Intervention participants admitted that they were not always honest with their provider and that they would probably be dishonest or exaggerate their adherence if they had not received adherence testing. Most intervention participants perceived adherence testing as having a positive impact on their self-reported adherence and other behaviors because they believed their adherence would be exposed through the test. As a result, their openness about adherence challenges helped facilitate additional conversations and a more targeted discussion around adherence.

> *"I was telling the truth because urine was even confirming for me." (Intervention participant, male, 36 years old)*

Providers echoed many of intervention participants' perspectives, as they also perceived the intervention as beneficial for improving discussions around adherence.

> *"I think between the two arms, in the intervention one, they get to have something that makes them to take their medication because they're like it's going to be seen. The others, they don't know about the test, so whether they tell you that I'm taking it right, it's not like the intervention arm where they know maybe I'll be caught. So I'll just have to say I didn't take them because there's a plate the way you ask them before, like I normally ask them before I do the test, and then they tell you all. 'Yes, I took my medication.' But with this intervention ones, they tell you the honest truth, you know. 'I forgot them maybe for five days.' 'No, someone took them from me.' Or 'I forgot. I left them at home and I was somewhere.' So you get the real story, comparing with the ones that they're always saying, 'No, I'm taking them correctly.'" (Healthcare provider, female, rural site)*

Half of intervention participants also emphasized that the intervention had a positive impact on the client-provider relationship. They perceived that adherence testing helped build trust between clients and providers as the test results provided evidence of their honesty. One intervention participant felt as though they were on a team with their providers working towards a common goal, while another participant explained that they had more time to get to know their provider while the adherence test was processing. Several intervention participants were also appreciative of being included in the testing process, as providers performed the test in real-time in the presence of the participant and also encouraged participants to interpret their own test results. The other half of participants perceived the intervention as having no effect on their relationship with their provider.

> *"[Our relationship] was going to differ [if there was no adherence testing] because there was going to be nothing confirming that the pill is indeed in my body. No further questions were going to be asked other than asking if you're taking pills and get another pill then leave like it happens in other clinics, people complain about that." (Intervention participant, female, 39 years old)*

Intervention coherence

The intervention procedures and rationale were well-understood by intervention participants and providers with the exception of a couple intervention participants who had forgotten how to interpret the test results by the time of their IDI at the six-month visit. However, the test's limited ability to detect only recent adherence was not fully understood by all intervention participants. Intervention participants had several misconceptions about the test, including: the test could detect adherence over an entire month, the test could detect if a pill was taken late one or more days over the past month, the test could confirm that the pills are absorbing and working correctly, the test could help uncover other issues interfering with drug absorption, and drugs or alcohol could interfere with the test results. Providers may have partially contributed to the misconceptions by not correcting participants' misunderstanding and withholding information about the test's limitations, particularly in regards to the test's detection window for tenofovir.

> *"So because we don't explain to them that if they don't take the treatment four days, if you didn't take the treatment four days ago. Because if you say that, then maybe they'll make sure that these four days, you're taking your treatment before you go to the clinic. So we don't give that information unnecessarily. So maybe this person has not been taking treatment like they're supposed to. Yeah. They have been taking treatment, but maybe at 9:00, maybe at 8:00 sometimes. So now you're not sure what's going to come then. I think that's the problem. And then when it comes back positive, they're relieved and like, 'yeah.'" (Healthcare provider, female, urban site)*

Burden

Overall, participants found the intervention to have little to no burden to PLWH and providers. POC urine tenofovir testing was summarized as quick, easy, convenient, and required little to no effort.

> *"It was comfortable because they put the test in front of me to see while we do the test and wait for the results, so everything was done out in the open. I think it's more convenient if they get them at the same time cause it takes only a few minutes. So, it's more convenient if they hear them [at] the [same] time they're there than hearing them any other way, and you get to see them for yourself. There's no waiting for the results to come back from the lab." (Intervention participant, female, 27 years old)*

> *"I think it's just easy. It's convenient because the test is right here. You do it while the participant is here. It's just, you know, I haven't seen anything that would cause me to be like inconvenienced. It doesn't take long." (Healthcare provider, female, rural site)*

Intervention participants were not able to draw comparisons to SOC in terms of the intervention's burden since they had never received SOC HIV treatment, but a few participants believed that the intervention may add a little extra time to each follow-up visit. Providers, on the other hand, believed that adherence testing did not add any additional time to participant's follow-up visits since they were able to perform other tasks while participants were collecting urine or while the test was processing for five

minutes. Some intervention participants and providers also felt that urine testing is acceptable since it's noninvasive compared to other tests that require needles and not burdensome to clients since it requires only a small amount of urine.

> *"I think urine is quite an acceptable means of testing. It's non-invasive. There's no needle stick. If I was a patient, I would find that method acceptable. It's comfortable. It's not time-consuming. So I think all those aspects of it, I'm very in favor of it therefore being a part of standard of care." (Healthcare provider, female, urban site)*

Opportunity costs

Many participants described feeling uncomfortable, worried, anxious, or fearful during their first adherence test, even if they were confident that their adherence was good over the prior month. Generally, these feelings dissipated by subsequent tests except when their adherence was poor in the prior month.

> *"In the first visit I was afraid. But as time went on, I got used to it." (Intervention participant, female, 25 years old)*

Providers also perceived intervention participants to be slightly uncomfortable during their first adherence test but comfortable during subsequent tests.

> *"I think for the first time, they'll be anxious. They'll like stand beside you and wait for the results. But once they've gotten used to it, they don't…they're just neutral." (Healthcare provider, female, urban site)*

Preferences and willingness to use

When intervention participants were asked about their preferred form of adherence monitoring (POC urine tenofovir testing or self-reported adherence), nearly all participants stated that they would

prefer POC urine tenofovir testing. However, one participant was neutral about their preference and only stipulated that they would choose POC urine tenofovir testing if it were quick, low cost, and cost-effective.

> *"I think I would prefer the test to be used because it will encourage me to take it, because it's not easy to take them to be honest. Taking pills every day is a story. So, for me it helped me because I thought it will be hard on me, but these tests motivated me because I know it will show." (Intervention participant, female, 38 years old)*

Similarly, all providers were very willing to use POC urine tenofovir testing for all PLWH, as they perceived the intervention as very acceptable and effective after their experience with it, though they had some skepticism about how willing providers would be to implement the test in other settings.

> *"Yeah, I would definitely be willing. As I've said, I think it just gives you a better picture of adherence so that you know how to better support and counsel the patient or participant. And I think if you do that early on, so it would just help establish them for a good, lifelong journey with their ART." (Healthcare provider, female, urban site)*

Appropriateness

The majority of participants perceived that the intervention was appropriate for their own care and treatment as well as for all PLWH in South Africa, particularly for the first five months of treatment when PLWH are beginning to establish adherence behaviors. One participant perceived the intervention as having little utility or value for their own care and for other PLWH who don't require additional adherence support. All providers perceived the intervention to be appropriate for the population included in this study.

> *"I think it can help many people nationally here in South Africa because in other clinics if it's your date you just go there ask your card, show your appointment card and they give you your treatment and go, so whether you use the one they gave you before they don't see that because there's no tests done on their visit just a follow-up of what has been done and to see if it's happening or not. So,*

> *if this kind of test can be implemented to all clinics for people using treatment, I think it can have much influence and things can change a lot on what the situation can be, because people can keep their viral load down and not going up because they'll use their treatment correctly." (Intervention participant, male, 40 years old)*

Feasibility

Overall, the intervention was perceived by providers to be very feasible to implement this intervention in SOC, though they predicted several implementation barriers that would need to be addressed or overcome to make the intervention successful for SOC. The implementation barriers included physical resource availability (functional bathrooms, urine collection containers), human resource requirements (staffing, training), acceptability from key stakeholders, costs, and time.

> *"I think this is revolutionary. It would really change a lot in terms of patient flow, somewhat, because obviously we're not doing urine testing for everybody. But yeah, we can look at an adjustment to the flow because it's such a test that can be done by a relatively lower level category of staff, it can be taken to scale very quickly as long as we have the kits available. And if there's strong, concrete messaging on the interpretation of the results, it's not very complicated to roll out. The issues that we had with viral load, for example, are far more complex, and far more convoluted than trying to operationalize and interpret something like this. So I think that there's a very low bar to have challenges in terms of rolling it out." (Healthcare provider, male, urban site)*

> *"I think in a clinical trial setting, so in our [clinic], we had all the infrastructure, but from my experience previously, in like the clinic-based settings or government settings, where you would want to implement where the biggest burden of disease is in terms of HIV, I think it would be a challenge to implement it just because they're so short in time, I mean short-staffed, so they try to turn over patients quickly, and I think the staff in the clinics when I perceive it as just an additional thing to do. And they're already probably overstretched in terms of their capacity, so…but I think if they are properly supported, and they can see that perhaps that would lead to better outcomes and less visits*

> *in the future because people are more compliant, and doing well on their treatment, that the long-term benefit would be there, and perhaps once they're in the routine of doing it, that it wouldn't actually be such a big ask of them." (Healthcare provider, female, urban site)*

Differentiated implementation strategies for POC urine tenofovir testing

We also explored potential target populations for POC urine tenofovir testing and strategies for its implementation. IDI participants suggested several innovative approaches for how adherence testing could be implemented for the greatest benefit. **Figure 2** summarizes themes from participants' exploration into differentiated implementation POC urine tenofovir testing as they fit within the elements and building blocks of differentiated service delivery.

Populations, clinical characteristics, and context

When asked about a target population for adherence testing, IDI participants most frequently indicated that adolescents and young adults (16-30 years old) living with HIV would benefit the most from POC urine tenofovir testing. Participants believed that adolescents and young adults struggle with adherence more than older populations and may be motivated to improve their adherence after receiving this intervention, particularly if offered outside of the clinic setting. IDI participants also felt that adherence testing could be beneficial for PLWH who had recently initiated ART, PLWH with a high viral load at a recent visit, older adults living with HIV, pregnant PLWH, PLWH experiencing mental health issues or memory loss, PLWH who transfer to a new clinic, PLWH with comorbidities and a high pill burden, fatigued clients (i.e., those who have been on treatment for a long period), PLWH who use alcohol or drugs, PLWH who default from care, and PLWH with suspected HIV drug resistance. Participants suggested that POC urine tenofovir testing could support the identification of HIV drug resistance if results don't match viral load test results or by establishing or confirming drug pressure prior to genotypic resistance testing. Some participants also believed that all PLWH receiving ART would benefit from regular POC urine tenofovir testing.

When

The majority of IDI participants felt that POC urine tenofovir testing would be most effective if it is implemented at every clinic visit or every ART refill visit, particularly for PLWH who recently initiated ART.

A couple providers suggested adherence testing could be conducted at random intervals for all PLWH to continue motivating optimal ART adherence while reducing the resources required for routine testing.

Where

Generally, IDI participants believed that outpatient clinics providing care for PLWH would be the most appropriate location for conducting POC urine tenofovir testing since it allows clients to be assessed for side effects or other health issues at the same time. Community-based settings were also suggested as an appropriate adherence testing venue by many IDI participants, including community centers, mobile clinics, adherence clubs, and clients' homes. Participants believed community-based adherence testing would be suitable for young PLWH, PLWH who are lost to follow-up, and people who are unable to access a clinic. However, a couple intervention participants had concerns about stigma and confidentiality if adherence testing is conducted at community-based settings. Hospitals, acute care settings, and pharmacies were also cited as potentially beneficial for conducting adherence testing.

Who

When asked who should be performing POC urine tenofovir testing and delivering test results to clients, most intervention participants and providers felt strongly that nurses should be performing the tests during clinic visits since they would be able to address any health or adherence concerns at the same visit. Several providers also believed a counselor may be an appropriate provider for adherence testing, as they can provide adherence counseling and support during the testing process. Overall, IDI participants felt that most healthcare workers would be able to perform adherence testing and delivery test result to clients, as the test requires minimal training and resources.

DISCUSSION

In this qualitative study among PLWH initiating ART in South Africa, we found an intervention of monthly POC urine tenofovir testing intervention over the first five months of treatment to be highly acceptable to PLWH receiving the intervention and healthcare providers delivering the intervention. No participants expressed negative attitudes about the intervention, and nearly all participants had very positive attitudes about the intervention. Generally, the intervention was perceived as having a low burden, few opportunity costs, and a number of positive effects and benefits to PLWH and providers. Though intervention participants had some misconceptions about the test's capabilities, these

misconceptions may have resulted in unforeseen benefits to participants, namely motivating participants to take their ART every day between tests. Additionally, intervention participants preferred the intervention over self-reporting their adherence at each visit, and providers were completely willing to use POC urine tenofovir testing for all PLWH. The intervention was also deemed to be appropriate for PLWH and potentially feasible for implementation in SOC. Overall, the positive themes that emerged from this acceptability analysis far outweighed the negative themes.

When we explored potential target populations and differentiated implementation strategies for POC urine tenofovir testing, participants generally perceived that the target population (PLWH initiating ART) and implementation strategy (monthly, clinic-based testing conducted by nurses in the first five months of care) for this study was appropriate and beneficial. Participants believed this intervention would also be beneficial for adolescents and young adults and other populations at risk of adherence challenges or defaulting on ART. They also offered several implementation strategies that should be explored for POC urine tenofovir testing, such as community-based testing, random testing, and testing delivered by counselors or other healthcare workers.

To our knowledge, STREAM HIV is the first trial to evaluate a monthly POC urine tenofovir testing intervention for PLWH initiating ART, and this qualitative sub-study provides the first evidence of participants' perceptions of and experiences with the intervention. In prior studies, POC urine tenofovir testing and other forms of drug-level testing, have been found to be acceptable and perceived as valuable for improving outcomes[52,57,58,60], but no studies have implemented and evaluated a monthly POC urine tenofovir testing intervention. Concerns about the test's utility and impact on client-provider trust and relations that have been revealed in prior studies[51,58,60] were generally not concerns for participants in our study. In fact, nearly all participants found the monthly POC urine tenofovir testing intervention to be very useful and beneficial and to have a positive impact on trust between clients and provider and the client-provider relationship. However, the intervention's perceived effectiveness for motivating improved adherence may have been bolstered as a result of participants' misconceptions about the test's adherence detection window, and we may not find the same impact if participants' misunderstandings are clarified. Additionally, our participants perceived the intervention to have a positive or neutral impact on client-provider trust and relations, though this effect likely resulted from the positive and supportive

feedback they received from the providers. The effects of this intervention on ART adherence, retention in care, and HIV viral suppression are not yet known, but participants in this qualitative study perceived the intervention to have an overall positive impact on adherence, engagement in care, and overall health and wellbeing.

As new non-TDF-based regimens become available, POC urine tenofovir testing may still be relevant. Recent findings indicate that POC urine tenofovir testing may also be suitable for PLWH receiving a tenofovir alafenamide (TAF)-based regimen, as detectable tenofovir levels are correlated with viral suppression.[65] Additionally, long-acting injectable regimens that do not contain tenofovir may not be a suitable or preferred regimen for all PLWH; therefore, oral regimens, like those containing TDF or TAF, should continue to be made available to PLWH who may prefer an oral regimen or who may not be eligible for injectable regimens.[66]

This study was subject to some limitations. We conducted IDIs with intervention participants while their POC viral load test was processing, so our sample did not include participants with viremia or who were lost to follow-up, which may have resulted in sample selection bias. Additionally, we only included intervention participants who had not received any SOC procedures, so they were not able to relate their experiences to those in SOC. Participants' responses in this qualitative study may also have been impacted by social desirability bias. Finally, this trial was conducted in research clinics, and our findings may not be generalizable to other settings.

CONCLUSIONS

Overall, monthly POC urine tenofovir testing in the first five months of treatment is highly acceptable to PLWH who recently initiated ART and to healthcare providers. Participants' perceptions of this intervention were overwhelmingly positive, with very few concerns and no perceived negative effects. When coupled with positive feedback and messaging from providers, a monthly POC urine tenofovir testing intervention may be an effective strategy for motivating optimal ART adherence and for facilitating open, honest communications about ART adherence challenges.

TABLES AND FIGURES

Table 1: Characteristics of qualitative study participants, N=28

	Intervention Participants n=20 n (%)	Healthcare Providers n=8 n (%)
Sex		
Male	10/20 (50.0%)	1/8 (12.5%)
Female	10/20 (50.0%)	7/8 (87.5%)
Age (years)		
≤ 25	1/20 (5.0%)	1/8 (12.5%)
> 25	19/20 (95.0%)	7/8 (87.5%)
Education		
Primary school	0/20 (0.0%)	0/8 (0.0%)
Did not pass matric	8/20 (40.0%)	0/8 (0.0%)
Passed matric	7/20 (35.0%)	0/8 (0.0%)
Tertiary	5/20 (25.0%)	8/8 (100%)
Provider type		
Enrolled nurse assistant	-	1/8 (12.5%)
Research nurse	-	4/8 (50.0%)
Clinician/doctor	-	3/8 (37.5%)
Time providing HIV care (years)		
≤ 5	-	2/8 (25.0%)
6-10	-	4/8 (50.0%)
> 10	-	2/8 (25.0%)
Travel time to clinic	-	
≤ 30 minutes	12/20 (60.0%)	-
31-59 minutes	8/20 (40.0%)	-
Partnership status		
No partner	2/20 (10.0%)	-
Stable partner & not married	14/20 (70.0%)	-
Married	4/20 (20.0%)	-
Partner's HIV status		
HIV-positive	8/18 (44.4%)	-
HIV-negative	0/18 (0.0%)	-
Unknown	12/18 (66.7%)	-
ART regimen at initiation		
TLD (TDF + 3TC + DTG)	18/20 (90.0%)	-
TEE (TDF + FTC + EFV)	2/20 (10.0%)	-
CD4 count		
0-199	10/20 (50.0%)	-
200-349	7/20 (35.0%)	-
350-499	1/20 (5.0%)	-
≥ 500	2/20 (10.0%)	-
POC urine tenofovir results over study follow-up		
0 undetectable results	17/20 (85.0%)	-
≥1 undetectable result(s)	3/20 (15.0%)	-

Figure 1. Thematic map of acceptability of monthly point-of-care urine tenofovir testing, organized by acceptability constructs

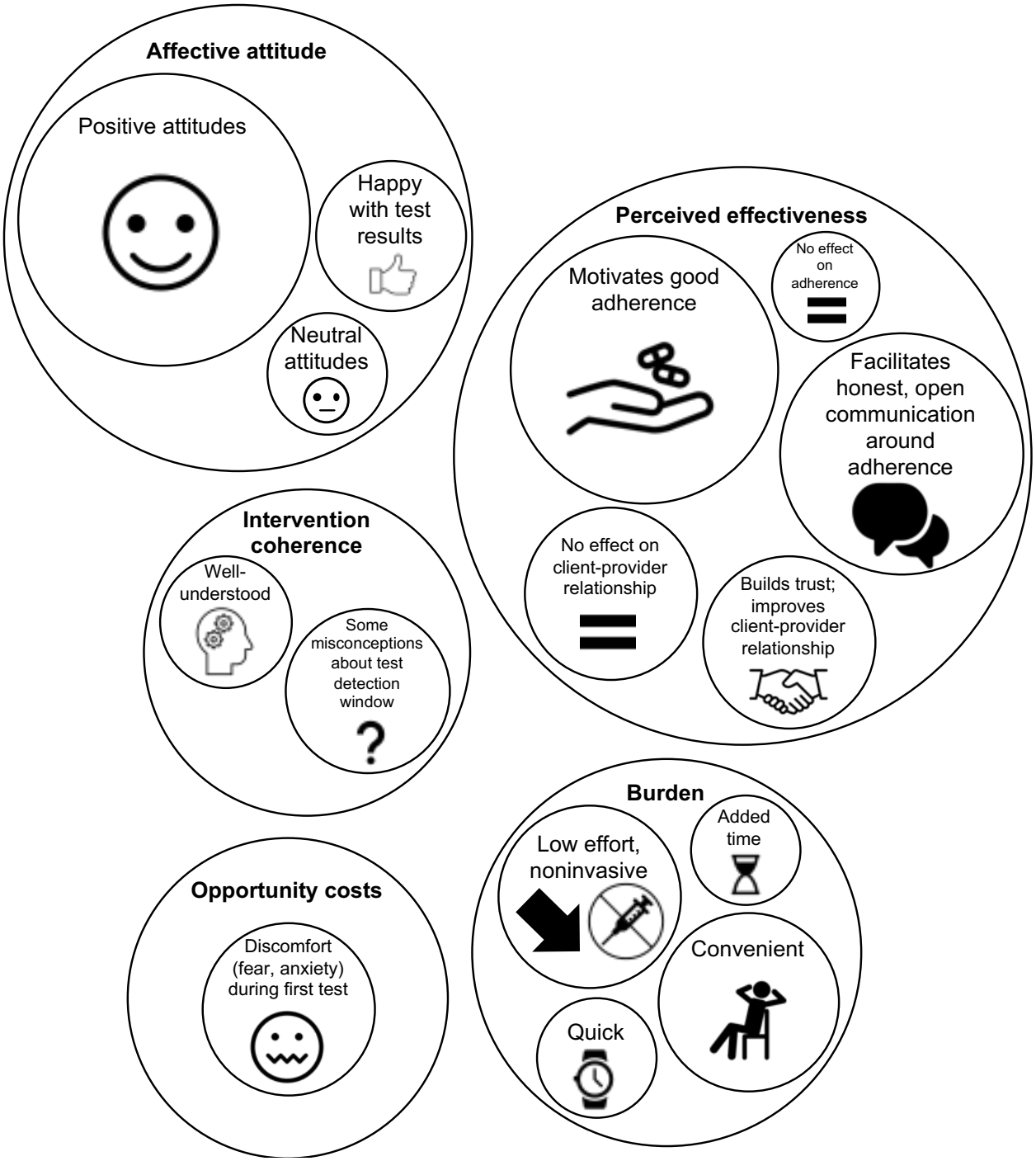


Table 2. Additional quotes from STREAM HIV in-depth interviews with study participants and healthcare providers

Theme	Quotes
Acceptability Constructs	
Affective Attitude	
Positive attitude	*"It made me happy because it meant I was doing something right. And also I understood when I was starting medication, the sister explained to me what happens, how things are going to go and the reason why the test is done." (Intervention participant, male, 43 years old)* *"These tests encouraged me because they are confirming the good work that I'm doing well in taking pills, and that's makes me happy and see that we're doing things well." (Intervention participant, male, 49 years old)* *"I liked it because as I have said it's encouraging me to take my treatment because if I don't it will show so I feel it's a good study and maybe others will be encouraged too to take their pills." (Intervention participant, female, 43 years old)*
Neutral attitude	*"I didn't have a problem because I was explained to in the beginning, I didn't have a problem." (Intervention participant, male, 43 years old)*
Burden	
Convenience	*"I think it's non-invasive, and it doesn't cause any prolonged waiting times or inconvenience." (Healthcare provider, female, urban site)*
Effort	*"I think it's user-friendly. If I can put it in that way. It's easy to read. It's easy to actually use it." (Healthcare provider, female, rural site)* *"I think the nurses are so streamlined in our study that it all happens very quickly, and the participants know they come, they need to give urine. So I think it's a very efficient process, and I think because the nurses are so efficient, and because it doesn't require too much effort, you know, in terms of getting the urine, waiting time, it doesn't really affect the two arms. There's not much difference." (Healthcare provider, female, urban site)* *"The test is…there is nothing like…there's nothing much you do with the test, so it doesn't take much of our time. Because we ask the participant to collect the urine, and then they come back with the urine, and then we start doing the test. Then you wait for like 5 minutes to give results. There's nothing much like we do in between. So we wait for the results. You do the test, and then we wait for the results, and then you disclose, and then we can continue with whatever else we're doing. It doesn't take much or like interfere with something else that we're doing now." (Healthcare provider, female, urban site)*
Opportunity Costs	
Anxiety, discomfort, embarrassment or fear	*"You get nervous even if you do things the right way and you think the test might say something opposite you know. It is like waiting for the test results at school, so seeing one line really made me feel happy that yah I am doing okay." (Intervention participant, male, 50 years old)* *"Yeah, at first I think I was very worried, but as time went I saw that it was helping me to continue staying healthy… I was worried… You know that when it's your first-time taking medication sometimes you feel down and it's like I was*

	not ready the first days, but as time goes on the test it was helping me to continue." (Intervention participant, female, 31 years old) *"I was scared because in my first month I used to forget the pills, and I'd go to bed without taking it and it was often so, I didn't know if it was going to show or not." (Intervention participant, female, 39 years old)* *"I always felt comfortable because I thought it was a good way that encourages me to take my treatment and it kept me fearful that they'd find out if I'm not taking pills. So it is better to take them so that if they say they're not found I would ask how if I know I take them all the time." (Intervention participant, female, 43 years old)* *"I think most would choose the one that doesn't use the test. I think the reasons would be feeling embarrassed carrying a class around with urine. Taking a pee all the time, always going to the toilet. Going to take a pee every time you go to the clinic, they might view that as a huge task." (Intervention participant, female, 25 years old)*
Perceived Effectiveness (and Secondary Benefits)	
Adherence	*"…maybe the thoughts of taking my pills on time stays on my mind because I'll be tested at the clinic. It's something that's always on my mind, and I'll confirm that too when I get to the clinic." (Intervention participant, female, 42 years old)* *"It's good. I think it will help others because most people are dodging because there's nothing to expose them because they are only asked questions like if you take pills correctly and they'll say yes, but knowing very well that you aren't taking it, you'll only be seen by defaulting. But if there's something to check you, you'd be careful to take it because no one wants to be caught doing bad things, so you'd be able to do the right thing because something will tell you that you didn't do well here." (Intervention participant, male, 40 years old)* *"To me personally it doesn't make much difference because I know I've been taking pills correctly, maybe it can make a difference to someone who sometimes cheats on taking pills. To me it doesn't, I'm willingly taking pills because I want to." (Intervention participant, male, 43 years old)* *"I think I would prefer the test to be used because it will encourage me to take it, because it's not easy to take them to be honest. Taking pills every day is a story. So, for me it helped me because I thought it will be hard on me, but these tests motivated me because I know it will show." (Intervention participant, female, 38 years old)* *"I think that there would be a difference [if there was no adherence testing], because if you're taking this [test], it makes you take your medication. And if you're going for your next appointment, you feel that you have to make your nurses proud and to show them that they are teaching me something make my life easy. If it wasn't for this test I don't think people would be taking their medication. It's very hard." (Intervention participant, female, 31 years old)* *"These tests encouraged me because they are confirming the good work that I'm doing well in taking pills, and that makes me happy and see that we're doing things well." (Intervention participant, male, 49 years old)*

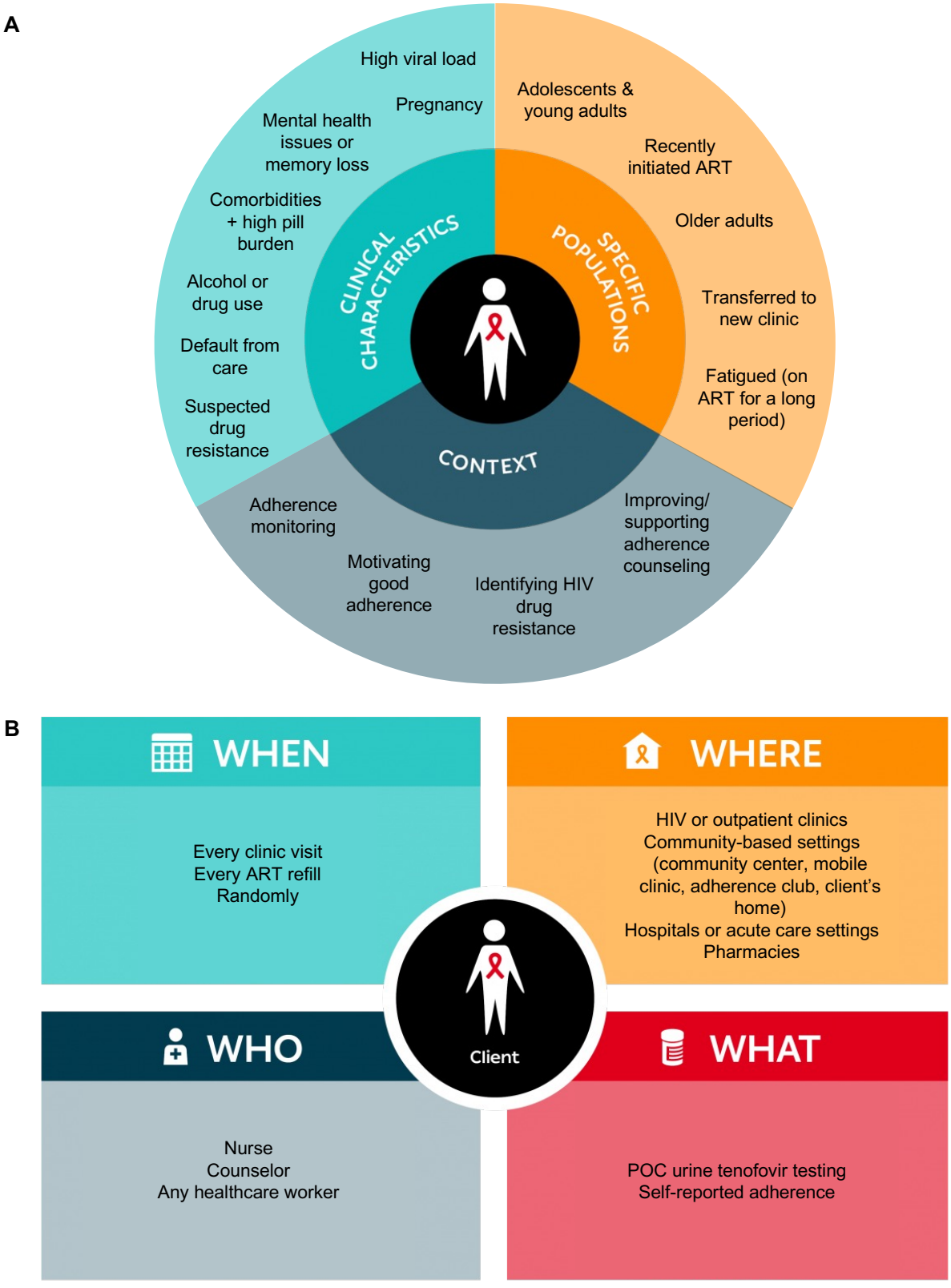
	"Yes, it can have an impact on people ensuring that they take their pills well because they'd know that when they get to clinic they'd be asked to pee, and it will show that the pill is not in their urine." (Intervention participant, female, 39 years old) *"…this test is just encouraging on its own, just by knowing that when you come you'll have to undergo this test and if I don't take my treatment the test will prove that. Meaning I'll be exposed that I'm not doing well, so it is a motivation on its own." (Intervention participant, male, 40 years old)* *"My only concern is it doesn't sort of give you a long-term view of their adherence because, you know, as long as they've been taking within those few days prior to their visit, and perhaps if they know they've got a visit coming up, they might be more compliant or adherent. Because now, in the back of their mind, they're thinking that, 'oh, I've got a clinic visit next week. Thinking about visits, I should be better with my treatment. Let me start taking my treatment.' Perhaps some of the longer times where you're away from the clinic that you're less adherent without contact." (Healthcare provider, female, urban site)* *"I think it'd actually have a positive outcome [if clinics started using this for everyone] because it would actually encourage them not to miss any dose. So I think it'll improve their adherence." (Healthcare provider, female, rural site)* *"There was no problem with it really and I found that it helps to motivate you to take your pills because you know that there is something that will show if you are not taking them. So, makes it easier for you to remember to take the pill because you have just started the treatment and sometimes, we have doubts that should you really take the pill or not but then you get a reminder that you should take them because something will tell on you if you don't take them." (Healthcare provider, male, urban site)*
Identifying adherence issues	*"I liked it, the way I perceive things, is that when something happens it must happen while you are looking at it, so that you can be enthusiastic as the person who is seeking help. But if you know that they don't check it at that specific time or you don't know where they are taking it and leave it at that…It is your life, so you need to know how everything is going now that they have tested you. So that they can also be enthusiastic because they can also see that this person cares about their life, therefore let's keep doing as we are supposed to." (Intervention participant, female, 37 years old)* *"I think also doctors will benefit. I think because hearing it from someone who self-reports who you can also see that their health is getting worse instead of getting better can be a challenge but if you have the test, you will know if you are dealing with someone who is taking their treatment or someone who has other underlying issues." (Intervention participant, female, 38 years old)* *"In life it is very nice to know where you stand with your health. It is not nice collecting medication and not getting tested. At the end of the day everything should be tested, even the car is tested. That helps and even encourages you to think you are doing the right thing." (Intervention participant, male, 50 years old)*

	"If I wasn't using the test, if maybe they just got the information and maybe not ask me the questions, they usually ask about me taking my pills without a record to prove if the pill was actually active in my blood. I'm an honest person so I'm always honest about my treatment, if I was a dishonest person there wouldn't be a relationship between me and the person assisting me. And also, I'd question how sure they are about my adherence to the treatment because I was just saying it with my mouth without any proof, I could have said anything. And also, I'd think that maybe they didn't know what they're doing cause how do you prove that I'm really taking them or if they just give it to me and I just throw them away." (Intervention participant, female, 27 years old) *"I think it just gives you a better picture of adherence so that you know how to better support and counsel the patient or participant. And I think if you do that early on, so it would just help establish them for a good, lifelong journey with their ART." (Healthcare provider, female, urban site)* *"It's something that would help you in terms of monitoring your participants and tracking their progress and whether their treatment is actually effective or not." (Healthcare provider, female, urban site)* *"So from my experience with patients, more often than not, they are not entirely truthful when it comes to it adherence. So, as much as it is about the patient, they're often not the most reliable with this. And we try to, personally even, veer towards more objective measures. So you know, you look at pill counts, you look at viral loads, you look at a urine-based tenofovir test as a more objective marker of adherence compared to what the perception of what the patient is trying to convey. I've never…I've had very few patients who just came and told me that they're struggling to take tablets. But when you've got the high viral load, or lack of tenofovir in the urine, then the discussion is a bit different. Because then I'm more targeted to say, "You know what, based on the test it looks like you might be struggling to take your doses every day. What's been your experience? What are the challenges?" And then they do open up. But generally speaking, if you ask them, "How is everything going?" "No, I'm taking my pills every day as I'm supposed to. No issues, no challenges." So I think it is useful in that way to kind of direct and be a bit more objective." (Healthcare provider, male, urban site)*
Self-report of adherence	*"I'd sometimes lie that I took pills well knowing that I did not and find out when the test is done." (Intervention participant, female, 33 years old)* *"I think it will be for the best if the nurse is told by the test that I have been or not taking the pills because with me I will not really tell the nurse the truth sometimes and she will not be sure herself if I am being honest or not." (Intervention participant, male, 37 years old)* *"It can have a big role because people will know that if they aren't taking pills, results will show that they're not, so it will have to be found out what is the problem and will not be able to deny as the detector is going to encourage people as we know some people would see them fit and well and decide to default but then if tests like this will keep on encouraging as results will tell every time you see a nurse." (Intervention participant, male, 49 years old)*

	"They're always disappointed [if they get a negative test result]. It always looks like there's something wrong with the test. But then, they'll tell you that they haven't been taking treatment. But then still, they're like disappointed. You know? They wanted it to be positive. But then they'll tell you the truth that, 'No, I haven't been taking my treatment.' Maybe 'I've come back at 10:00' or 'I'm working at the restaurant now' or 'I've been traveling with work.' But still, not look happy with the results." (Healthcare provider, female, urban site)
Client-provider relationship and communications	*"The results have good impact…because we have a conversation, they ask questions, are patient with you. I didn't feel hesitant." (Intervention participant, female, 37 years old)* *"It played a big role in maintaining our relationship with the nurses not that I was doing all this for them, but it was encouraging me to carry on so that the nurses will be happy as well, because every time I come here, I get tested, it also encourages me to continue to take my pills well." (Intervention participant, male, 26 years old)* *"With most of our participants, they are quite adhering. So I would actually praise them for taking their medication and adhering to their medication. So it would be more of a congrats and well done kind of approach." (Healthcare provider, female, rural site)*
Preferences and Willingness to Use	
Preferences	*"I would choose the test because the test really ensures, because verbally you can say you take your treatment well, while knowing very well that you don't. But there is nothing a nurse could do, don't just believe what you're telling them with your mouth." (Intervention participant, female, 25 years old)* *"I would prefer using the adherence test to make sure that my relationship with the health provider is honest." (Intervention participant, female, 27 years old)* *"I think it will be for the best if the nurse is told by the test that I have been or not taking the pills because with me I will not really tell the nurse the truth sometimes and she will not be sure herself if I am being honest or not. Sometimes I will say that I have been taking them while I wasn't. So I prefer the test." (Intervention participant, male, 37 years old)* *"I'd choose doing tests because even if I can report honestly but not everyone will do that and nurses wouldn't be able to prove the truth of what is reported." (Intervention participant, male, 49 years old)* *"That would depend on time I have, but this this thing doesn't take even five minutes, so if I had to choose… I don't care about anything because it doesn't take time to do this thing, even though I take these pills correctly. I don't have to prove to anyone, but if you want to see for yourself, it's fine I won't say anything. But I cannot just volunteer to take it just to see what it will say because I know I take my pills well." (Intervention participant, male, 43 years old)* *"I think I would do the test. I think because this one would prove. They will see the results. It will prove that I am actually taking the medication because just saying that oh I am talking the medication it won't prove anything by telling." (Intervention participant, female, 31 years old)*

	"Personally, [I prefer] the test for me. It's because doing it set me free. Because sometimes I get there and don't feel like talking. But if I know I will do the test then I'll know that yeah I can be free and believe it. But as for me I am good with it." (Intervention participant, female, 27 years old)
Willingness to use POC urine tenofovir test	*"[I would be] 100% [willing]. Because since we started, because before we started STREAM, I'd never heard of this test. But then, since we've started, in seeing the response from participants as well, it looks like a good thing to do, especially for them, the participants. So I think doing this for everyone would also benefit both the clinic or the department and also participants." (Healthcare provider, female, urban site)*
Appropriateness	
Value and usefulness	*"I saw it simple and right for a person who's not informed of medical things, though I don't know more the science behind it showing results based on what nurses and doctors wish to see. But it makes it easy to see if you are doing well or not and to have something practical thing happening in front of you, and you get to be explained to as well even before conducting the test." (Intervention participant, male, 49 years old)* *"I would love [if all HIV clinics began using adherence testing for all people taking ARVs] because I love to see people well. I have seen in some other clinics you`ll find that a person will be given medication without checking if they use it or not. So, if all clinics can use this test even the number of people that forget to take their medication will decrease and those who get sick from defaulting as well, so it will be a good thing if this test would be available at other clinics as well." (Intervention participant, male, 26 years old)*
Feasibility	
Barriers to implementation	*"It should be used. It should be used. It's not a difficult test to perform. It's not a difficult test to interpret either. So I mean, it just means that people have to be willing to do it. Sort of like with urine, TB urine LAM. You know, it's there, but not everyone is actually using it even though it's available. And I think this would be the same." (Healthcare provider, female, urban site)* *"So I don't know the financial aspect of it, and I've worked in both public and private healthcare. So I finished my community service, and then I moved across to private healthcare. And if there's anything I have learned, most of the decisions made in this country are guided by finance. Not really what's actually beneficial to patients or what's the best care for patients. So they try to do what they can do. I mean, it's an overburdened system. So I don't know what the barriers are like in terms of cost. I don't know what the test kit costs. So I think that would be one of the biggest hurdles. If it were affordable, then I'm sure they would be able to roll it out. But if it's going to be very expensive, then it may not be a feasible thing, considering the amount of HIV we treat in this country and the size of the population in this country." (Healthcare provider, female, urban site)* *"I think training as well needs to be done appropriately. I mean a simple thing like screening for TB has become such an issue next door, you know. It's something that should be your bread and butter if you're treating HIV patients. And it's not being done effectively next door. So if we do roll this out, the training needs to be done appropriately." (Healthcare provider, female, urban site)*

Figure 2. Thematic map of implementation perspectives for monthly point-of-care urine tenofovir testing, organized by elements (A) and building blocks of differentiated service delivery



CHAPTER 2: ASSOCIATION OF RECEIVING AN ORAL PRE-EXPOSURE PROPHYLAXIS DELIVERY MODEL SUPPORTED WITH A PREFERRED HIV TESTING MODALITY AND CONTINUATION OUTCOMES IN KENYA

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ABSTRACT

Introduction

Dynamic choice models of HIV prevention—specifically, choices for product type, HIV testing modality, and service location—have resulted in significant increases in biomedical prevention coverage compared to standard-of-care. However, little is known about how preferences for HIV prevention models impact outcomes in other settings and populations. We aimed to explore the association of receiving a preferred HIV testing modality to support PrEP delivery on PrEP continuation outcomes using data from a recently completed randomized controlled trial testing a simplified model of PrEP delivery supported with HIV self-testing in Kenya.

Methods

The JiPime-JiPrEP trial (NCT03593629) enrolled PrEP clients (≥18 years) in Kiambu County, Kenya. At enrollment, participants stated their preferred HIV testing modality (clinic-based or HIVST) and were randomized 2:1 to semiannual PrEP dispensing supported with interim HIVST or quarterly dispensing with clinic-based HIV testing (standard-of-care). We categorized participants as 'preferred' if the HIV testing modality supporting their assigned PrEP delivery model matched their preference and 'non-preferred' if it did not. Participants were followed for 12 months. We used binomial regression models, adjusting for sex, serodifferent partnership status, and study group, to estimate risk differences (RDs) for continuity in HIV testing (≥3 tests), PrEP refilling (at six and 12 months), and PrEP adherence (detectable tenofovir-diphosphate in dried blood spots at six and 12 months).

Results

From May 2018 to February 2020, we screened 527 individuals and enrolled/randomized 495 participants. The median age was 33 years (interquartile range 27-40) and 66.6% (329/494) were female. At enrollment, 77.3% (382/494) of participants reported a preference for HIVST and 22.7% (112/494) a preference for clinic-based HIV testing; 59.7% (295/494) were randomized to a PrEP delivery model that matched their preference. There were no statistically significant differences between the preferred and non-preferred groups in HIV testing (preferred: 67.1%, non-preferred: 62.3%; RD 7.0%; 95% CI -3.0%, 17.0%), PrEP refilling (preferred: 55.9%, non-preferred: 57.8%; RD -1.6%; 95% CI -12.1%, 8.8%), or PrEP adherence (preferred: 42.7%, non-preferred: 36.7%; RD 7.9%; 95% CI -1.9%, 17.8%). Additionally,

50.0% (70/140) of preferred and 45.2% (42/93) of non-preferred participants changed their preference for HIV testing modality at study exit.

Conclusions

In Kenya, PrEP continuation outcomes were similar between participants who did and did not receive a PrEP delivery model supported with their preferred HIV testing modality, but many participants' preferences changed over time and were influenced by the model of care they received. Our findings suggest that models of care incorporating clients' initial preferences may not result in improved outcomes, and patients may prefer the model of care that they receive even if it wasn't their initial preference.

KEY WORDS

pre-exposure prophylaxis (PrEP), HIV testing, PrEP refilling, PrEP adherence, differentiated service delivery, preference, implementation science

INTRODUCTION

Pre-exposure prophylaxis (PrEP) is highly effective for preventing HIV when used as prescribed, and the World Health Organization (WHO) recommends PrEP for all people at substantial risk of HIV acquisition.[21,67] Despite the expansion of PrEP worldwide, uninterrupted access to PrEP services is not equitable to all, and many people experience barriers to initiating PrEP and staying in care, such as costs, time, and stigma associated with receiving PrEP services.[68] In particular, frequent (quarterly) clinic visits required for PrEP refilling, HIV testing, and other clinical and counseling services can be a significant burden for clients receiving daily, oral PrEP and can drive some clients to disengage from care.

Differentiated service delivery (DSD) models can help reduce client-level barriers to PrEP services by providing person-centered care tailored to each client's unique needs and preferences to improve efficiency, access, and outcomes.[69,70] DSD models differ from standard-of-care (SOC) in terms of the people providing or supporting care, the type of care offered, the timing or frequency of care delivery, and the setting or location where care is offered.[64] HIV self-testing (HIVST) can support DSD models of PrEP services by allowing for same-day PrEP initiation in settings where rapid diagnostic HIV testing (RDT) is not available or supporting PrEP continuation; for example, allowing for quarterly HIV testing to be performed in non-clinical settings where PrEP is dispensed or for testing be performed by clients between PrEP refill visits.[71–73] When provided with DSD PrEP delivery to reduce the frequency of clinic visits, home-based HIVST may also reduce costs associated with clinic-based HIV testing, give clients more autonomy to self-manage their care, be more convenient, offer more privacy, and be the preferred HIV testing method for many people.[28,74]

The WHO and Joint United Nations Programme on HIV/AIDS (UNAIDS) recommend a person-centered approach for HIV prevention to better respond to the specific needs of each individual and to allow for shared decision-making between clients and their providers.[1,70] The WHO also recommends integrating self-managed care, such as HIVST, to improve care and health outcomes.[75] Person-centered DSD models of care that incorporate shared decision-making and clients' preferences may empower clients and increase success of these programs through improved health outcomes, greater satisfaction with care, and better allocation of resources.[13,14,76,77] Three recent randomized trials conducted in East Africa (the SEARCH SAPPHIRE trials) in outpatient departments, ante/postnatal care clinics, and

community settings evaluated the effect of providing participants with choices for HIV prevention product (PrEP or post-exposure prophylaxis), HIV testing modality, and service location.[16–18] These dynamic choice trials found that offering dynamic choice models of HIV prevention significantly increased biomedical prevention coverage compared to SOC HIV prevention.[16–18] Still, little is known about how receiving a preferred HIV prevention model impacts outcomes in other populations and settings.

In an individual-level randomized, non-inferiority, implementation trial (JiPime-JiPrEP) in Kenya, we found that semiannual PrEP dispensing supported with interim HIVST was generally non-inferior to SOC quarterly PrEP dispensing for HIV testing, PrEP refilling, and PrEP adherence at 6 and 12 months.[71,72] The trial also found variations in PrEP continuation across different priority populations, suggesting that this DSD intervention may be non-inferior or even superior to SOC for some populations (i.e., women not in known serodifferent couples) but not all.[71,72] In this study, we used data from the JiPime-JiPrEP trial to evaluate the association of receiving an oral PrEP delivery model supported with a preferred HIV testing modality and key PrEP continuation outcomes among men and women in known HIV serodifferent partnerships and women not in a known serodifferent partnership.

METHODS

Study Design

We conducted a prospective cohort study nested within the JiPime-JiPrEP trial (ClinicalTrials.gov: NCT03593629) to assess the association of receiving a preferred HIV testing modality to support PrEP delivery on three PrEP continuation outcomes over 12 months of follow-up: HIV testing, PrEP refilling, and PrEP adherence. The JiPime-JiPrEP trial is a completed randomized, non-inferiority implementation trial to determine the effect of semiannual PrEP dispensing supported with interim HIVST ("intervention") on HIV testing, PrEP refilling, and PrEP adherence compared to standard-of-care (SOC) quarterly PrEP dispensing.[78] The primary outcomes of this trial and details of the trial design and procedures have been published elsewhere.[78]

Study Setting and Population

The JiPime-JiPrEP trial was conducted at the Partners in Health Research and Development research clinic in Kiambu County, Kenya, a peri-urban county adjacent to the capital Nairobi with an HIV

prevalence of 4% among adults.[79] Individuals were eligible for trial participation if they were ≥18 years, HIV-negative (determined by rapid diagnostic testing), had initiated PrEP one month prior, were refilling their PrEP and intending to continue use, and identified as one of three priority populations: men in a known HIV serodifferent partnership, women in a known HIV serodifferent partnership, or women not in a known HIV serodifferent partnership with behaviors associated with risk of HIV aquisition.[80] The trial excluded individuals who were participating in another HIV prevention trial or were not willing to be randomly assigned to the intervention.

Study Procedures

At enrollment, participants were randomized 2:1 to the intervention or SOC. Randomization assignments were prepared for each of the three priority population groups using variable block sizes. Participants assigned to the intervention group were scheduled for semiannual clinic visits (every six months) and received a six-month PrEP supply and two HIV self-test kits (either oral fluid or blood-based) to complete at the midpoint between clinic visits. Participants in the intervention groups also received HIVST training, an informational brochure on HIVST (in English or Kiswahili), and access to a 24-hour toll-free helpline to answer questions about HIVST; they were told to use the supplemental HIV self-test kit at their discretion. Participants assigned to the SOC group were scheduled for quarterly clinic visits and received a three-month PrEP supply at each visit.

At each scheduled visit, all participants received PrEP services according to the 2018 Kenya National PrEP Guidelines,[80] including an oral PrEP regimen of tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg (preferred) or lamivudine 300 mg (alternative), rapid diagnostic testing for HIV, counseling on PrEP adherence and HIV risk reduction, pregnancy testing for women, and a clinical exam that includes syndromic screening for sexually transmitted infections and assessment of side effects. Participants in an HIV serodifferent partnership were recommended to discontinue PrEP if their partner had consistently used ART for at least six months, consistent with the national guidelines.[80] All participants were followed for 12 months, and those who had not returned for a 12-month visit by 15 months post-enrollment were traced by the study team to complete study exit and data collection

procedures. At six and 12 months, participants also provided fingerprick blood samples for dried blood spot (DBS) samples for assessment of PrEP adherence.

Participants completed questionnaires administered by a research team member in the language of their choice (English or Kiswahili) at enrollment (prior to randomization), six months, and 12 months. Questionnaires collected data on participants' self-reported HIV testing behaviors, HIV testing preferences, and other behaviors and experiences relevant to the trial. All participants were given the opportunity to use two types of HIV self-tests (oral fluid and blood-based) at the 12-month visit prior to stating their HIV testing preference. All data were collected and stored using CommCare, an electronic data collection platform (Dimagi, Cambridge, MA, USA).

Exposure and Outcome Variables

Our primary exposure variable for this analysis was receiving an oral PrEP delivery model supported with a preferred HIV testing modality. To measure participants preferred HIV testing modality, we asked them to state their preference (among the options clinic-based HIV testing, oral-fluid HIVST, or blood-based HIVST) at enrollment, prior to randomization. Their preferences were determined after participants were provided with a brief overview of the intervention and the types of HIV testing that could support PrEP delivery in the trial. We categorized participants as receiving their preferred HIV testing model (i.e., "preferred" group) if their stated HIV testing preference at enrollment matched their randomization group (i.e., those who preferred HIVST randomized to the intervention group and those who preferred clinic-based HIV testing randomized to the SOC group).

We measured the association between receiving a preferred HIV testing model and the following outcomes related to PrEP continuation: recent HIV testing, PrEP refiling, and PrEP adherence. Our HIV testing outcomes included: (1) recent HIV testing (past six months) at six months, (2) recent HIV testing (past six months) at 12 months, and (3) continuous HIV testing (≥three times since enrollment) by 12 months. Our PrEP refilling outcomes then included: (1) PrEP refilling at six months, (2) PrEP refilling at 12 months, and (3) PrEP refilling at both six and 12 months. Finally, our PrEP adherence outcomes included: (1) any detectable PrEP drug concentration using tenofovir-diphosphate (TFV-DP) at six months, (2) any detectable TFV-DP at 12 months, and (3) any detectable TFV-DP at both six and 12 months.

Each outcome was binary and was dependent on participants' retention at the 12-month follow-up visit. Participants were considered retained in care at the six-month visit if they returned for follow-up ≤14 days prior to their next scheduled follow-up visit, and were considered retained in care at the 12-month visit if they returned for follow-up ≤15 months post-enrollment. Recent HIV testing was self-reported by participants at each follow-up visit. PrEP refilling was determined through electronic pharmacy refill records. TFV-DP concentrations were measured by liquid chromatography tandem mass spectrometry using the collected DBS samples and have a 17-day half-life in blood.

Statistical Analyses

We descriptively summarized participants' baseline characteristics and compared baseline demographics between the preferred and non-preferred groups using t-tests (for continuous variables) and chi-squared tests (for binary variables). To understand the effect of receiving a preferred HIV testing model on PrEP continuation, we conducted analyses comparing the preferred and non-preferred groups to estimate any differences in recent HIV testing, PrEP refilling, or PrEP adherence. For each outcome measure related to PrEP continuation, we compared the preferred group to the non-preferred group using binomial regression models with identity link to estimate the risk difference (RD) and 95% confidence interval (CI). Each model was adjusted for priority population (men in known serodifferent partnership, women in known serodifferent partnership, or women not in known serodifferent partnership) and study group (intervention or SOC). In our analyses, we exclude participants who did not state their preferred HIV testing modality at baseline. We also conducted stratified analyses for each outcome measure for participants who did and did not change their HIV testing preference during the follow-up period. We also conducted a sensitivity analyses for our PrEP adherence outcome using a TFV-DP threshold of ≥700 fmol/punch using the modeling approach described for the primary PrEP adherence outcomes.

To better understand the effects of the intervention on participants' preferences over the study follow-up period, we conducted additional analyses to compare HIV testing preferences between the intervention and SOC groups. We descriptively summarized participants' preferences for frequency of each HIV testing option (only HIVST; only clinic-based HIV testing; or sometimes HIVST, sometimes clinic-based HIV testing) and type of HIV self-test (oral fluid, blood-based, or neither). We then estimated

differences in HIV testing preference (HIVST vs. clinic-based testing) between the intervention and SOC groups at six and 12 months using RDs and 95% CIs using the same models described above.

All analyses were performed using Stata/SE v16.1 (College Station, TX, USA).

Ethical Considerations

The JiPime-JiPrEP trial received ethical approvals from the University of Washington Human Subjects Division (STUDY00003750) and the Kenya Medical Research Institute Scientific Ethics Review Unit. All participants provided written informed consent.

RESULTS

The JiPime-JiPrEP trial screened 527 individuals and enrolled 495 participants between May 28, 2018 and February 24, 2020; all follow-up procedures were completed by May 24, 2021. We included 494 participants in this secondary analysis; one participant was excluded due to not reporting their HIV testing preference at the enrollment visit (**Figure 1**). At enrollment, clinic-based HIV testing was preferred by 112 participants (22.7%) and HIVST was preferred by 382 (77.3%). In this analysis, 295 participants (59.7%) were randomly assigned to the preferred group (i.e., their preferred HIV testing modality) and 199 (40.3%) to the non-preferred group (i.e., their non-preferred HIV testing modality). Overall, 66.6% (329/495) were female, 77.3% (382/495) were married, 59.7% (295/495) were in an HIV serodifferent partnership, and their median age was 33 years (interquartile range: 27-40) (**Table 1**). Baseline characteristics were generally balanced between the preferred and non-preferred groups.

Association of receiving a preferred HIV testing modality on PrEP continuation outcomes

Overall, there were no significant differences in the HIV testing, PrEP refilling, and PrEP adherence outcomes between the preferred and non-preferred groups at six months, 12 months, or over the entire follow-up period (**Table 2**). Recent HIV testing at six months was 83.1% (245/295) in the preferred and 84.4% (168/199) in the non-preferred group (RD -1.20%; 95% CI -8.96%, 6.56%), and at 12 months was 70.9% (209/295) in the preferred and 68.8% (137/199) in the non-preferred group (RD 4.09%; 95% CI -5.49%, 13.67%). Consistent HIV testing (≥3 times since enrollment) was 67.1% (198/295) in the preferred and 62.3% (124/199) in the non-preferred group (RD 6.96%; 95% CI -3.04%, 16.95%). PrEP refilling at six months was 77.3% (228/295) in the preferred group and 81.4% (162/199) in

the non-preferred group (RD -3.88%; 95% CI -12.37%, 4.61%), and at 12 months was 59.7% (176/295) in the preferred and 62.3% (124/199) in the non-preferred group (RD -0.47%; 95% CI -10.73%, 9.79%). At both six and 12 months, PrEP refilling was 55.9% (165/295) in the preferred and 57.8% (115/199) in the non-preferred group (RD -1.65%; 95% CI -12.07%, 8.78%). PrEP adherence at six months was 59.0% (174/295) in the preferred and 60.8% (121/199) in the non-preferred group (RD -2.44%; 95% CI -12.33%, 7.45%), and at 12 months was 46.8% (138/295) in the preferred and 41.7% (83/199) in the non-preferred groups (RD 6.25%; 95% CI -3.81%, 16.31%). PrEP adherence at both six and 12 months was 42.7% (126/295) in the preferred and 36.7% (73/199) in the non-preferred group (RD 7.93%; 95% CI -1.91%, 17.78%).

In a subgroup analysis among participants who maintained their testing preference throughout the follow-up period, HIV testing at least three times since enrollment was significantly higher in the preferred group compared to the non-preferred group (RD 24.07%; 95% CI 12.06%, 36.08%), but PrEP refilling and adherence at both six- and 12-month visits were not significantly different between preferred and non-preferred participants (**Table 3**). Among participants who changed their preference by 12 months, HIV testing, PrEP refilling, and PrEP adherence were generally not different between preferred and non-preferred groups. We also conducted a sensitivity analysis for PrEP adherence for all participants using a threshold of ≥700 fmol/punch and found no significant difference between preferred and non-preferred participants for PrEP adherence using this threshold (**Supplemental Table 2**).

Association of six-month PrEP dispensing supported with interim HIVST on participants' preferred HIV testing modality

At enrollment, HIV testing preferences were evenly distributed across study groups with most (77.3%, 382/494) preferring HIVST over clinic-based testing (**Figure 1**). The intervention had a significant effect on HIV testing preferences at both follow-up visits. HIVST was preferred over clinic-based testing by 57.69% more participants (95% CI 49.20%, 66.18%) in the intervention compared to the SOC group at six months (**Table 4**). At 12 months, however, the intervention resulted in significantly fewer preferences for HIVST (RD -9.38%; 95% CI -17.63%, -1.13%). Among those who returned for one or more follow-up visits, most (55.1%, 254/461) changed their HIV testing preference at least once during the 12-month follow-up period (**Figure 2**). At six months, when provided with choices of oral fluid HIVST, blood-based

HIVST, or neither, participants were more likely to choose the testing modality that they received in the study; however, at 12 months, nearly all participants, regardless of study group, chose one of the two HIVST options with the majority in all groups choosing oral fluid HIVST (**Supplemental Figure 2**).

DISCUSSION

In this secondary analysis of a randomized trial, we found no significant differences in PrEP continuation outcomes between those who received an oral PrEP delivery model supported with a preferred HIV testing modality and those who received a non-preferred HIV testing modality. However, more than half of participants changed their HIV testing preference at least once over the study period, which was largely influenced by the study group in which they were randomly assigned. At six months, preference for HIVST was significantly higher in the intervention group compared to the SOC group; yet, at 12 months, this preference was significantly lower in the intervention group compared to the SOC group. Though we did find HIV testing was significantly higher among those who maintained the same HIV testing preference throughout the study, we interpret this finding with caution since their 12-month stated preference was likely influenced by their behaviors throughout the study.

Our analysis offers a unique insight into PrEP participants' behaviors one year after being randomly assigned to receive a preferred or non-preferred HIV testing modality. Unlike other recent studies that have found significant improvements in PrEP coverage when provided with a choice-based model of HIV prevention services, we did not find any significant improvements in PrEP continuation when participants were randomly assigned to a preferred service delivery model.[16–18] The JiPime-JiPrEP trial, however, differs from other trials as participants' stated preference at enrollment did not influence the allocation to a PrEP and HIV testing service model. It's possible that participants provided with a dynamic choice model are motivated to improve their behaviors when they are aware that their choices and preferences are accepted and provided by their providers. The SEARCH SAPPHIRE trials (described above) also differed from the JiPime-JiPrEP trial as they offered a choice for the product type (PrEP vs. post-exposure prophylaxis) and provided care in non-PrEP clinic settings (outpatient departments, ante/postnatal care clinics, and the community), which may have influenced participants' behaviors.[16–18]

This secondary analysis had several limitations. Participants' preferences were not considered for the assignment of a PrEP dispensing model supported with different HIV testing forms; therefore, our

findings do not demonstrate outcomes from a model of PrEP delivery that incorporates participants' preferences in a shared decision-making process. The trial excluded individuals who were not willing to be randomized, which may have led to selection bias, as individuals who were reluctant to experience the intervention or who had a strong preference for SOC PrEP delivery and HIV testing were not included in this trial. Participants were not asked about their PrEP dispensing preferences, so it's possible that their PrEP dispensing preference did not align with their HIV testing preference. We found that participants' exposure to receiving a preferred HIV testing modality varied over the study period due to changing preferences; however, we are unable to determine the temporality of the relationship between participants' behaviors and their preferences after enrollment. All outcome measures were reliant on participants to returning to the clinic, and the HIV testing outcome was self-reported by participants.

CONCLUSIONS

Our study found that participants who received an oral PrEP delivery model supported with a preferred HIV testing modality did not have significantly different PrEP continuation outcomes to those who received a non-preferred model. We also found that participants' preferences changed over time and were highly influenced by the model of care that they experienced, overall indicating that people's preferences are shaped by experience, are dynamic, and are ever-changing. Models of care incorporating clients' initial preferences may not result in improved outcomes for PrEP continuation, though incorporating clients' preferences into a shared decision-making process with providers may offer other benefits for clients and should still be explored. Delivery of PrEP and HIV testing services should be flexible and tailored to each individual, with some emphasis on people's preferences, but should include shared decision-making with providers.

TABLES AND FIGURES

Figure 1. Exposure group assignment

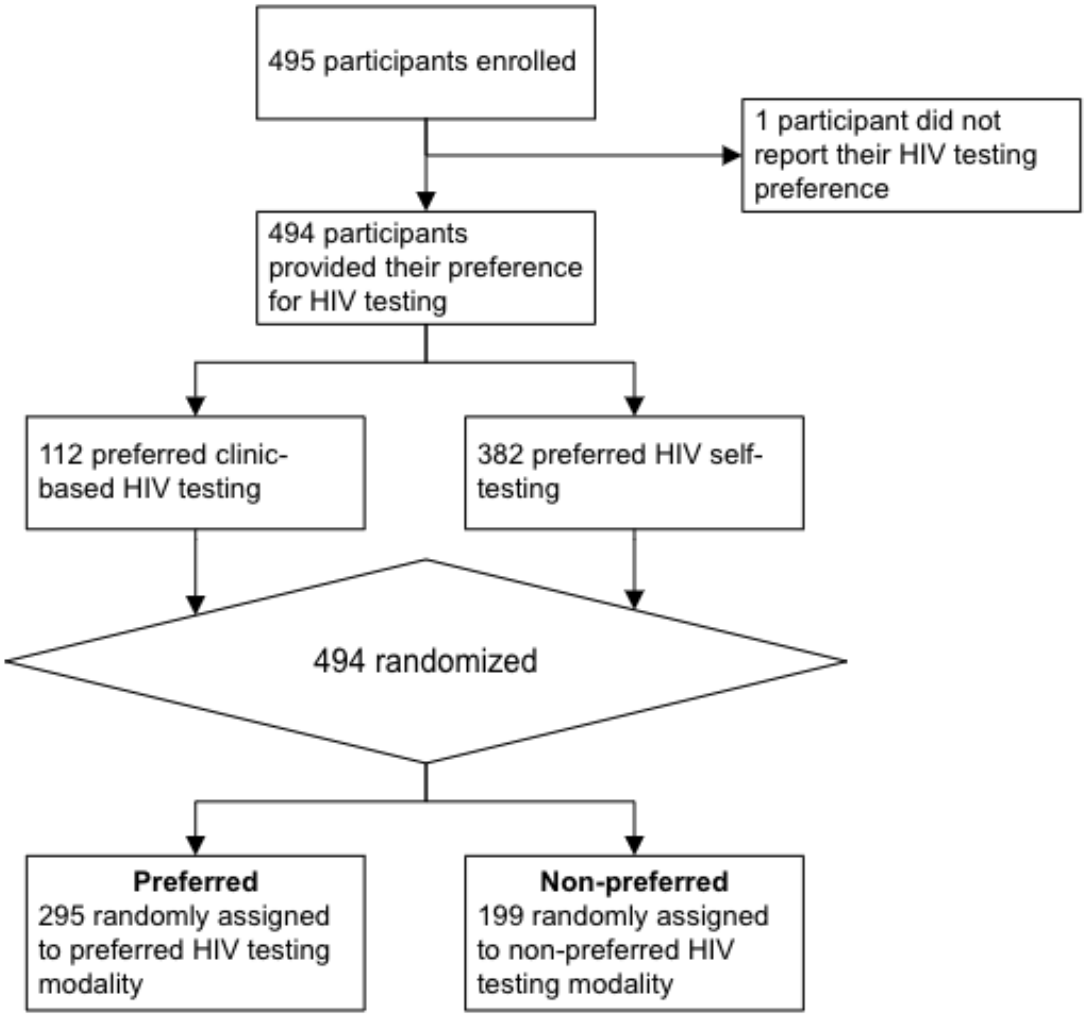


Table 1. Participants' baseline demographic characteristics, by group

Characteristic	Preferred (received preferred HIV testing modality) n=295	Non-preferred (received non-preferred HIV testing modality) n=199	Overall N=494	p-value
Female	203 (68.8%)	126 (63.3%)	329 (66.6%)	0.21
Age, median (IQR)	32 (28-40)	33 (27-40)	33 (27-40)	0.44
Travel time to clinic				0.44
<30 minutes	9 (3.1%)	6 (3.0%)	15 (3.0%)	
30-59 minutes	72 (24.4%)	55 (27.6%)	127 (25.7%)	
1-2 hours	59 (20.0%)	48 (24.1%)	107 (21.7%)	
>2 hours	155 (52.5%)	90 (45.2%)	245 (49.6%)	
Years of education, median (IQR)	9 (8-12)	9 (8-12)	9 (8-12)	0.96
Married[1]	226 (76.6%)	156 (78.4%)	382 (77.3%)	0.85
In HIV serodifferent partnership	169 (57.3%)	126 (63.3%)	295 (59.7%)	0.19
Partner is on ART	172 (58.3%)	127 (63.8%)	299 (60.5%)	0.16
Currently pregnant[2]	11 (3.7%)	9 (4.5%)	20 (4.1%)	0.75
Preferred HIV testing method				<0.01
Clinic-based HIV testing	39 (13.2%)	73 (36.7%)	112 (22.7%)	
HIVST	256 (86.8%)	126 (63.3%)	382 (77.3%)	
Randomization assignment				<0.01
Clinic-based HIV testing (standard of care)	39 (13.2%)	126 (63.3%)	165 (33.4%)	
HIVST (intervention)	256 (86.8%)	73 (36.7%)	329 (66.6%)	
Sexual Behaviors				
Number of sex partners (past month), median (IQR)	1 (1-1)	1 (1-1)	1 (1-1)	0.25
Number of sex acts (past month), median (IQR)[3]	8 (5-12)	8 (4-12)	8 (4-12)	0.27
Inconsistent condom use (past month)[4]	241 (81.7%)	164 (82.4%)	405 (82.0%)	0.37
Exchanged sex for goods/money (past month)[5]	25 (8.5%)	24 (12.1%)	49 (9.9%)	0.18
PrEP disclosure to ≥1 person[6]	62 (21.0%)	28 (14.1%)	90 (18.2%)	0.06
Prevalence of likely depression[7]	14 (4.8%)	13 (6.5%)	27 (5.5%)	0.42
Any social harm, past 3 months[8]	25 (8.5%)	15 (7.5%)	40 (8.1%)	0.89

Abbreviations: ART=antiretroviral therapy; IQR=interquartile range

[1]Marriage status not reported by 1 (0.3%) participant in preferred group.

[2]Pregnancy status not reported by 6 (3.0%) participants in non-preferred group and 12 (4.1%) participants in preferred group.

[3]Number of sex acts not reported by 6 (3.0%) participants in non-preferred group and 18 (6.1%) participants in preferred group.

[4]Condom use categorized as inconsistent if condoms not used during every sex act in the past month; inconsistent condom use not reported by 8 (4.0%) participants in non-preferred group and 20 (6.8%) participants in preferred group.

[5]Exchange of sex for goods/money not reported by 6 (3.0%) participants in non-preferred group and 17 (5.8%) participants in preferred group.

[6]Reported PrEP disclosure to at least one other person besides one's main sexual partner in serodifferent couples.

[7] Likely depression = score of 10 or greater on Patient Health Questionnaire 9-item (PHQ-9) depression scale.

[8]Social harm includes any verbal, physical, or emotional abuse by a sexual partner; social harm not reported by 1 (0.5%) participant in non-preferred group and 2 (0.7%) participants in preferred group.

Table 2. PrEP continuation outcomes by exposure group at six months, 12 months, and throughout the entire follow-up period among all participants (N=494)

Outcome	Preferred (received preferred HIV testing modality) n=295 n (%)	Non-preferred (received non-preferred HIV testing modality) n=199 n (%)	Preferred vs. non-preferred Risk difference (95% CI)[1]
6-month Follow-up			
Returned to clinic	247 (83.7%)	169 (84.9%)	
Tested for HIV (any in past 6 months)	245 (83.1%)	168 (84.4%)	-1.20% (-8.96%, 6.56%)
Refilled PrEP (at 6-month visit)	228 (77.3%)	162 (81.4%)	-3.88% (-12.37%, 4.61%)
Adherent (any TFV-DP detected)	174 (59.0%)	121 (60.8%)	-2.44% (-12.33%, 7.45%)
12-month Follow-up			
Returned to clinic	218 (73.9%)	143 (71.9%)	
Tested for HIV (any in past 6 months)	209 (70.9%)	137 (68.8%)	4.09% (-5.49%, 13.67%)
Refilled PrEP (at 12-month visit)	176 (59.7%)	124 (62.3%)	-0.47% (-10.73%, 9.79%)
Adherent (any TFV-DP detected)	138 (46.8%)	83 (41.7%)	6.25% (-3.81%, 16.31%)
Entire Follow-up Period			
Returned to clinic	218 (73.9%)	143 (71.9%)	
Tested for HIV (≥3 times since enrollment)	198 (67.1%)	124 (62.3%)	6.96% (-3.04%, 16.95%)
Refilled PrEP (at both 6- and 12-month visits)	165 (55.9%)	115 (57.8%)	-1.65% (-12.07%, 8.78%)
Adherent (any TFV-DP detected at both 6- and 12-month visits)	126 (42.7%)	73 (36.7%)	7.93% (-1.91%, 17.78%)

[1]All models adjusted for study population (men in HIV serodifferent couple, women in HIV serodifferent couple, women singly enrolled) and study group (SOC or intervention)

Table 3. PrEP continuation outcomes over entire follow-up period, by HIV testing preference at 12 months

Outcome	Preferred (received preferred HIV testing modality) n=295 n (%)	Non-preferred (received non-preferred HIV testing modality) n=199 n (%)	Preferred vs. non-preferred Risk difference (95% CI)[1]
Participants with same HIV testing preference from baseline to 12 months	**n=172**	**n=112**	
Returned to clinic	140 (81.4%)	86 (76.8%)	
Tested for HIV (≥3 times since enrollment)	130 (75.6%)	76 (67.9%)	24.07% (12.06%, 36.08%)
Refilled PrEP (at both 6- and 12-month visits)	107 (62.2%)	69 (61.6%)	4.04% (-15.84%, 23.91%)
Adherent (any TFV-DP detected at both 6- and 12-month visits)	82 (47.7%)	43 (38.4%)	13.55% (-5.20%, 32.29%)
Participants who changed HIV testing preference from baseline to 12 months	**n=95**	**n=66**	
Returned to clinic	78 (82.1%)	57 (86.4%)	
Tested for HIV (≥3 times since enrollment)	68 (71.6%)	48 (72.7%)	-1.77% (-15.65%, 12.11%)
Refilled PrEP (at both 6- and 12-month visits)	58 (61.1%)	46 (69.7%)	-8.96% (-23.76%, 5.85%)
Adherent (any TFV-DP detected at both 6- and 12-month visits)	44 (46.3%)	30 (45.5%)	2.01% (-13.27%, 17.28%)

[1]All models adjusted for study population (men in HIV serodifferent couple, women in HIV serodifferent couple, women singly enrolled) and study group (SOC or intervention)

Figure 2. Changes in HIV testing preferences over study follow-up, by group

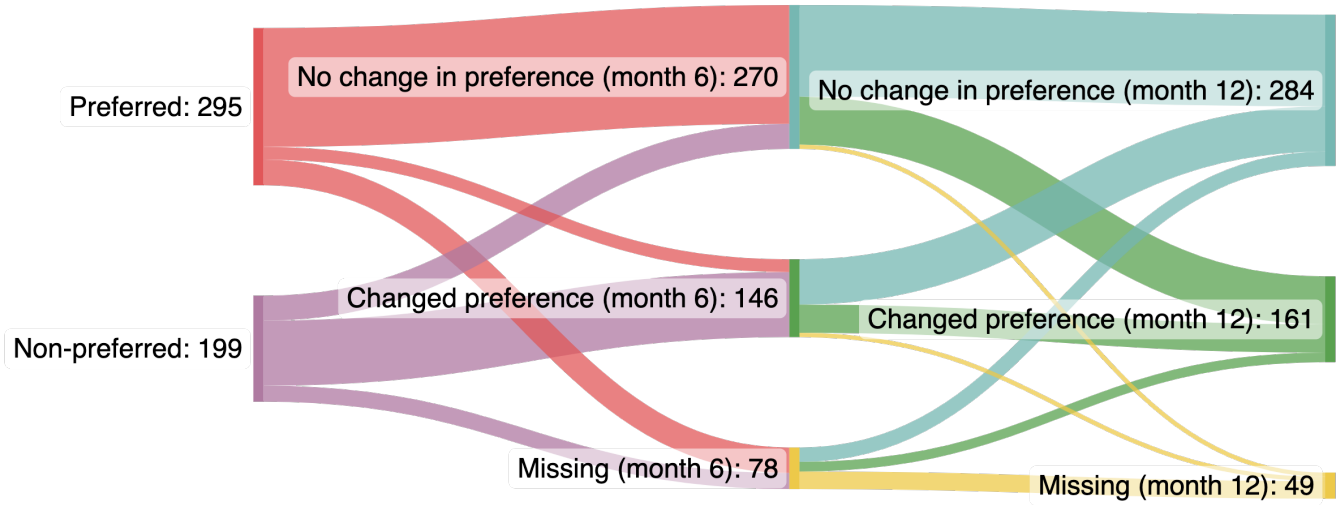


Table 4. HIV testing preferences at months six and 12, by randomization assignment (N=495)

HV testing preference	Intervention (n=329) n (%)	Standard of care (n=166) n (%)	Intervention vs. SOC Risk difference (95% CI)[1]
6-month Follow-up			
Returned to clinic[2]	277/329 (84.2%)	140/166 (84.3%)	
Clinic-based testing	26/277 (9.4%)	94/140 (67.1%)	REF
HIVST	251/277 (90.6%)	46/140 (32.9%)	57.69% (49.20%, 66.18%)
12-month Follow-up			
Returned to clinic[2]	294/329 (89.1%)	152/166 (91.0%)	
Clinic-based testing	87/294 (29.6%)	31/152 (20.4%)	REF
HIVST	207/294 (70.4%)	121/152 (79.6%)	-9.38% (-17.63%, -1.13%)

[1]All models adjusted for study population (men in HIV serodifferent couple, women in HIV serodifferent couple, women singly enrolled) and baseline testing preference
[2]Includes participants who returned after conducting extensive follow-up procedures

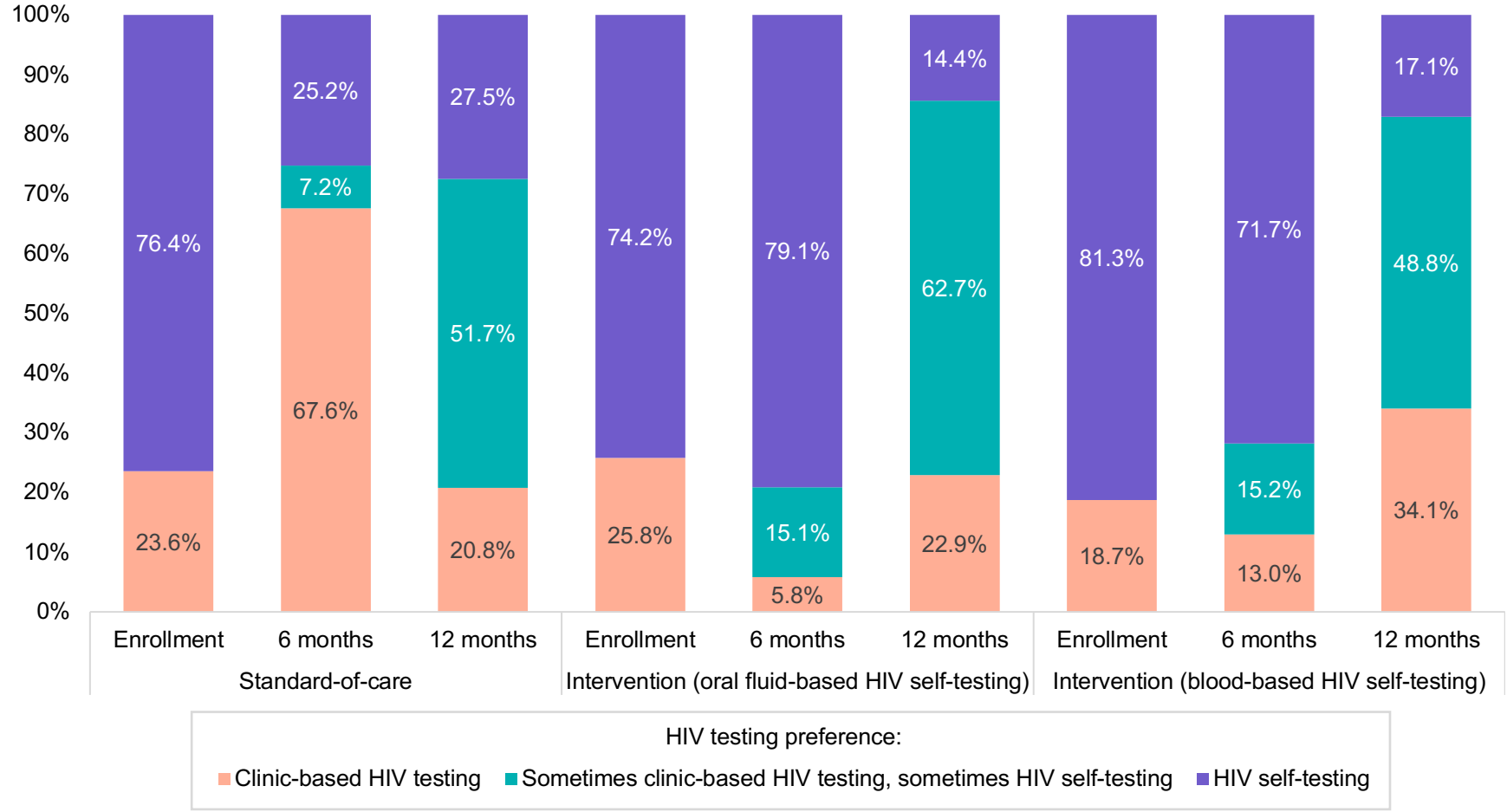
SUPPLEMENTAL TABLES AND FIGURES

Supplemental Table 1. Sensitivity analysis to evaluate higher PrEP adherence threshold

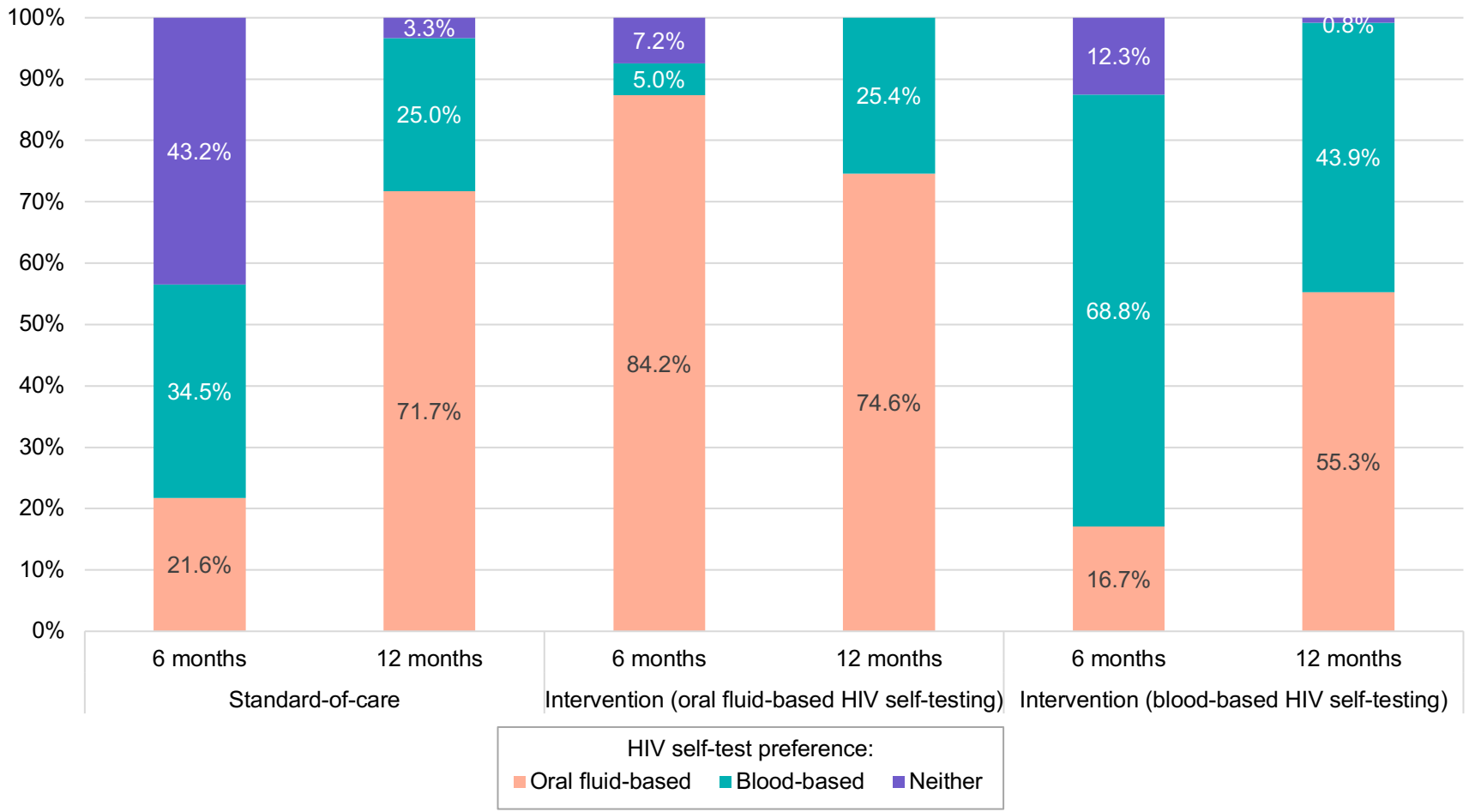
Outcome	Preferred (received preferred HIV testing modality) n=295 n (%)	Non-preferred (received non-preferred HIV testing modality) n=199 n (%)	Preferred vs. non-preferred Risk difference (95% CI)[1]
Returned to clinic[2]	218 (73.9%)	143 (71.9%)	
Adherent (TFV-DP ≥700 fmol/punch at 12-month visit)	96 (32.5%)	60 (30.2%)	0.54% (-8.42%, 9.49%)
Adherent (TFV-DP ≥700 fmol/punch at both 6- and 12-month visits)	84 (28.5%)	45 (22.6%)	3.09% (-5.02%, 11.21%)

[1]All models adjusted for study population (men in HIV serodifferent couple, women in HIV serodifferent couple, women singly enrolled) and study group (SOC or intervention)

Supplemental Figure 1. HIV testing preferences at each visit, by randomization assignment



Supplemental Figure 2. HIVST preferences at months six and 12, by randomization assignment



CHAPTER 3: EFFECT OF SEMIANNUAL ORAL PRE-EXPOSURE PROPHYLAXIS DISPENSING SUPPORTED WITH INTERIM HIV SELF-TESTING ON SEXUAL BEHAVIORS IN KENYA

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ABSTRACT

Background

Semiannual PrEP dispensing supported with interim HIV self-testing (HIVST) resulted in comparable and non-inferior PrEP continuation outcomes compared to quarterly PrEP dispensing with clinic-based HIV testing, the standard-of-care (SOC), in Kenya. We assessed the effects of this intervention, which reduced the number of annual clinics visits and associated counseling opportunities in half, on participants' sexual behaviors at one year.

Methods

The JiPime-JiPrEP trial (NCT03593629) was a randomized implementation trial conducted in Thika, Kenya among HIV-negative adults ≥18 years who had been using PrEP for one month. Participants were randomized 2:1 to: (1) semiannual PrEP dispensing with interim HIVST (six-month PrEP supply, two HIV self-tests, and semiannual clinic visits) or (2) SOC PrEP dispensing (three-month PrEP supply, clinic-based HIV testing, and quarterly clinic visits). Participants self-reported their sexual behaviors at every clinic visit and were followed for 15 months. We estimated risk differences (RDs) for inconsistent condom use and multiple sex partners (both in the past month) at six and 12 months using binomial regression models adjusted for sex, HIV serodifferent partner status, and the corresponding baseline measure.

Results

From May 2018 to February 2020, we enrolled 495 participants (intervention: 329; SOC: 166); 67% (330/495) were women, 60% (295/495) were in a known HIV serodifferent partnership, and the median age was 33 years (IQR 27-40). At six months, inconsistent condom use did not differ significantly between the intervention (90%, 224/248) and SOC (87%, 107/123) groups (RD 3.1%, 95% CI -3.4%, 9.6%); findings that remained consistent at 12 months (intervention: 91%, 222/243; SOC: 94%, 121/129; RD -1.0%, 95% CI -5.8%, 3.8%). Additionally, having multiple sex partners was not significantly different between groups at six months (intervention: 7%, 19/270; SOC: 6%, 8/133; RD -2.7%, 95% CI -7.1%, 1.6%) and 12 months (intervention: 8%, 22/289; SOC: 5%, 7/147; RD 2.9%, 95% CI -1.5%, 7.2%). No HIV seroconversions occurred over the study follow-up period.

Conclusions

In this trial, semiannual PrEP dispensing supported with interim HIVST did not significantly impact participants' sexual behaviors. These findings further emphasize that this differentiated PrEP service delivery model is safe, supporting its use to help simplify PrEP delivery in Kenya and similar settings.

KEY WORDS

pre-exposure prophylaxis (PrEP); HIV self-testing (HIVST); differentiated service delivery (DSD); sexual and reproductive health; sexual behaviors; implementation science; randomized controlled trial

INTRODUCTION

Highly effective HIV prevention strategies, like daily, oral pre-exposure prophylaxis (PrEP), are now widely available in many settings with a high HIV burden, and the number of people receiving PrEP is rapidly increasing due to scale-up initiatives.[68] To support the growing volume of PrEP clients and provide equitable PrEP access to those who could benefit, without compromising quality of care or outcomes, more efficient models of PrEP delivery are needed.[70] For oral PrEP, differentiated service delivery (DSD) models that differentiate the who, what, where, and when of service delivery can increase efficiencies for clients and health systems, reduce costs, and improve service access, particularly for clients who are unable to attend quarterly clinic visits.[69,70] HIV self-testing (HIVST) can further support multi-month PrEP dispensing and other DSD models by allowing continuation of quarterly HIV testing outside of the clinic setting and ensuring HIV seroconversions are identified as early as possible.[70]

We conducted a randomized non-inferiority trial in Kenya (JiPime-JiPrEP) to evaluate the effect of a DSD intervention, which included semiannual PrEP dispensing supported with interim HIVST to be conducted from home between clinic visits.[78] This novel model of PrEP delivery resulted in comparable recent HIV testing, PrEP refilling and PrEP adherence outcomes compared to standard-of-care (SOC) quarterly PrEP dispensing.[71,72] Other studies have found multi-month PrEP delivery models to be acceptable, feasible, and effective for increasing PrEP initiations and coverage.[31,32,81] Additionally, a recent systematic review concluded that interventions utilizing HIVST to support PrEP delivery were acceptable, feasible, and preferred over SOC PrEP delivery models.[82] Further, the World Health Organization (WHO) recommends HIVST-supported models of multi-month PrEP delivery but cautions that regular interactions between providers and clients are still needed for adherence and HIV risk reduction counseling and provision of other integrated services, such as family planning, mental health, and screening for sexually transmitted infections (STIs).[70]

In Kenya, oral PrEP is currently offered as a comprehensive, individualized prevention plan, which includes routine, quarterly assessments of PrEP adherence, side effects, HIV, STIs, and pregnancy, as well as HIV risk reduction counseling.[83] The DSD model of PrEP dispensing and HIV testing offered in the JiPime-JiPrEP trial did not compromise HIV testing, PrEP refilling, or PrEP adherence, three of the key components of Kenya's comprehensive prevention plan.[71,72] However, this

DSD model, which features semiannual clinic visits, may have some potential opportunity costs for participants since it provides fewer opportunities for behavioral risk assessments, clinical monitoring, and other sexual and reproductive health services, such as condom distribution and counseling on HIV/STI risk reduction. Risk compensation behaviors following PrEP initiation have been a particular concern for PrEP programming, as confidence in HIV protection through PrEP use could potentially lead to more risky sexual behaviors, such as inconsistent condom use or more sex partners. Many studies have since negated this hypothesis that PrEP use may lead to risk compensation.[84] However, risk compensation behaviors may still be a concern for multi-month PrEP delivery when counseling and other sexual and reproductive health services are provided less frequently.[70,85]

To better understand the impact semiannual PrEP dispensing supported with interim HIVST may have on HIV prevention, we evaluated the effect of the intervention on JiPime-JiPrEP trial participants' sexual behaviors, including their condom use and prevalence of multiple sexual partners – both prespecified secondary outcomes, at one year.

METHODS

Study Design

We used data from the JiPime-JiPrEP trial (ClinicalTrials.gov: NCT03593629), an individual-level randomized, unblinded, non-inferiority implementation trial.[78] The primary results from this trial, which measured the impact of semiannual PrEP dispensing supported with interim HIVST on PrEP continuation outcomes have been reported elsewhere.[72,86] In this secondary analysis, we evaluated the effect of this DSD PrEP delivery intervention on participants' sexual behaviors at six and 12 months.

Study Setting and Population

JiPime-JiPrEP was conducted at the Partners in Health and Research Development research clinic in Thika, Kenya, a peri-urban community about 40 km from the capital of Nairobi. Eligible trial participants were adults (≥18 years), not living with HIV (confirmed by a rapid diagnostic test), who had initiated PrEP one month prior, and were refilling PrEP. We recruited two priority populations: (1) men and women in HIV serodifferent partnerships and (2) women not in a known serodifferent partnership (singly enrolled women). The study excluded individuals who were participating in another HIV prevention trial or were not willing to be randomly assigned to the intervention.

Study Procedures and Data Collection

Participants were randomized 2:1 to: (1) the intervention group, which included semiannual PrEP dispensing with interim HIVST (six-month PrEP supply, two HIV self-tests, and semiannual clinic visits); or (2) the SOC group, which included SOC PrEP dispensing (three-month PrEP supply, clinic-based HIV testing, and quarterly clinic visits). All participants were receiving a daily, oral PrEP regimen of either tenofovir disoproxil fumarate 300 mg/emtricitabine 200 mg (preferred) or lamivudine 300 mg (alternative). Participants in the intervention group also received HIVST training and an HIVST informational brochure (available in either English or Kiswahili, the local languages) at enrollment, were given access to a 24-hour toll-free helpline to answer questions about HIVST, were asked to complete an HIV self-test at the midpoint between refill visits (i.e., three months after a refill visit), and were encouraged to use the extra self-test as a backup or for partner testing (if they felt comfortable).

At each scheduled clinic visit, all participants received PrEP services according to the 2018 Kenya National PrEP Guidelines, including PrEP dispensing, rapid diagnostic HIV testing, counseling on PrEP adherence and HIV risk reduction, pregnancy testing for women, and a clinical exam that includes syndromic screening for STIs and assessment of potential PrEP side effects.[80] Per Kenyan guidelines, PrEP continuation was encouraged for participants who continued to report behaviors associated with risk for HIV acquisition on the Ministry of Health's PrEP Rapid Assessment Screening Tool (RAST), an eight-item tool routinely being used at public clinics to determine PrEP eligibility.[80] PrEP discontinuation was encouraged if a participant's HIV risk status changed to low risk, as determined using the RAST, or if their partner has achieved viral suppression through sustained ART use (for participants in a serodifferent partnership).[80] All participants completed clinic visits at enrollment, six months, and 12 months; participants in the SOC group additionally completed clinic visits at three and nine months. By 15 months, if a participant had not returned for a 12-month follow-up visit, they were traced by the study team to complete study exit procedures and data collection.

At each visit, participants also completed questionnaires administered by a member of the research team in either English or Kiswahili, which included questions on participants' demographics and sexual behaviors. All data were collected and stored using the CommCare mobile data collection platform

(Dimagi, Cambridge, MA, USA). More details on the study procedures can be found in the published trial protocol.[78]

Sexual Behavior Outcomes

For all participants, we measured the effect of the intervention on inconsistent condom use and multiple sex partners, both in past month. To measure inconsistent condom use, we asked clients to self-report number of sex acts in past month and number of times a condom was used in past month, if these two numbers were inconsistent, we categorized their condom use as such. Additionally, we asked clients to self-report their number of sex partners in the past month, if this number exceeded one, we categorized them as having multiple sexual partners. For singly enrolled women, we also measured the effect of the intervention on their last sexual partner's HIV status (positive or unknown) and engagement in transactional sex (past month). To measure engagement in transactional sex, participants' self-reported if they had ever exchanged sex for money or favors in the past month. All outcome variables were binary and were recorded at each clinic visit.

Statistical Analyses

For each outcome measure, we calculated the proportions by study group and estimated the risk difference (RD) and 95% confidence interval (CI) using binomial regression models with identity link for each timepoint (months six and 12). For each model, we adjusted for study population (men in an HIV serodifferent partnership, women in an HIV serodifferent partnership, or singly enrolled women) and the baseline measure corresponding with each outcome. We encountered a convergence problem for the multiple sex partners outcome using binomial regression models; therefore, we used generalized linear regression models with identity link modified with robust standard errors for this outcome variable. We hypothesized that the effect of the intervention on sexual behaviors would be modified by HIV serodifferent partnership status, age group, and marital status. Therefore, we conducted a subgroup analysis for each outcome measure among singly enrolled women, a stratified analysis by age group (<25 years, ≥25 years) among all participants, and a stratified analysis by marital status (married, unmarried) among singly enrolled women. All analyses were intent-to-treat complete case analyses and completed in Stata/SE v16.1 (College Station, TX, USA).

Additionally, we conducted a sensitivity analysis among only participants who returned for a follow-up visit by 15 months, excluding participants who were traced by the study team using extensive follow-up procedures, to explore if the differences in sexual behaviors were affected by non-retention.

Ethical Considerations

The JiPime-JiPrEP trial received ethical approvals from the University of Washington Human Subjects Division (STUDY00003750) and the Kenya Medical Research Institute Scientific Ethics Review Unit. All participants provided written informed consent.

RESULTS

We screened 527 individuals and enrolled 495 participants between May 28, 2018 and February 24, 2020; all follow-up procedures were completed by May 24, 2021 (**Figure 1**). We randomized 329 participants to the intervention group and 166 to the SOC group (**Table 1**). Sixty percent (295/495) of participants were men and women in a known HIV serodifferent partnership, and 40% (200/495) were women singly enrolled. Participants' median age was 33 years (interquartile range [IQR] 27-40 years), and 77% (382/495) were married. Participants' baseline demographic characteristics were evenly balanced across study groups.

Among all participants, there were no significant differences in inconsistent condom use or multiple sex partners at six or 12 months between the intervention and SOC groups (**Figure 2**). Inconsistent condom use in the past month was reported by 90.3% (224/248) in the intervention group and 87.0% (107/123) in the SOC group at six months (RD 3.10%; 95% CI -3.37%, 9.57%). At 12 months, inconsistent condom use was reported by 91.4% (222/243) in the intervention group and 93.8% (121/129) in the SOC group (RD -1.02%; 95% CI -5.83%, 3.79%). At six months, the prevalence of having multiple sex partners in the past month was 7.0% (19/270) in the intervention group and 6.0% (8/133) in the SOC group (RD -2.73%; 95% CI -7.08%, 1.62%). At 12 months, 7.6% (22/289) of participants in the intervention group reported multiple sex partners in the past month, compared to 4.8% (7/147) in the SOC group (RD 2.85%; 95% CI -1.48%, 7.18%).

We found similar results all sexual behavior outcomes in our subgroup analyses among singly enrolled women (**Figure 3**) with no significant differences between groups except for the prevalence of having multiple sex partners in the past month at the 12-month visit. The difference in inconsistent

condom use between the intervention and SOC groups was -4.04% (95% CI -11.70%, 3.61%) at month six and 0.66% (95% CI -7.38%, 8.69%) at month 12. The prevalence of having multiple sex partners in the past month was similar between groups at six months (RD 4.64%; 95% CI -3.79%, 13.06%) but was higher in the intervention group at month 12 (RD 7.24; 95% CI 0.12%, 14.37%). Similarly, there were no significant differences between the intervention and SOC groups in last sex partner's HIV status or engagement in transactional sex in past month at either timepoint.

We found no significant differences in sexual behaviors across the follow-up period in our analyses stratified by age group (<25 and ≥25 years old) (**Supplemental Table 1**). In stratified analyses among singly enrolled women, there were also no differences in sexual behaviors between the intervention and SOC groups in either married or unmarried women (**Supplemental Table 2**).

In a sensitivity analysis among only participants who were retained by 15 months, the RDs for both sexual behavior outcomes were similar to those among all participants who returned for an exit visit (**Supplemental Table 3**). No HIV seroconversions occurred during the 15-month follow-up.

DISCUSSION

In this secondary analysis of a randomized non-inferiority trial, a DSD model of semiannual PrEP dispensing supported with interim HIVST did not have a significant impact on participants' sexual behaviors, specifically condom use and multiple sex partners, despite having fewer opportunities for sexual and reproductive health services that would typically be offered on a quarterly basis. Additionally, in our subgroup analysis among singly enrolled women, the intervention did not have a significant effect on consistent condom use, multiple sex partners, last sex partner's HIV status, or engagement in transactional sex. Semiannual PrEP dispensing supported with interim HIVST was also found to be non-inferior to SOC quarterly PrEP dispensing for HIV testing and PrEP persistence (refilling and adherence).[71,72] Together, these findings indicate that semiannual PrEP delivery and clinic visits, when offered with interim HIVST, is likely safe and will not impact sexual behaviors for clients in HIV serodifferent partnerships and women who are not in an HIV serodifferent partnership.

These findings further support the implementation of this DSD model in Kenya and similar settings to reduce the number of PrEP clinic visits for clients and health systems and expand access to PrEP, particularly for clients who are unable to attend clinic visits every three months. PrEP clients may

benefit from this DSD model of PrEP dispensing and HIV testing because it reduces the number of clinic visits, which could result in transportation, childcare, and/or opportunity cost (e.g., missed work) savings for many clients.[87] This DSD model also incorporates self-managed care for clients, which may offer more privacy and may promote autonomy and self-efficacy among clients. Providers and health systems can also benefit from this DSD model as it will reduce the number of PrEP clinic visits, which in turn will reduce healthcare costs and the burden on human resources.[74]

Concerns about reduced frequency of clinic visits may still exist, such as misalignment with scheduling of other health services (e.g., contraception), delayed side effect assessments, delayed STI testing, and delayed HIV diagnoses due to the lower sensitivity of HIV self-tests, which could result in HIV drug resistance. Aligning PrEP visits with other health services, such as family planning visits, and with partners' antiretroviral therapy refills for those in HIV serodifferent partnerships should be explored, as it could further enhance the success of this DSD model. In our study, participants were enrolled and began receiving the intervention one month after initiating PrEP; thus, many side effects could be identified prior to enrolling in a DSD model. Frequent creatinine testing may also not be necessary for younger clients and for those with a higher creatinine clearance (≥90 mL/min) at PrEP initiation, as was found in a meta-analysis of kidney function in people receiving PrEP.[88] The WHO does not currently have guidelines on the frequency of STI testing for people using PrEP, and a recent meta-analysis of various STI screening frequencies for PrEP clients did not find sufficient evidence to recommend an optimal STI screening frequency.[89,90] However, the WHO does recommend integration of differentiated STI screening tools such as STI self-testing, self-sampling, or telehealth services for screening of STI symptoms, which could support DSD models of PrEP delivery and prevent delayed STI diagnoses, particularly for PrEP clients at higher risk of STI acquisition.[70] Additionally, a recent mathematical modeling study predicted that missed HIV infections resulting from HIVST in people receiving PrEP would not have a significant impact on PrEP-associated HIV drug resistance compared to rapid diagnostic antibody testing or nucleic acid amplification testing if HIVST is expanded to support PrEP initiations in western Kenya.[91]

This analysis had some limitations that should be considered. We only included participants who had been using PrEP for one month and who were in one of three priority populations (men in HIV serodifferent partnership, women in HIV serodifferent partnership, or singly enrolled women), so these

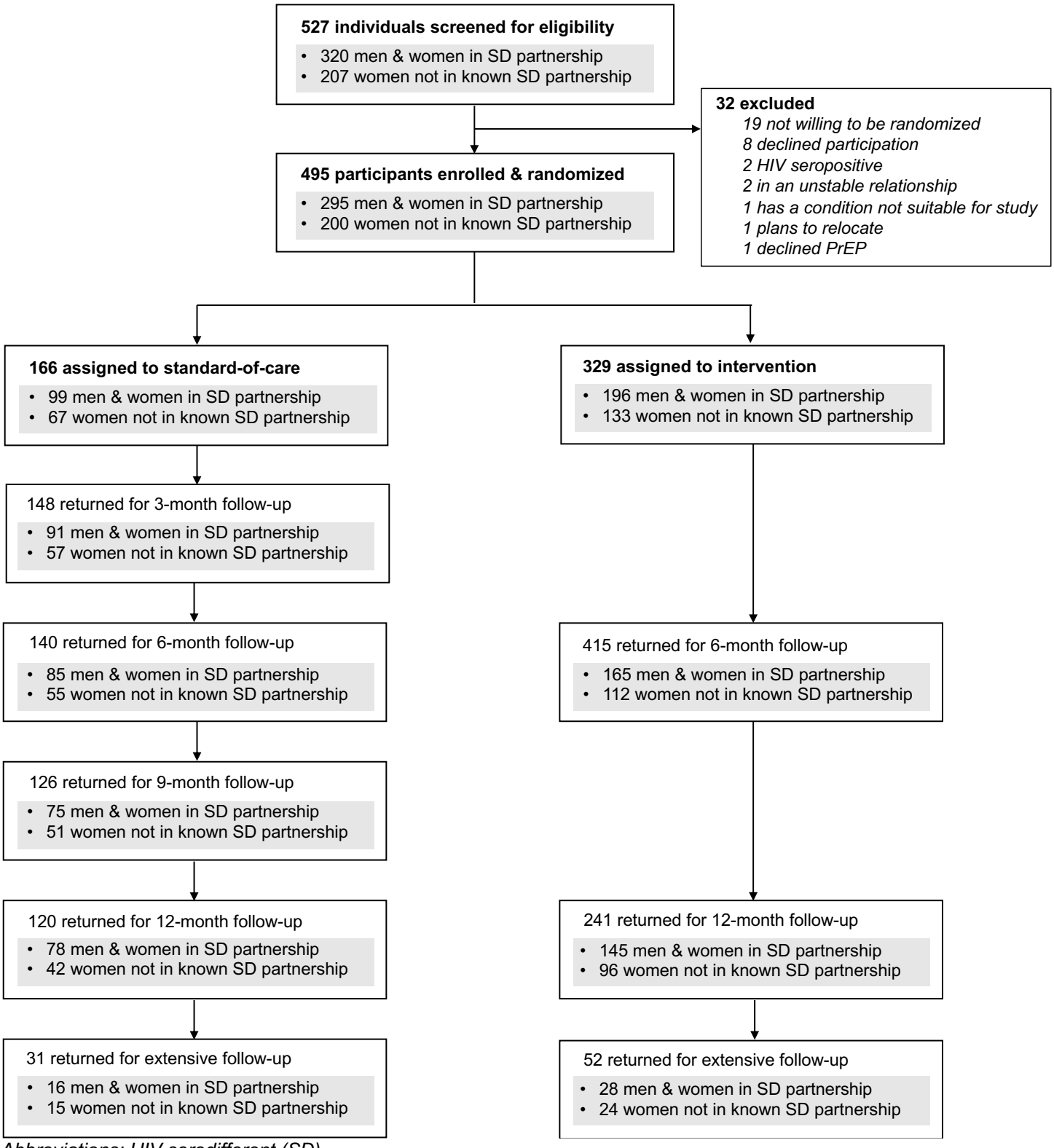
findings may not apply to people initiating PrEP or other priority populations. This study was conducted in a PrEP research clinic, so our findings may not be generalizable to other settings, for example, healthcare facilities with fewer resources. All our outcome measures relied on participants returning to the clinic and on their self-reported sexual behaviors, which may be subject to social desirability bias or selection bias if our outcome measures are associated with loss to follow-up. We also didn't collect reasons for sexual behaviors in this study (e.g., planning to conceive), which would have provided more context on participants' behaviors during the study follow-up.

CONCLUSIONS

In a secondary analysis of a randomized non-inferiority implementation trial, we found that a DSD model of semiannual PrEP dispensing supported with interim HIVST did not have a significant impact on the sexual behaviors of men and women in an HIV serodifferent partnership and singly enrolled women. This trial found that semiannual PrEP dispensing supported with interim HIVST reduced the frequency of clinic visits and reduced costs without compromising HIV testing, PrEP refilling, PrEP adherence, or sexual behaviors.[30,71,72] Overall, this DSD model of PrEP dispensing and HIV testing is safe and efficient and can help simplify PrEP delivery in Kenya and similar settings.

TABLES AND FIGURES

Figure 1. JiPime-JiPrEP trial CONSORT diagram



Abbreviations: HIV serodifferent (SD)

Table 1. Participants' baseline demographic characteristics, by study group (N=495)

Characteristic	Intervention (n=329) n (%)	SOC (n=166) n (%)
Study Population		
Men in HIV serodifferent partnership	110 (33.4%)	55 (33.1%)
Women in HIV serodifferent partnership	86 (26.1%)	44 (26.5%)
Women not in known HIV serodifferent partnership	133 (40.4%)	67 (40.4%)
Age, median (IQR)	32 (27-40)	33 (28-40)
Travel time to clinic		
<30 minutes	8 (2.4%)	7 (4.2%)
30-<60 minutes	85 (25.8%)	42 (25.3%)
1-<2 hours	71 (21.6%)	36 (21.7%)
>2 hours	165 (50.2%)	80 (48.2%)
Years of education, median (IQR)	8 (8-12)	10 (8-12)
Married	256 (77.8%)	126 (75.9%)
Currently pregnant (among women)	14 (6.4%)	6 (5.4%)
Using modern method of contraception[1] (among women)	102 (46.6%)	59 (53.2%)
Fully circumcised (among men)	102 (92.7%)	50 (90.9%)
Sexual Behaviors		
Frequency of sex (past month), median (IQR)	8 (4-12)	8 (4-12)
Inconsistent condom use (past month)[2]	261 (79.3%)	144 (86.8%)
Multiple sex partners (past month)	32 (9.7%)	19 (11.5%)
Last sex partner living with HIV or unknown HIV status	295 (89.7%)	151 (91.0%)
Engaged in transactional sex (past month)[3]	29 (8.8%)	20 (12.1%)
PrEP disclosure to ≥1 person[4]	62 (18.8%)	28 (16.9%)
Self-efficacy score, median (IQR)[5]	38 (30-40)	37 (29-40)
Prevalence of likely depression[6]	22 (6.7%)	5 (3.0%)
Verbal/physical/emotional abuse (any in past 3 months)	30 (9.1%)	10 (6.0%)

Abbreviations: interquartile range (IQR); oral fluid-based (OF); pre-exposure prophylaxis (PrEP); standard-of-care (SOC)

[1]Modern methods of contraception include oral, injectable, implants, and intrauterine devices (IUDs)

[2]Inconsistent condom use defined as not using condoms during every sex act; missingness for inconsistent condom use=5.9%

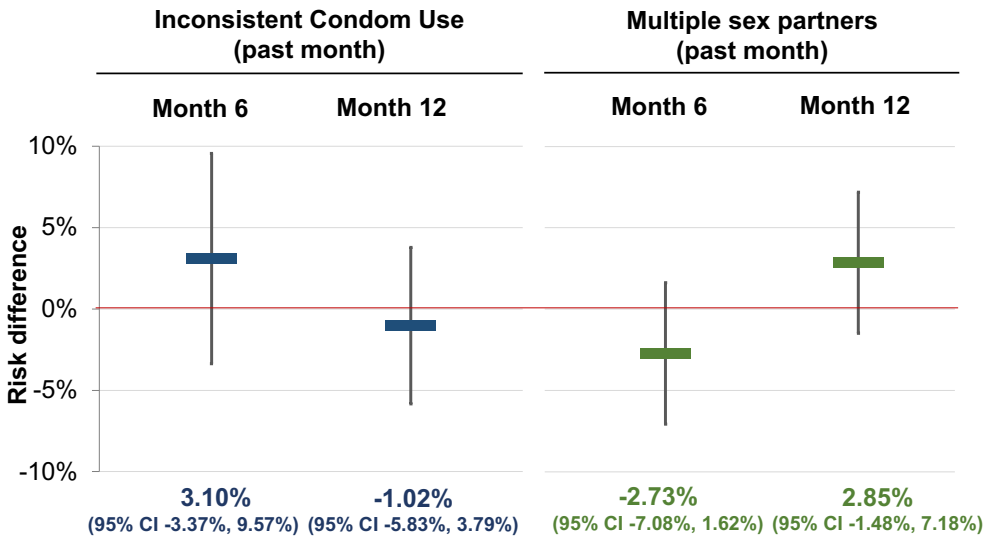
[3]Missingness for engagement in transactional sex=4.8%

[4]PrEP disclosure to at least one other person besides one's main sexual partner in HIV serodifferent partnership

[5]Self-efficacy score calculated using the General Self-Efficacy Scale (low=10, high=40)

[6]Likely depression defined by a score of 10 or greater on Patient Health Questionnaire 9-item (PHQ-9) depression scale

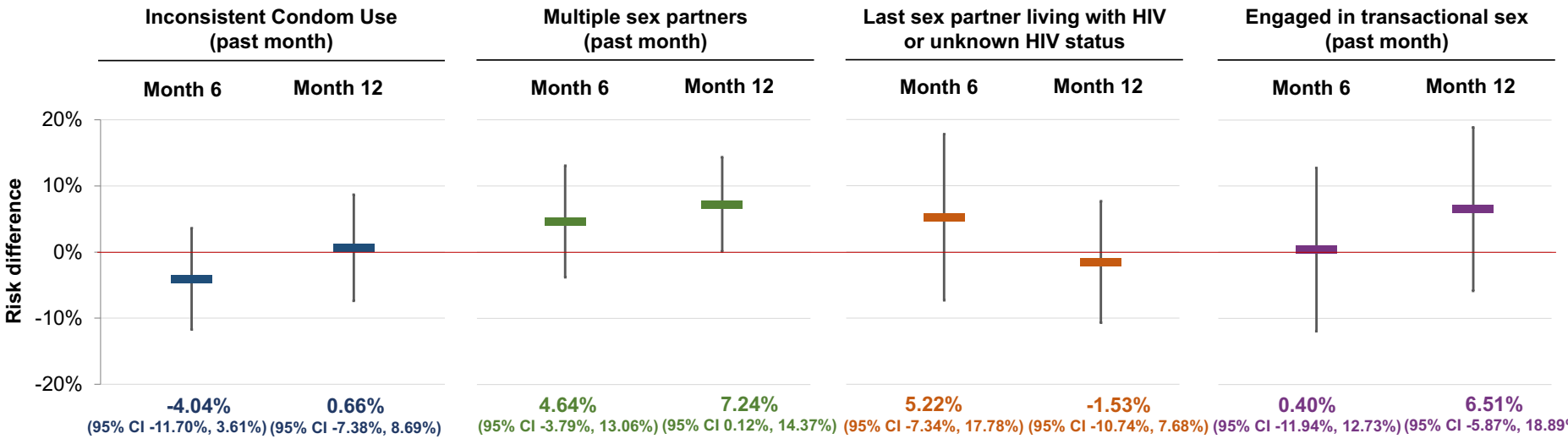
Figure 2. Effect of six-monthly PrEP dispensing supported with HIV self-testing on inconsistent condom use and multiple sex partners, among all participants (N=495)[1]



SOC (N=166)	87.0% (107/123)	93.8% (121/129)	6.0% (8/133)	4.8% (7/147)
Intervention (N=329)	90.3% (224/248)	91.4% (222/243)	7.0% (19/270)	7.6% (22/289)

Abbreviations: confidence interval (CI); pre-exposure prophylaxis (PrEP); standard-of-care (SOC)
[1]All analyses adjusted for study population (men in HIV serodifferent partnership, women in HIV serodifferent partnership, and women not in known serodifferent partnership) and corresponding baseline measure (inconsistent condom use or multiple sex partners)

Figure 3. Effect of six-monthly PrEP dispensing supported with HIV self-testing on sexual behaviors among women not in known serodifferent partnership (N=495) [1]



	Inconsistent Condom Use (past month)		Multiple sex partners (past month)		Last sex partner living with HIV or unknown HIV status		Engaged in transactional sex (past month)	
	Month 6	Month 12	Month 6	Month 12	Month 6	Month 12	Month 6	Month 12
SOC (N=67)	91.1% (41/45)	95.2% (40/42)	9.8% (5/51)	7.3% (4/55)	81.1% (43/53)	91.2% (52/57)	18.4% (9/49)	20.0% (9/45)
Intervention (N=133)	91.1% (82/90)	93.5% (86/92)	15.7% (17/108)	14.4% (17/118)	85.5% (94/110)	89.0% (105/118)	18.1% (17/94)	24.5% (23/94)

Abbreviations: confidence interval (CI); pre-exposure prophylaxis (PrEP); standard-of-care (SOC)
[1]All analyses adjusted for corresponding baseline measure of sexual behavior

SUPPLEMENTAL TABLES AND FIGURES

Supplemental Table 1. Proportions and effect size estimates of sexual behaviors among all participants, by age group

Outcomes	Standard-of-care n (%)	Intervention n (%)	Intervention vs. standard-of-care Risk difference (95% CI)[1]
<25 years old	**n=27**	**n=49**	
Month 6			
Returned to clinic	21/27 (77.8%)	33/49 (67.4%)	
Inconsistent condom use in past month	16/18 (88.9%)	26/28 (92.9%)	3.95% (-11.82%, 19.71%)
Multiple sex partners in past month	2/21 (9.5%)	3/33 (9.1%)	-1.78% (-14.29%, 10.72%)
Month 12			
Returned to clinic	21/27 (77.8%)	36/49 (73.5%)	
Inconsistent condom use in past month	14/15 (93.3%)	23/25 (92.0%)	-8.00% (-20.06%, 4.06%)
Multiple sex partners in past month	2/21 (9.5%)	4/36 (11.1%)	-1.72% (-13.85%, 10.41%)
≥25 years old	**n=139**	**n=280**	
Month 6			
Returned to clinic	119/139 (85.6%)	244/280 (87.1%)	
Inconsistent condom use in past month	91/105 (86.7%)	198/220 (90.0%)	2.79% (-4.51%, 10.09%)
Multiple sex partners in past month	6/112 (5.4%)	16/237 (6.8%)	0.44% (-3.54%, 4.42%)
Month 12			
Returned to clinic	130/139 (93.5%)	257/280 (91.8%)	
Inconsistent condom use in past month	107/114 (93.9%)	199/218 (91.3%)	-0.49% (-5.69%, 4.72%)
Multiple sex partners in past month	5/126 (4.0%)	18/253 (7.1%)	3.44% (-0.29%, 7.16%)

Abbreviations: confidence interval (CI)

[1]All analyses adjusted for study population (men in HIV serodifferent partnership, women in HIV serodifferent partnership, and women not in known serodifferent partnership) and corresponding baseline measure (inconsistent condom use or multiple sex partners)

Supplemental Table 2. Proportions and effect size estimates of sexual behaviors among women not in known serodifferent partnership, by marital status

Outcomes	Standard-of-care n (%)	Intervention n (%)	Intervention vs. standard-of-care Risk difference (95% CI)[1]
Married women not in known serodifferent partnership[2]	**n=33**	**n=67**	
Month 6			
Returned to clinic	28/33 (84.9%)	60/67 (89.6%)	
Inconsistent condom use in past month	21/22 (95.5%)	42/49 (85.7%)	-9.40% (-18.41%, -0.39%)
Multiple sex partners in past month	2/26 (7.7%)	5/57 (8.8%)	-0.27% (-9.91%, 9.36%)
Last sex partner living with HIV or unknown HIV status	23/27 (85.2%)	50/60 (83.3%)	-3.12% (-19.27%, 13.03%)
Engaged in transactional sex in past month	2/24 (8.3%)	3/52 (5.8%)	-3.66% (-16.34%, 9.03%)
Month 12			
Returned to clinic	29/33 (87.9%)	62/67 (92.5%)	
Inconsistent condom use in past month	19/20 (95.0%)	40/45 (88.9%)	-0.66% (-12.65%, 11.34%)
Multiple sex partners in past month	1/28 (3.6%)	5/61 (8.2%)	6.95% (0.15%, 13.75%)
Last sex partner living with HIV or unknown HIV status	27/29 (93.1%)	54/60 (90.0%)	-3.61% (-15.04%, 7.83%)
Engaged in transactional sex in past month	3/23 (13.0%)	6/44 (13.6%)	2.10% (-13.58%, 17.78%)
Unmarried women not in known serodifferent partnership[2]	**n=32**	**n=66**	
Month 6			
Returned to clinic	25/32 (78.1%)	52/66 (78.8%)	
Inconsistent condom use in past month	19/21 (90.5%)	40/41 (97.6%)	2.33% (-9.94%, 14.60%)
Multiple sex partners in past month	3/23 (13.0%)	12/51 (23.5%)	10.70% (-3.91%, 25.30%)
Last sex partner living with HIV or unknown HIV status	18/24 (75.0%)	44/50 (88.0%)	14.89% (-4.60%, 34.37%)
Engaged in transactional sex in past month	7/23 (30.4%)	14/42 (33.3%)	4.73% (-19.17%, 28.62%)
Month 12			
Returned to clinic	27/32 (84.4%)	58/66 (87.9%)	
Inconsistent condom use in past month	20/21 (95.2%)	46/47 (97.9%)	2.56% (-8.76%, 13.88%)
Multiple sex partners in past month	3/26 (11.5%)	12/57 (21.1%)	8.38% (-5.03%, 21.79%)
Last sex partner living with HIV or unknown HIV status	24/27 (88.9%)	51/58 (87.9%)	0.67% (-13.98%, 15.32%)
Engaged in transactional sex in past month	6/21 (28.6%)	17/50 (34.0%)	11.36% (-9.53%, 32.25%)

Abbreviations: confidence interval (CI); pre-exposure prophylaxis (PrEP)
[1]All analyses adjusted for corresponding baseline measure
[2]Marriage status missing for 2 participants in standard-of-care group

Supplemental Table 3. Sensitivity analyses among participants retained at 12-month visit

Outcomes	Standard-of-care n (%)	Intervention n (%)	Intervention vs. standard-of-care Risk difference (95% CI)[1]
Returned to clinic[1]	120/166 (72.3%)	241/329 (73.3%)	
Inconsistent condom use in past month	98/103 (95.2%)	189/203 (93.1%)	-0.06% (-0.07%, -0.06%)
Multiple sex partners in past month	5/119 (4.2%)	15/237 (6.3%)	1.96% (-2.50%, 6.42%)

Abbreviations: confidence interval (CI)

[1]All analyses adjusted for study population (men in HIV serodifferent partnership, women in HIV serodifferent partnership, and women not in known serodifferent partnership) and corresponding baseline measure (inconsistent condom use or multiple sex partners)

[2]Excludes participants who returned after 15 months for a scheduled 12-month visit (e.g., returned after extensive follow-up procedures were used)

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