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Improving Pre-Exposure Prophylaxis Delivery for Young Women in Kenya

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Abstract

Improving Pre-Exposure Prophylaxis Delivery for Young Women in Kenya

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The rollout of pre-exposure prophylaxis (PrEP) for HIV prevention to priority populations, including young women, is expanding in sub-Saharan Africa. However, existing barriers to PrEP rollout at the individual, community and policy levels could slow progress and impede the success of PrEP implementation programs. In order to achieve success in HIV prevention, it is crucial to address these barriers, particularly among young women, a population especially vulnerable to HIV. In this dissertation, we evaluated the links among risk perception, sexual behavior and PrEP adherence in serodiscordant couples, evaluated the impact of incorporating HIVST in PrEP delivery for young women and assessed the cost of delivering PrEP to young women.

In Aim 1, we used data from HIV-negative adults enrolled in a study of PrEP and antiretroviral therapy for HIV-serodiscordant couples in Kenya and Uganda to examine associations between: 1) condom use and risk perception and 2) risk perception and PrEP adherence. In Aim 2, we offered HIV self-testing (HIVST) to young women enrolled in a PrEP implementation study in two family planning clinics and assessed satisfaction with HIV testing and clinic experience, and the impact of HIVST on PrEP delivery procedures. In Aim 3, using the same population as that in Aim

2, we used micro-costing methods to estimate the incremental cost of delivering PrEP to young women.

We found that sexual behavior aligned with perceived HIV risk, which can facilitate an HIV-negative individual's decisions about PrEP use. Additionally, we found HIVST to be feasible and acceptable for young women using PrEP, highlighting the need to evaluate its utility to streamline PrEP delivery and provide more testing options for young women on PrEP. Lastly, using practical data from PrEP implementation, we estimated the cost of delivering PrEP to young women, providing valuable data to inform budget impact and cost-effectiveness analyses as well as local resource allocation for scale-up of PrEP delivery to young women. Collectively, these studies addressed some of the barriers to PrEP delivery, proposed solutions to these barriers and drew attention to priority research needs for PrEP delivery to young women.

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Table 1. Baseline characteristics of participants by gender

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DEDICATION

For my grandma, Tabitha Amollo Ochola,
You did not have the opportunity to go to school because your parents had to prioritize educating your brothers. Yet somehow, you are so wise, and have such a deep appreciation for the value of education.

– and –

For my parents, Agnes Adoyo Wanga and Joshua Matiba Wanga,
You are not here to celebrate this achievement with me, but your memories continue to lift me up in the toughest of times.

Chapter 1. Introduction

Since the beginning of the epidemic nearly four decades ago, great milestones have been reached in the fight against HIV. In east and southern Africa, the region with the largest number of people living with HIV in the world, the estimated number of new infections for all ages has declined by 28% since 2010 [1]. The gender disparity in the number of new infections in the region has persisted though; since 2016, new infections in young women aged 15-24 years has remained 2.4 times higher than that in young men of the same age. Some reasons behind this disparity include findings that young women acquire HIV infection five to seven years earlier than their male counterparts, lack of access to healthcare and education, gender-based and intimate partner violence, poverty, transactional sex, child marriage and biological factors [2]. To mitigate the influence of factors contributing to women's higher rates of HIV acquisition, researchers have evaluated several behavioral HIV prevention programs among women, such as cash transfers [3, 4], risk reduction counseling to address violence, and school-based interventions [5-7], and found reductions in HIV incidence and HIV-risk behaviors with these interventions.

Pre-exposure prophylaxis (PrEP) is a more recent biomedical intervention that has been added to the HIV prevention toolkit for at-risk populations, and evidence from randomized, placebo-controlled clinical trials has overwhelmingly shown that oral PrEP is safe, and effective, if adherence is high, in both men and women [8-11]. Two earlier trials among African women failed to demonstrate benefit of PrEP for HIV prevention due to very low adherence to study medication as measured by plasma tenofovir levels [12, 13]. In one trial, compared to older married women, younger single women had lower adherence to PrEP [12]. Findings of low adherence among young women have motivated additional studies in this population, including demonstration and implementation studies [14], to assess PrEP awareness and factors that influence PrEP uptake, adherence and retention. While some countries such as Kenya have already issued national guidelines for PrEP delivery, uncertainties about the financial implications of PrEP delivery could slow down progress of PrEP roll out to populations at risk. Using data from PrEP studies conducted in Kenya, the work in this dissertation will contribute data on: (1)

behavioral factors that influence PrEP uptake and adherence; (2) HIV self-testing as an innovative strategy to improve the efficiency of PrEP delivery and (3) the economic cost of delivering PrEP to young women.

Risk perception, sexual behavior and PrEP adherence (Chapter 2)

Risk perception plays a key role in uptake of HIV prevention interventions. Studies in sub-Saharan Africa have found links between risk perception and sexual behavior in men and women. For example, a woman's risk perception of acquiring HIV infection from her partner was found to be the strongest predictor of condom use among South African couples [15]. In a study in Zambia, men were more likely to have multiple sex partners and to report lower HIV risk perception compared to women [16]. In Kenya, a positive association was found between risky sexual behavior and perception of HIV risk; risky sexual behavior was more common among young men and women [17]. Collectively, these data provide evidence that perception of some HIV acquisition risk may motivate individuals to take preventative measures.

Few studies have investigated how PrEP adherence could also be related to sexual behavior and HIV risk perception in at-risk populations. In a qualitative study among participants from one of the earlier PrEP trials [13], women who were in the moderate to high adherence groups reported that they believed themselves to be at risk or that the study drug would reduce their risk of acquiring HIV [18]. A follow-up study of this cohort found a positive association between risk perception and PrEP adherence (OR: 2.0, 95%CI: 1.1-3.5), and also that having multiple partners, not knowing a partner's serostatus, and having condomless sex were significantly associated with perception of HIV risk [19]. While these studies provide evidence of a link between sexual behavior, perceived HIV risk and PrEP adherence, information is lacking on longitudinal assessment of the association between risk perception and sexual behavior and risk perception and PrEP adherence, by gender, among serodiscordant couples. *In Aim 1 of this dissertation, we will assess the link between: (1) risk perception and sexual behavior and (2) risk*

perception and PrEP adherence among HIV-negative members of mutually-disclosed HIV serodiscordant couples who were enrolled in a PrEP demonstration project in Kenya and Uganda.

HIVST in PrEP delivery (Chapter 3)

Studies evaluating HIV self-testing (HIVST) in different key populations and settings have shown high acceptability, uptake, and accurate use of HIVST among both men and women in sub-Saharan Africa [20-27]. A systematic review and meta-analysis of literature to compare reliability of HIV rapid diagnostic tests when self-testing is used versus when a trained healthcare worker performs testing found that self-testers can reliably perform HIV testing [28]. These studies demonstrate acceptability and uptake of HIVST, and also provide evidence for the feasibility of facility-based self-testing to individuals at risk, including young women [20, 23, 26].

A negative HIV test is a pre-requisite for PrEP initiation or refill, which is recommended to occur on a quarterly basis. In busy and understaffed clinics, this volume of HIV testing could create inefficiencies and negatively impact PrEP programs, including reducing numbers willing to start or continue on PrEP and providers willing to prescribe PrEP. Moreover, long clinic waiting times in family planning (FP) clinics have been cited as a barrier to attending clinic [29]. In contexts where PrEP delivery is integrated in FP clinics, long clinic waiting times also become a barrier to successful PrEP implementation and compound other barriers to PrEP such as inadequate transportation and inflexible work schedules. Therefore, HIVST could be used as a tool to streamline PrEP delivery for young women. *In the second aim of this dissertation, we will evaluate, in a pilot study nested in a PrEP implementation project of PrEP delivery for young women in Western Kenya, the uptake of HIVST, the factors associated with uptake of HIVST and the impact of HIVST on PrEP delivery procedures*.

Cost of PrEP delivery for young women (Chapter 4)

In addition to the need to improve PrEP delivery efficiency, there is a need to evaluate the cost of PrEP delivery. While domestic funding for HIV response in eastern and southern Africa has been increasing since 2010, in 2018, 59% of total HIV resources in this region came

from external sources including the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United States (bilateral) and other international donors [30]. Given the existing resource demands for long-standing HIV prevention interventions (condom distribution, HIV testing, prevention of mother-to-child transmission, voluntary medical male circumcision, STI treatment and diagnosis, and post-exposure prophylaxis), decision-makers need informed data on the resource requirements of PrEP to make informed decisions when allocating resources. Multiple mathematical modeling studies have suggested that PrEP is a cost-saving intervention when used as combination HIV prevention intervention for young women [31-33]. However, these studies have been limited by the use of fixed cost estimates that are not from real-world PrEP implementation. To date, only one study has evaluated the cost of PrEP delivery for young women in eastern Africa [34] and more primary costing studies are needed. *In Aim 3 of this dissertation, we will estimate, from a provider perspective, the economic cost of PrEP delivery for young women in two family planning clinics in Western Kenya*.

Thus, in summary the aims of this dissertation will address three of the fundamental components of PrEP implementation including HIV risk assessment, HIV testing and PrEP delivery cost. The collective impact of this work will provide evidence to guide policy and future research on approaches to support and improve PrEP delivery for young women.

Chapter 2. Sexual behavior and perceived HIV risk among HIV-negative members of serodiscordant couples in East Africa

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Sexual behavior and perceived HIV risk among HIV-negative members of serodiscordant couples in East Africa

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Running head: Sexual behavior and risk perception

ABSTRACT

HIV risk perception may influence the use of HIV prevention interventions. Using data from HIV-negative adults enrolled in a study of pre-exposure prophylaxis (PrEP) and antiretroviral therapy for HIV-serodiscordant couples in Kenya and Uganda, we examined associations between: 1) condom use and risk perception and 2) risk perception and PrEP adherence. Two-thirds of HIV-negative partners reported condomless sex with their HIV-positive partner or another partner in the month prior to study enrollment. Compared to those who reported no condomless sex, participants who reported condomless sex during the month prior to study visit had 5-fold higher odds of reporting "high risk" vs "no risk" perception (36.3 versus 10.9%: aOR=4.9, 95% CI: 3.4-6.9). Reporting condomless sex in the most recent sex act was associated with increased odds of perceiving some HIV risk (aOR for high risk=7.3, 95% CI 4.9-10.8; aOR for moderate risk=4.8, 95% CI 3.5-6.7; aOR for low risk=3.5, 95% CI 2.7-4.6). We found no significant association between risk perception and PrEP adherence. Sexual behavior aligned with perceived HIV risk, which can facilitate an HIV-negative individual's decisions about PrEP use.

Key words: HIV, risk perception, serodiscordant, condomless sex, PrEP

INTRODUCTION

Risk perception is an important factor in the uptake of HIV prevention interventions, but studies have found mixed results on HIV prevention behaviors that influence of risk perception [35]. Some factors that have been significantly associated with perception of high risk for HIV among people living in high-burdened settings in East and Southern Africa include single marital status, not knowing a partner's HIV status, gender, having multiple partners, and being in an age-disparate partnership [16, 19, 36, 37]. Substantial evidence supports the idea that sexual behavior also influences HIV risk perception – people reporting condomless sex or more frequent sex often have higher risk perception [15-17, 19, 36, 38, 39]. However, among serodiscordant couples, misconceptions about HIV serodiscordance have been associated with lower perception of risk and inconsistent or no condom use [40, 41]. Other barriers to condom use include male partners' reluctance to use condoms, women's difficulties in negotiating condom use, alcohol use, and the desire to have children [41]. These findings highlight the need to further investigate the association between risk perception and sexual behavior among serodiscordant couples and other at-risk populations.

In 2015, the World Health Organization (WHO) issued its first recommendation for pre-exposure prophylaxis (PrEP) to be used by people with substantial risk of acquiring HIV as a HIV prevention strategy [42]. By March 2019, an estimated 465,000-475,000 individuals were using PrEP globally, including 55 countries [43]. Adherence is strongly correlated with the level of protection afforded by PrEP [44], and challenges with adherence have been identified, especially among young women, limiting the individual benefit of PrEP for HIV prevention [12, 13]. In addition to factors such as pregnancy and breastfeeding status [8, 45], age <25 years [8, 12, 46, 47], being single [12], partner awareness and support [19, 48], social stigma [49], mobility patterns [50], and side effects [10, 12, 47, 49], multiple studies have found associations between risk perception and PrEP adherence, with individuals who report moderate to high HIV risk perception also having higher PrEP adherence [19, 48, 51-54].

Most studies to date which evaluated the association between sexual behavior and risk perception have been cross-sectional and unable to determine temporal relationships. Furthermore, the assessment of the association between perceived HIV risk and PrEP adherence is still not widely studied. In the current study, we used longitudinal data to prospectively assess the associations between sexual behavior and risk perception, as well as risk perception and PrEP adherence among high risk HIV-serodiscordant couples participating in an open-label evaluation of PrEP for HIV-negative partners during antiretroviral therapy (ART) initiation by HIV-positive partner with follow-up to 24 months.

METHODS

Study Population

Participants were HIV serodiscordant couples from the Partners Demonstration Project, an implementation science-driven evaluation of PrEP delivery integrated with ART in Kenya (Kisumu and Thika) and Uganda (Kabwohe and Kampala) between November 2012 and January 2015 [55, 56] – full eligibility criteria and study procedures have been reported elsewhere [57]. Following enrollment, participants attended visits one month after enrollment then 2 months later, then quarterly thereafter for a maximum of 24 months. At enrollment, HIV-negative partners were offered PrEP (as a daily regimen of oral emtricitabine/tenofovir disoproxil fumarate (FTC/TDF)), and PrEP discontinuation was encouraged once the partner living with HIV had used ART for at least 6 months if there was no indication of poor adherence, outside partners, or immediate plans for the woman to become pregnant. All HIV-positive partners were ART-naïve at enrollment and initiated ART according to national guidelines.

Data Collection

Demographic, clinical, and sexual behavior data were collected via self-report using standardized interviewer administered questionnaires. At enrollment and annually, the 16-item Hopkins Symptoms Checklist for Depression (HSCL-D) [58], the 4-item Rapid Alcohol Problems Screen (RAPS4) [59], and the 10-item Duke-UNC Functional Social Support Scale Screening [60]

were used to screen for depression, alcohol dependence, and social support, respectively. PrEP adherence was monitored using medication event monitoring system (MEMS) caps, which electronically monitor the time and date of pill-bottle closings. Adherence was calculated during follow up for each study period with MEMS cap data as actual openings divided by the expected number of openings since the last visit – a value ≥80% was considered high adherence [61].

Statistical Analyses

Descriptive methods were used to summarize cohort characteristics. The primary outcome of interest was a self-reported perceived risk of HIV acquisition, which was measured quarterly by asking the following: "In general, what do you think is your risk of getting HIV from your partner?" Responses included: "high risk", "moderate risk", "low risk", "no risk", and "don't know". The key behavioral exposures assessed for an association with risk perception (collected quarterly) were: 1) any condomless sex with study or non-study partner in the past month and 2) condom use during the most recent sexual intercourse with a study partner. Any condomless sex was calculated based on the number of times the participant had sex in the past month; if the difference between this and the number of times the participant used a condom was >0, then the participant was categorized as having had condomless sex. If this difference was zero (i.e. 100% condom use) or if a participant reported no sex, then the participant was categorized as having had no condomless sex.

Generalized logistic regression was used to compare the odds of being in one category of HIV risk perception relative to perceiving no HIV risk dependent on condom use. Separate models for each measure of condom use were adjusted for time in study, age category, gender, whether married/cohabiting with study partner, social support index, years that their serodiscordant status was known, abuse (verbally, physically or emotionally) by study partner, alcohol dependence, probable depression, and PrEP adherence based on *a priori* knowledge of the association of each factor with sexual behavior and risk perception [15-17, 19, 36, 38, 39]. Based on commonly seen differences in the ways men and women report sexual behavior [16, 37], we conducted analyses

stratified by gender. To evaluate the effect of risk perception on PrEP adherence, we repeated the adjusted models above with PrEP adherence as the outcome and risk perception as the exposure.

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and significance level evaluated at an alpha level of 0.05.

Ethical statement

The study protocol was approved by the Human Subjects Division at the University of Washington (#STUDY00001674) and Ethics Review Committees overseeing each study site: Scientific Ethics Review Unit at the Kenya Medical Research Institute (SSC No. 2441), the Ethics Review Committee of Kenyatta National Hospital (P286/05/2012), and the AIDS Research Committee of the Uganda National Council of Science and Technology (ARC 135 and ARC126). All participants provided written informed consent.

RESULTS

Participant characteristics

A total of 908 seronegative participants were included in this study, 89% of individuals had 24 months of follow up and the median duration of PrEP use was 12 months [interquartile range (IQR): 6, 18]. At enrollment, the median age of the population was 30 years [IQR: 26, 36], and 8.6% of female participants and 13.6% of male participants had a partner living with HIV who was virally suppressed (<1,000 copies/mL, Table 1). Participants reported knowing their serodiscordant status for a median of 3.0 months [IQR: 3.0, 9.1] and having cohabited with their study partner for a median of 2.8 years [IQR: 0.8, 7.0].

Trends in risk perception and sexual behavior

During follow-up, men tended to report perception of no risk more frequently than women (38% vs 24% of observations, $\chi^2 = 87.2$, $p<0.001$) (Figure 1). The frequency of condomless sex declined from 66% at enrollment to 31% at the first month of follow up and then fluctuated between

31% and 37% from month 3 to month 24 (Figure 2). There was evidence of a linear increase in the proportion of reporting condomless sex over time (χ^2 = 102.8, $p<0.001$), which was driven by changes between enrollment and the first month of follow up.

Association between sexual behavior and risk perception

Individuals who reported any condomless sex had almost five-fold higher odds of reporting themselves as “high risk” for HIV acquisition than those who reported no condomless sex (adjusted odds ratio [aOR]=4.7; 95% CI: 3.4-6.9, Table 2). Correspondingly, condomless sex was associated with ~4-fold higher odds of reporting “moderate risk” (aOR=4.4; 95% CI: 3.3-5.9) and ~3-fold higher odds of reporting “low risk” (aOR=2.9; 95% CI: 2.3-3.6). Not using a condom during the most recent sex with study partner was significantly associated with nearly three to seven-fold increase in odds of perceiving some risk of HIV acquisition (aOR for high risk=7.3, 95% CI 4.9-10.8; aOR for moderate risk=4.8, 95% CI 3.5-6.7; aOR for low risk=3.5, 95% CI 2.7-4.6).

Although there was no interaction between sexual behavior and risk perception ($p>0.05$), in gender-stratified models, we observed a stronger association of condomless sex and perceiving HIV risk among women than men (e.g. aOR=7.2, 95% CI 3.9-13.2 in women versus aOR=4.3, 95% CI 2.7-6.9 in men for the association of high risk perception and reporting condomless sex). In all models with any condomless sex as the exposure, the effect estimates of associations comparing the “don’t know” versus “no” risk perception category fell between those of moderate and low risk perception categories.

Association between risk perception and PrEP adherence

Among all HIV negative partners enrolled in the Partners Demonstration project, 97% initiated PrEP. Tenofovir was detected in 81% of plasma samples and 71% of individuals had high adherence by MEMS caps data [56]. Overall, compared to those who reported a risk perception of none, those who reported high, moderate, and low risk perception had 8% lower odds, 12% higher odds and 17% higher odds, respectively, of having high PrEP adherence, but

these associations were not statistically significant (Table 3). We found similar results in separate models for women and men.

DISCUSSION

In a PrEP demonstration study in Kenya and Uganda, we evaluated the effect of 1) sexual behavior on HIV risk perception and 2) HIV risk perception on PrEP adherence among HIV-negative participants. Reporting condomless sex (either in general or at the last sex act specifically) was associated with having greater HIV risk perception, yet HIV risk perception was not associated with PrEP adherence. Condom use was also associated with the likelihood of reporting moderate/great risk perception of HIV in a recent study in South Africa [36]. In our study, men reported having no perceived risk for HIV more frequently than women. These results are consistent with studies in Zambia and Mozambique where men were more likely to have multiple sex partners and to report lower risk perception than women [16, 17], and condom use at last sex was more prevalent among men and women whose perceived risk aligned with past and current sexual behavior [37].

Contrary to results from a quantitative study that found a positive association between risk perception (small/moderate/high vs. none) and good adherence (OR: 2.0; 95% CI: 1.1-3.5) [19], we did not find that the level of risk perception was associated with PrEP adherence. In addition to being in mutually disclosed serodiscordant partnerships, the HIV-negative individuals in this study received considerable PrEP counseling [62], likely greater than that received by those who attend public health facilities. This increased awareness of HIV risk possibly contributed to high PrEP adherence regardless of what risk perception was reported during visits and may explain our null findings.

Although our study and others show evidence that having condomless sex is associated with greater odds of perceiving that one has risk for HIV, measuring risk perception remains a challenge. Presently, three studies have investigated the accuracy and validity of HIV risk

perception scales and individual items. The first evaluated the "perceived risk of HIV infection scale", which measures perceived risk using likelihood estimates, intuitive feelings about risk, and the salience of the risk of HIV infection [63]. In the second study, risk perception scales were developed from items measuring perceived risk and perceived vulnerability [64]. The third study assessed risk using four questions: two about general perceived risk, and two about partner-specific perceived risk [65]. The scales developed in these studies demonstrated good reliability and validity. However, their use in other settings is still limited since they were conducted in specific settings and populations in Ethiopia [64] and the US [63, 65].

Most studies, including ours, have evaluated risk perception using a single question about the likelihood of getting HIV at a past or future time and a Likert scale with 4-5 response options [16, 19, 36, 37, 66, 67]. Some have grouped scale responses to formulate a binary variable ("high vs low" or "some vs none") [16, 36, 66], which limits assessment of the effect of different levels of risk perception. Another limitation to a one-question approach for assessing risk perception is the inability to evaluate drivers of risk perception such as partner's or own sexual behavior and whether participants understand the HIV risk posed by that behavior. This "imperfect" measurement of risk perception may also explain our inability to detect a significant association with PrEP adherence. Some studies have used qualitative methods to assess risk perception in greater detail [38]. One strength of our study is that we assessed risk perception quarterly over a 24-month period, creating frequent opportunities for individuals to evaluate their personal HIV risk and sexual behavior.

The observed alignment of sexual behavior and risk perception in our study suggests that some individuals understand how certain behaviors influence their risk of HIV infection. While this finding is encouraging, studies that have indicated a misalignment between risk perception and actual risk, particularly among men [16, 37] and young women [36], highlight the need to assess the alignment of true HIV risk (or exposure) and risk perception. This relationship is particularly important in the context of PrEP, because if measured more comprehensively, risk perception,

among other factors, could influence uptake and adherence to PrEP. Identification of times when risk perception is misaligned with PrEP adherence would present opportunities to potentially increase adherence to PrEP through HIV counseling or to promote alternative HIV prevention strategies [68].

Results from our study highlight the potential role for HIV risk perception to influence use of PrEP and other prevention strategies. As discussed in recommendations for programmatic success of global PrEP roll-out [69], it is essential for PrEP implementers and providers to conduct holistic sexual health assessments, such as high quality measurement of risk perception and the evaluation of actual HIV risk and the salience of HIV risk, to guide conversations about PrEP as a HIV prevention option for clients. As PrEP becomes more available, there is an opportunity for its delivery to incorporate counseling for HIV risk perception, sexual behavior, and PrEP adherence, which integrates the complexities and dynamics of a client's life. Understanding how these factors are linked, through research, can aid in developing and improving guidelines and programmatic tools available to providers.

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Partners Demonstration Project Team

Coordinating Center (University of Washington) and collaborating investigators (Harvard Medical School, Johns Hopkins University, Massachusetts General Hospital): Jared Baeten (protocol chair), Connie Celum (protocol co-chair), Renee Heffron (project director), Deborah Donnell (statistician), Ruanne Barnabas, Jessica Haberer, Harald Haugen, Craig Hendrix, Lara Kidoguchi, Mark Marzinke, Susan Morrison, Jennifer Morton, Norma Ware, Monique Wyatt

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Data management: DF/Net Research

Data availability

Data are available upon request to the authors' research center by emailing icrc@uw.edu.

Competing interests

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Figure 1. Frequency of risk perception by month: overall and by gender

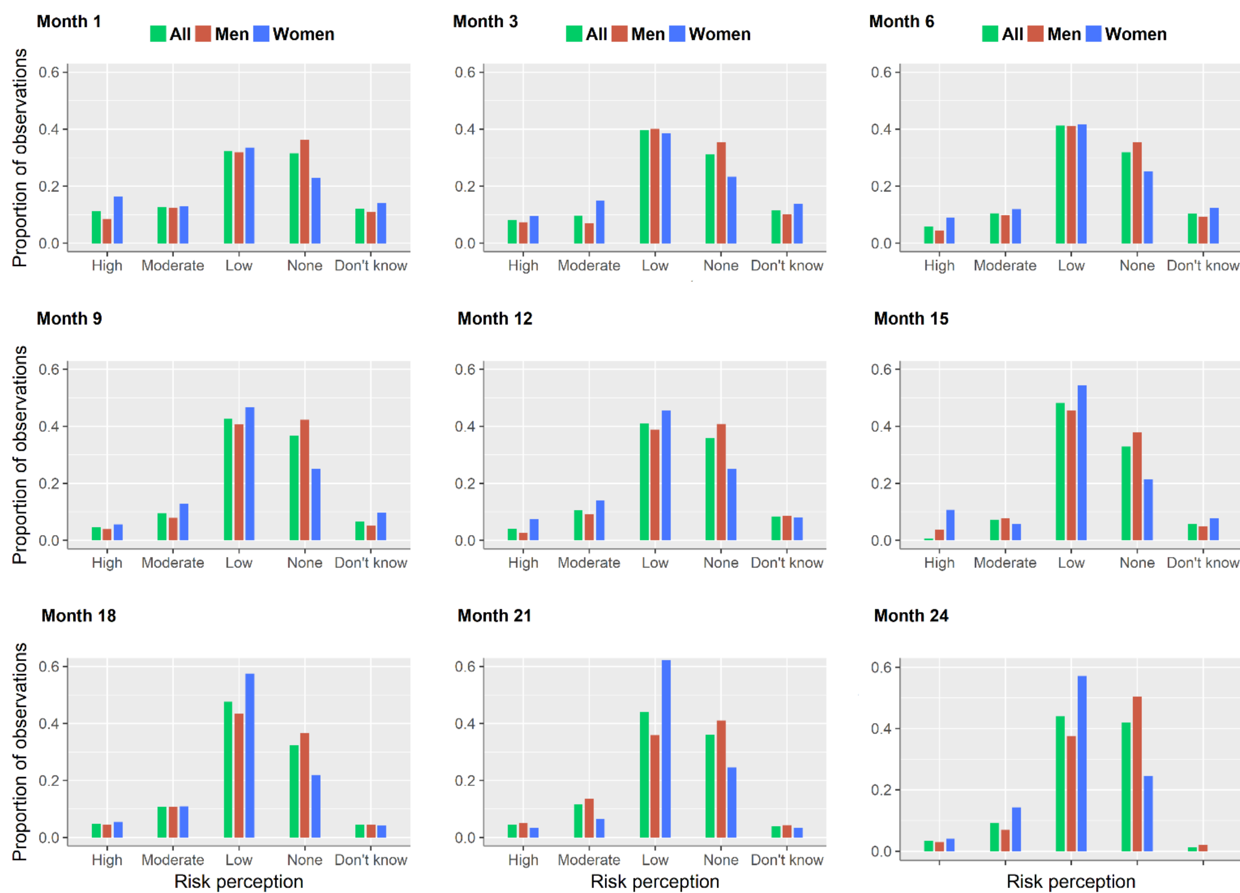

Figure 2. Distribution of observations over time by condomless sex

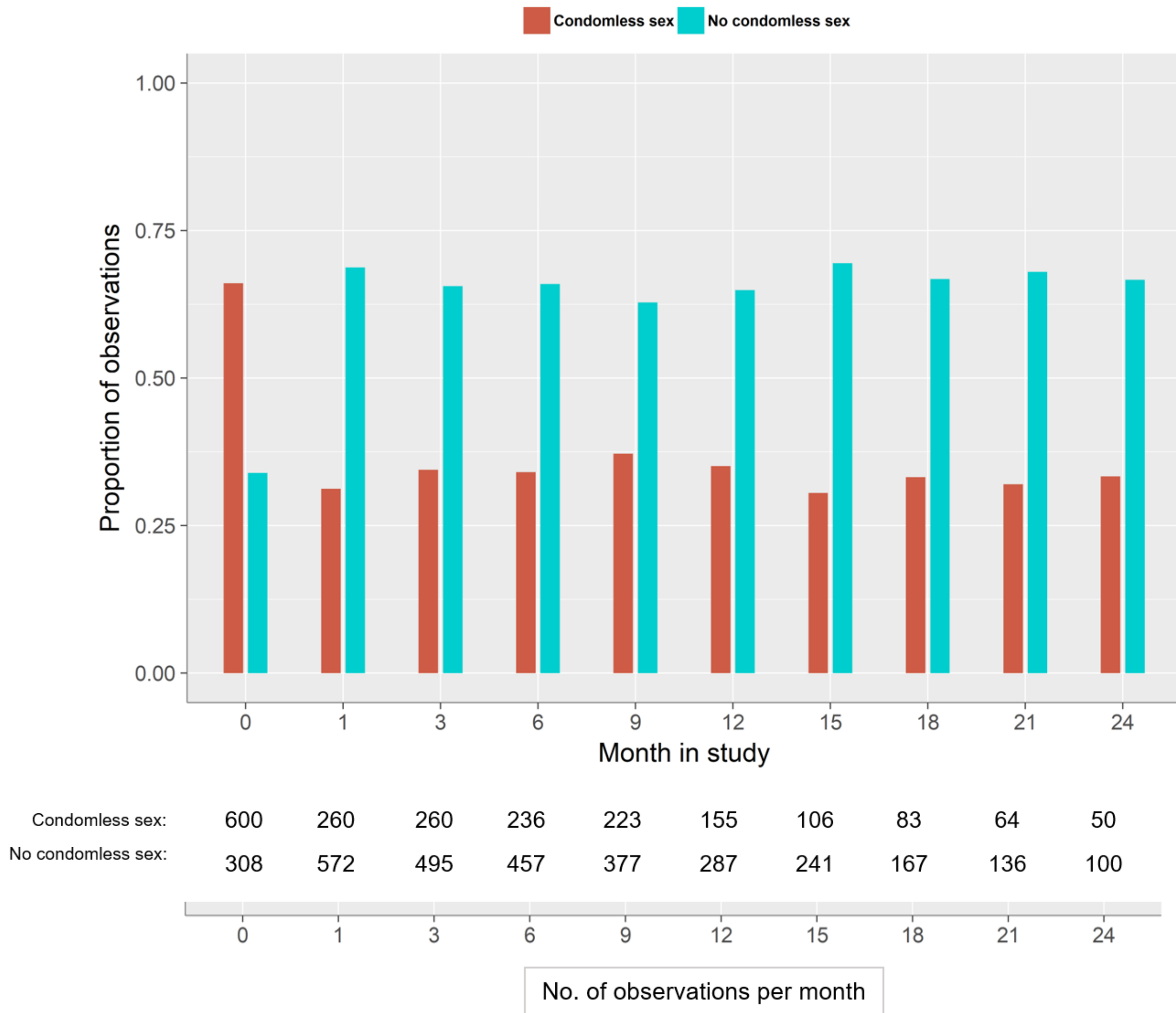

Table 1. Baseline characteristics of participants by gender

Variable	Female (n = 317) n (%) or median [IQR]	Male (n = 591) n (%) or median [IQR]
Age in years		
≤ 24	82 (25.9)	99 (16.8)
25-29	89 (28.1)	177 (29.9)
30-34	64 (20.2)	117 (19.8)
35-39	45 (14.2)	75 (12.7)
≥ 40	37 (11.7)	123 (20.8)
Married or cohabiting with partner	315 (99.4)	575 (97.3)
Years serodiscordant status known	0.1 [0.1, 0.6]	0.1 [0.1, 0.2]
Years cohabiting with partner	5.0 [1.5, 10.3]	2.0 [0.6, 5.0]
Social support, mean score[a]	3.6 [3.2, 3.9]	3.7 [3.2, 4.0]
Number of sex acts, past month	4.0 [3.0, 8.0]	6.0 [3.0, 12.0]
Number of condomless sex acts, past month	1.0 [0.0, 4.0]	2.0 [0.0, 6.0]
Reporting any partners outside of the study partner, past month	4 (1.3)	69 (11.7)
Abuse by study partner, last 3 months[b]	1 (0.3)	1 (0.2)
Alcohol dependence, last 1 year[c]	49 (15.5)	133 (22.5)
Probable depression, last 1 year[d]	39 (12.3)	51 (8.6)
HIV viral load (copies/ml) of the partner living with HIV		
<1000	27 (8.6)	79 (13.6)
< 10,000	60 (18.9)	196 (33.2)
10,000-49,999	74 (23.3)	191 (32.3)
≥ 50,000	183 (57.7)	204 (34.5)
Circumcised (men only)		
Circumcised	-	393 (66.5)
Uncircumcised	-	198 (33.5)
Effective contraception (women only)[e]		
Yes	110 (34.7)	-
No	207 (65.3)	-
STI Symptoms[f]	16 (5.1)	7 (1.2)

n = number; IQR = interquartile range; [a]Social support measured using the Duke-UNC Social Support Scale
[b]Abuse = verbally, physically or economically; [c]Alcohol dependence screened using the Rapid Alcohol Problems Screen (RAPS4); [d]Depression screened using the Hopkins Symptoms Checklist for Depression (HSCL-D); [e]Effective contraception = oral, implant, IUD, surgical, injectable); [f]STI symptoms = genital ulcer disease, vaginitis, cervicitis, pelvic inflammatory disease, urethritis.

Table 2. Adjusted associations between sexual behavior and perceived risk of getting HIV

	N[a] (%) Any condomless sex	N[a] (%) No condomless sex	Adjusted OR (95% CI) Any condomless sex[b]	N[a] (%) No condom use in last sex with study partner	N[a] (%) Condom use in last sex with study partner	Adjusted OR (95% CI) No condom use during most recent sex with study partner[b]
Risk perception: Overall						
High	143 (36.3)	143 (10.9)	4.7 (3.4, 6.9)	107 (46.9)	129 (11.8)	7.3 (4.9, 10.8)
Moderate	210 (45.6)	233 (16.6)	4.4 (3.3, 5.9)	152 (55.7)	254 (20.8)	4.8 (3.5, 6.7)
Low	667 (72.7)	1058 (47.4)	2.9 (2.3, 3.6)	472 (79.6)	1033 (51.6)	3.5 (2.7, 4.6)
Don't know	164 (39.5)	211 (15.2)	3.7 (2.7, 5.0)	116 (48.9)	195 (16.8)	4.9 (3.4, 7.0)
None	251 ([c])	1174 ([c])	-	121 ([c])	968 ([c])	-
Risk perception: Women						
High	66 (62.3)	68 (18.7)	7.2 (3.9, 13.2)	51 (68.0)	63 (21.1)	8.2 (3.9, 17.3)
Moderate	80 (66.7)	94 (24.2)	6.5 (3.7, 11.5)	58 (70.7)	106 (31.0)	5.3 (2.8, 10.3)
Low	223 (84.8)	391 (23.6)	3.8 (2.4, 6.1)	162 (87.1)	368 (60.9)	3.8 (2.1, 6.9)
Don't know	64 (61.5)	85 (22.4)	5.4 (3.0, 9.7)	52 (68.4)	79 (25.1)	6.3 (3.2, 12.3)
None	40 ([c])	295 ([c])	-	24 ([c])	236 ([c])	-
Risk perception: Men						
High	77 (26.7)	75 (7.9)	4.3 (2.7, 6.9)	56 (36.6)	66 (8.3)	7.1 (4.3, 11.7)
Moderate	130 (38.1)	139 (13.7)	4.0 (2.9, 5.7)	94 (49.2)	148 (16.8)	4.9 (3.3, 7.2)
Low	444 (67.8)	667 (43.1)	2.8 (2.1, 3.6)	310 (76.2)	665 (47.6)	3.5 (2.6, 4.8)
Don't know	100 (32.2)	126 (12.5)	3.3 (2.2, 4.8)	64 (39.8)	116 (13.7)	4.3 (2.8, 6.8)
None	211 ([c])	879 ([c])	-	97 ([c])	732 ([c])	-

[a]N = number of observations over the duration of the study
[b]OR (95% CI) adjusted for time, age, gender (only in overall model), married/cohabiting, mean social support, years serodiscordant status known, abuse by study partner, alcohol dependence, probable depression and PrEP adherence; all p-values < 0.001.
[c]percent varies with comparison, e.g., for "high" vs. "none" risk perception, the OR compares 63.7% of observations with any condomless sex versus 89.1% with no condomless sex.

Table 3. Adjusted associations between perceived risk of getting HIV and $\geq$80% PrEP adherence

Risk perception	**Overall**		**Women**		**Men**	
	N[a] (%) with adherence to PrEP[c]	Adjusted OR (95% CI)	N[a] (%) with adherence to PrEP[c]	Adjusted OR (95% CI)	N[a] (%) with adherence to PrEP[c]	Adjusted OR (95% CI)
High[b]	40 (83.3)	0.9 (0.7, 1.3)	20 (90.9)	0.8 (0.4, 1.3)	20 (76.9)	1.0 (0.7, 1.6)
Moderate[b]	69 (92.0)	1.1 (0.8, 1.5)	34 (97.1)	1.2 (0.7, 2.0)	35 (87.5)	1.1(0.8, 1.5)
Low[b]	213 (87.7)	1.2 (1.0, 1.4)	88 (88.9)	1.0 (0.7, 1.5)	125 (86.8)	1.3 (1.0, 1.6)
Don't know[b]	49 (84.5)	0.9 (0.7, 1.2)	30 (96.8)	0.9 (0.5, 1.8)	19 (70.4)	0.8 (0.6, 1.2)
None	210 (89.0)	Reference	58 (89.2)	Reference	152 (88.9)	Reference

[a]N = number of observations over the duration of the study
[b]OR (95% CI) adjusted for any condomless sex, age, gender (only in overall model), married/cohabiting, mean social support, years serodiscordant status was known, abuse by study partner, alcohol dependence and probable depression.
[c]Adherence to PrEP = observed divided by expected number of MEMS cap openings ≥80%

Chapter 3. Uptake and impact of facility-based HIV self-testing on PrEP delivery: a pilot study among young women in Kisumu, Kenya

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Uptake and impact of facility-based HIV self-testing on PrEP delivery: a pilot study among young women in Kisumu, Kenya

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Running head: HIV self-testing and PrEP delivery

Key words: PrEP; HIV testing; self-testing; counseling; standard of care; satisfaction

ABSTRACT

Introduction: HIV testing is a required part of delivery of pre-exposure prophylaxis (PrEP) for HIV prevention. However, repeat testing can be challenging in busy, under-staffed clinical settings, which could negatively impact PrEP uptake and continuation. We prospectively evaluated optional facility-based HIV self-testing (HIVST) among young women using PrEP in an implementation program.

Methods: We collected data from young women receiving PrEP at two family planning facilities in Kisumu, Kenya. At each PrEP follow-up visit, women were given the option to choose between provider-initiated testing and HIVST. We used assessed factors associated with HIVST uptake and compared satisfaction with HIV testing and clinic experience between acceptors and decliners of HIVST.

Results: A total of 172 women were offered HIVST at 202 PrEP follow-up visits. The median age was 21 years, 27% had multiple partners and 15% reported previously using HIVST. HIVST was accepted at 34.7% (70/202) of visits. Age (adjusted relative risk [aRR] 1.09 per year, 95% CI [confidence interval] 1.01 to 1.18), never being married (aRR 1.81, 95% CI 1.11 to 2.95) and having more PrEP follow-up visits (aRR 1.13 per visit, 95% CI 1.04 to 1.23) were associated with HIVST uptake. Compared to HIVST decliners, HIVST acceptors were more likely to be very happy with their overall testing experience (73% vs. 47% of visits, p=0.003) and were more likely to say they would use HIVST in the future (96% vs. 76%, p<0.001). Women who accepted HIVST had shorter visits than those choosing standard provider-initiated HIV testing (median [IQR]: 33 [32, 38] vs 54 [41.5, 81] minutes, p=0.003).

Conclusions: In this pilot evaluation in Kenya, about one-third of women using PrEP opted for HIVST over provider-initiated testing, and those choosing HIVST spent less time in the clinic and were generally satisfied with their experience. HIVST in PrEP delivery is feasible and has the

potential to simplify PrEP delivery and give clients testing autonomy. Additional studies are needed to explore optimal HIV retesting strategies in PrEP delivery, including the use of HIVST in PrEP at a larger scale and in different settings.

INTRODUCTION

As the scale-up of pre-exposure prophylaxis (PrEP) increases globally, barriers to PrEP implementation still remain. At the healthcare system level, a significant barrier is the complexity of PrEP delivery due to required regular HIV testing and monitoring in PrEP users [70, 71]. Integrating PrEP into routine primary care settings is feasible [72] and can facilitate reaching potential PrEP candidates, promote patient-centered care, destigmatize PrEP, and aid in dissemination of knowledge about PrEP to the broader community [73]. However, PrEP could add a burden on health systems, necessitating investigation of ways to simplify PrEP delivery.

Several studies in Sub-Saharan Africa have shown high acceptability, uptake and accurate use of HIV self-testing (HIVST) in men and women in populations such as adolescents [20, 23, 74], female sex workers and their partners [22, 27], and partners of women seeking antenatal and postnatal care [21, 27]. In the context of using PrEP, HIVST testing has been shown to be highly acceptable by mutually disclosed serodiscordant couples [25] and female sex workers who are interested in PrEP [75]. Nevertheless, most studies of HIVST have only evaluated HIVST for screening [20, 25, 27, 76-80] and to date, no study has evaluated the integration of facility-based HIVST in PrEP delivery and its use as a tool to optimize patient flow and visit efficiency.

HIV testing is necessary before starting or restarting PrEP, and at least every three months during PrEP use; some guidelines additionally recommend testing one month after starting PrEP [81]. In busy and understaffed clinics, this volume of testing (i.e., four repeat tests per year per person continuously on PrEP) could create inefficiencies and negatively impact PrEP programs, including reducing numbers willing to start or continue on PrEP due to long wait times and providers willing to prescribe PrEP. Therefore, incorporating strategies to streamline re-testing may reduce staff time and associated costs [82] and improve PrEP delivery efficiency. We conducted an evaluation of facility-based HIVST aimed to streamline PrEP delivery. We measured HIVST uptake, assessed factors associated with HIVST uptake, evaluated satisfaction with PrEP delivery, and the impact of HIVST on PrEP delivery processes.

METHODS

Study setting, population and design

Prevention Options for Women Evaluation Research (POWER) is an ongoing implementation science study evaluating PrEP delivery to young women in Kenya and South Africa [14]. We enrolled women attending PrEP follow-up visits at the two POWER study sites – both family planning clinics – in Kisumu, Kenya (Jaramogi Oginga Odinga Teaching and Referral Hospital and Kisumu Medical Education Trust). Eligibility criteria for the POWER cohort were age 16-25 years, able and willing to provide written informed consent, recently sexually active (defined as having had vaginal intercourse at least once in the previous three months) and HIV uninfected based on a negative HIV rapid test on the date of enrollment.

We evaluated our study outcomes in two periods: a “standard of care period” (14 weeks), during which outcomes were evaluated under standard of care with no HIVST offered, and a subsequent “HIVST period” (17 weeks), during which women were given the option to choose between provider-initiated testing and counseling (PITC) and HIVST. Those who chose HIVST were directed to a private location where detailed HIVST instructions were posted on the wall in three languages (English, Kiswahili, and Luo). We used an unassisted HIVST approach, but clients could ask providers for clarifications if needed. We used the OraQuick® HIV Self-Test (OraSure Technologies, USA) kit, one of the three test kits that have been approved for HIVST by the Kenya Ministry of Health [83]. OraQuick® detects HIV 1/2 antibodies in oral fluid (mouth swab/saliva) samples and has been shown to have high sensitivity (87.9%) and specificity (98.0%) when used by lay individuals in Kenya [84].

Ethical considerations

The POWER study protocol was reviewed and approved by the Institutional Review Boards (IRBs) at the University of Washington and the Human Subjects Review Committees at each clinical site. We obtained IRB approval for the protocol for POWER and the nested HIVST

pilot study as well as other related documents from the IRBs at the University of Washington and the Kenya Medical Research Institute. The study included women of ages 16-25 years (an age-group that contributes a large proportion of the burden of HIV in Sub-Saharan Africa), and we followed local guidelines for consent for those under 18 years of age.

Data collection and outcomes

We collected data between February and November 2019. At the end of each visit, participants completed a standardized researcher-administered questionnaire to assess demographics and study outcomes. For a total of 40 participants (10 per clinical site per period), we also observed and recorded the time within and between PrEP delivery procedures. HIVST results were read by the participants and by a HIV testing services counselor. The primary outcomes of interest were HIVST uptake, testing experience (how easy testing was, how easy it was to understand test results, what was liked most about testing, and how long waited for testing), satisfaction with testing (how happy with overall HIV testing and whether would recommend HIVST in the future), satisfaction with clinic visit (how rated overall clinic experience and how happy with: how treated in clinic, clarity of explanations given by providers, time given to ask questions, involvement in making decisions about PrEP use, clinic waiting time) and duration of key PrEP delivery procedures (HIV testing, counseling, PrEP dispensing and waiting). We also assessed reasons for testing choice (PITC or HIVST), and for considering HIVST in the future.

Statistical Analyses

We described the number and proportion of women who accepted HIVST, and response categories for each experience and satisfaction outcome by study period. We used log-Poisson generalized estimating equations (GEE) with robust standard errors and independence correlation structure to assess factors related to HIVST uptake. We present relative risks (RRs) adjusted for site and baseline covariates identified *a priori* (age, education, marital status, multiple partnerships, baseline prior use of HIVST and number of follow-up visits in the POWER cohort at

enrollment in this study) [77, 85]. To compare differences in experience and satisfaction between those who accepted HIVST and those who declined HIVST, we performed score tests of exposure (questionnaire item) coefficients from site-adjusted log-Poisson GEE models with robust standard errors and independence correlation structure. For the assessment of the impact of HIVST, we described the median and interquartile range of the duration of each PrEP delivery procedure and used the Wilcox test to compare times between acceptors and decliners; as a sensitivity analysis, we repeated the comparsion excluding waiting times longer than 30 minutes. We used two-sided p-values and considered them significant if <0.05. We used SAS version 9.4 (SAS Institute Inc., Cary, NC) and R version 3.6.1 (www.r-project.org) for analyses.

RESULTS

Participant characteristics

Overall, 249 women contributed 362 PrEP follow-up visits during the study period: 160 visits (148 women) during the standard of care period and 202 visits (172 women) during the period when HIVST was offered, with a maximum of three observations per person. Seventy-one (28.5%) women had at least one visit during both periods, 12 had two visits during the standard of care period and 30 had two visits during the HIVST period. The median age was 21 years [interquartile range (IQR): 19, 23], most women had never married (69.1%), had only one partner (72.6%), and had completed up to secondary school (41.8%) (Table 4). Most also reported they had never used HIVST (85.5%).

Uptake of HIVST

During the HIVST period, HIVST was accepted at 70 (34.7%) of 202 visits (Table 5). Of the 172 women who had a visit during the HIVST period, 55 (32.0%) accepted HIVST at their first opportunity; among 30 who attended clinic twice during the HIVST period, six accepted and 12 declined HIVST at two consecutive visits, three initially accepted then later declined HIVST, and nine declined then later accepted HIVST.

Older age (adjusted risk ratio [aRR] 1.09 per year, 95% CI [confidence interval] 1.01 to 1.18, p-value=0.025), being never married (aRR 1.81, 95% CI 1.11 to 2.95, p-value=0.017) and having more PrEP follow-up visits (aRR 1.13 per visit, 95% CI 1.04 to 1.23, p-value=0.005) were associated with an increased chance of HIVST uptake (Table 4). Highest education completed, multiple partnerships, and prior use of HIVST were not significantly associated with uptake of HIVST.

HIVST was successfully completed in 68 visits, and women correctly read their test results 94% (N=64) of the time; one woman who had a positive result reported indeterminate results and three women, two with positive results and one with a negative result, were unable to interpret their results. Of the 68 HIV self-tests completed, four (5.9%) and one (1.5%) were reactive and invalid, respectively – follow-up testing of these five cases by a trained provider on the same day, per the Kenyan national HIV testing algorithm, yielded negative results.

Testing experience and satisfaction

In general, women were either happy or very happy (98% visits) with their overall testing experience (Table 5). Most women found their testing easy/very easy (95% visits) and their HIV test results easy/very easy to understand (94% visits). For HIVST acceptors, privacy/confidentiality was what they cited liking most about HIVST (34%), and in 96% of acceptor visits, women said they would repeat HIVST in the future and recommend HIVST to others. For HIVST decliners, not being comfortable with testing alone was the main reason for declining HIVST (33% visits), getting counseling during testing was liked most about PITC (63% visits), and personal empowerment/taking charge of ones' health was the main reason to consider HIVST in the future (51%).

Comparing HIVST acceptors and HIVST decliners, there was no statistically significant difference in prior use of HIVST, ease of understanding test results, and time spent waiting for HIV testing/HIVST kit ($p>0.05$). Still, HIVST acceptors found their HIV testing experience very easy compared to HIVST decliners (40% visits vs. 28% visits). HIVST acceptors were more likely

to be very happy with their overall testing experience than decliners (73% visits vs. 47% visits, p-value=0.003). Finally, HIVST acceptors were more likely to say they would repeat HIVST than decliners were to say they would consider HIVST in the future (96% visits vs. 76% visits, p-value<0.001).

Clinic experience and satisfaction

There were no statistically significant differences in satisfaction with the clinic visit experience between HIVST acceptors and HIVST decliners (p-value>0.05) (Table 6). In most visits, women were either happy or very happy (>90% of visits in each period) with their clinic experience, including how they were treated, the clarity of explanations given by providers, the time they had to ask questions, their involvement in making decisions about PrEP use, and how long they had to wait in the clinic. Likewise, in most visits, women rated their overall clinic experience as good (96% visits) (Table 6).

HIVST and PrEP delivery processes

Total visit time was shorter for those using HIVST compared to those who declined HIVST (median 33 vs. 54 minutes, p-value=0.003) (Table 7), and total visit time during standard of care period was comparable to that of those declining HIVST (median 55 vs. 54 minutes). HIV testing itself was actually longer for HIVST (median [IQR]: 27 [26, 30] vs 15 [13, 17.5], p-value=0.001) and PrEP dispensing time was slightly shorter for HIVST acceptors (median [IQR]: 2.5 [1, 3] vs. 4 [3.3, 4], p-value=0.01). Median waiting time was longer for HIVST decliners than HIVST acceptors (11 minutes vs. 2 minutes), although this difference was not statistically significant. In sensitivity analysis omitting waiting times longer than 30 minutes, the total time spent in the clinic was still shorter for HIVST acceptors than HIVST decliners (median 33 minutes vs. 46 minutes, p-value=0.014).

DISCUSSION

In this pilot study of HIVST in PrEP delivery, women chose HIVST over PITC at about one-third of visits, successfully completed HIVST in 97% of visits, and correctly read their HIVST results 94% of the time. In general, women were satisfied with their HIV testing and clinic experience, and compared to HIVST decliners, HIVST acceptors were more likely to say they would use HIVST in the future. Age, marital status and number of PrEP visits were associated with uptake of HIVST, and HIVST decliners spent more time at the clinic than HIVST acceptors.

Some proposed ways to improve PrEP delivery scale-up include simplifying laboratory monitoring, task-shifting from doctors to nurses, differentiated models of PrEP service delivery, minimization of emphasis on adherence as a requirement to start/continue PrEP and less focus on risk in PrEP messaging [86]. HIVST has not been commonly used within PrEP programs, but our results suggest that HIVST offers one strategy to facilitate testing and streamline PrEP refill visits in busy clinical settings. Unlike common HIVST delivery models (community-based and secondary distribution) which can have challenges with linkage to care [87], facility-based HIVST allows individuals to present their results before their PrEP refill and seek immediate help with testing when needed. Consistent with other studies, we found that personal empowerment/taking charge of ones' health was the main reason for considering HIVST in the future [25, 88], and that privacy/confidentiality was what was liked most about HIVST [89].

HIVST took longer than PITC, but the total time spent at the clinic was significantly shorter among those who used HIVST. Unlike the sequential pattern of PrEP procedures for those who chose PITC, HIVST acceptors could continue with other PrEP procedures (taking vitals, and counseling on PrEP, risk reduction, family planning and sexually transmitted infections) while waiting for their HIVST to run; this contributed significantly to the observed difference in total time spent in clinic. PrEP users in Sub-Saharan Africa have reported that practicalities of PrEP use such as finding time for appointments and service delivery environment (including clinical staff capacity) play a key role in their considerations for PrEP use [90]. Our findings that HIVST reduced

the overall time spent in clinic underscore the potential for HIVST to promote PrEP rollout in clinics that have limited capacity to even deliver existing services.

The average age in this study was 21 years. Adolescents in Sub-Saharan Africa have expressed the need for PrEP implementers to provide HIV prevention options that consider different facets of their lives such as their perception of risk, the dynamics of their relationships, and their concerns about PrEP side effects and the burden of PrEP use [90]. In our study, we found that some women preferred HIVST while others preferred PITC during their PrEP visits. Having more PrEP follow-up visits before enrollment in the HIVST study was also positively associated with choosing HIVST, suggesting that women who had used PITC multiple times knew what to expect during HIV testing and counseling and were comfortable testing alone during subsequent PrEP visits. Thus, HIVST could be used as an approach to expand retesting options for women in real world PrEP implementation. One study among adolescents found that over 80% preferred directly assisted facility-based HIVST over standard PITC [20] – it is possible that directly assisted HIVST for first-time users could have improved uptake of HIVST in our study.

This was a pilot evaluation and it has important limitations. The main limitation of this study is the short duration of the HIVST period; those who initially declined HIVST might have chosen HIVST had they been given more opportunity to do so. The observed HIVST time, which was significantly longer than PITC, could have been reduced had our study been longer, allowing for HIVST acceptors to use HIVST again with greater familiarity with HIVST procedures. Similarly, we introduced unassisted HIVST among women who were already enrolled in a PrEP program and accustomed to PITC; a program that used HIVST from the start might have found greater uptake. Finally, women participating in this evaluation were enrolled in a research study and HIVST in more programmatic settings could find different results; importantly, procedures in our study such as PITC, laboratory testing and PrEP dispensing were integrated into standard clinic procedures, allowing for their evaluation within existing clinical settings. Despite these potential limitations, our study provides important evidence on the feasibility, uptake and impact of HIVST

in PrEP delivery, and is the first study to investigate unassisted facility-based HIVST in a PrEP context.

CONCLUSIONS

This pilot evaluation of HIVST in the context of PrEP shows that facility-based HIVST in PrEP delivery is feasible and can reduce visit times. More studies are needed to understand how HIVST could be used not only to screen for HIV but also as a tool to streamline PrEP delivery and offer the flexibility for PrEP users to choose the type of testing they want during their PrEP visits.

Competing interest

All authors have no conflict of interest related to this work.

Authors' contributions

VW and JMB contributed to study conception and design. VW, VO, LK, and JFM contributed to data collection, data management and study coordination. VW, JPH and JMB contributed to analysis and interpretation of the data. VW and JMB contributed to drafting of the manuscript. All authors contributed to critical review and revision of the manuscript and approved the final version of the manuscript.

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Table 4. Characteristics of women (overall and by HIVST period), and associations with HIVST uptake

Variable	Overall† (N=249)	HIVST acceptors† (N=55)	HIVST decliners† (N=117)	Associations with HIVST uptake during HIVST period (N‡ = 202)	
				Adjusted RR§ (95% CI)	p-value
Age (years)	21.0 [19.0, 23.0]	22.0 [19.0, 23.5]	21.0 [19.0, 23.0]	1.09 (1.01, 1.18)	0.025
Highest education completed					
Primary	81 (32.5)	18 (32.7)	42 (35.9)	1.12 (0.49, 2.58)	0.718
Secondary	104 (41.8)	19 (34.5)	47 (40.2)	0.99 (0.42, 2.31)	0.978
Tertiary	25 (10.0)	8 (14.5)	12 (10.3)	1.29 (0.52, 3.21)	0.579
Vocational training	22 (8.8)	6 (10.9)	7 (6.0)	1.33 (0.55, 3.22)	0.522
No schooling completed	17 (6.8)	4 (7.3)	9 (7.7)	Reference	
Marital status					
Never married	172 (69.1)	40 (72.7)	72 (61.5)	1.81 (1.11, 2.95)	0.017
Ever married	77 (30.9)	15 (27.3)	45 (38.5)	Reference	
Number of current sex partners					
Only 1 partner	180 (72.6)	37 (67.3)	82 (70.7)	1.02 (0.69, 1.53)	0.894
> 1 partner	68 (27.4)	18 (32.7)	34 (29.3)	Reference	
Used HIVST in the past					
Yes	36 (14.5)	8 (14.5)	19 (16.2)	0.94 (0.61, 1.46)	0.781
No	213 (85.5)	47 (85.5)	98 (83.8)	Reference	
Number of POWER cohort follow-up visits at enrollment in the HIVST study	1.0 [0.0, 3.0]	2.0 [0.0, 4.0]	1.0 [0.0, 3.0]	1.13 (1.04, 1.23)	0.005

†Number (N) (%) or median [interquartile range (IQR)]; ‡Number of observations by acceptors (70) and decliners (132);
§Adjusted for site and other variables (age, marital status, education, baseline prior use of HIVST and number of POWER cohort follow-up visits at enrollment in the HIVST study)

Table 5. HIV testing experience and satisfaction

		HIVST period		
	Standard of care period (n=160)	Acceptors (n=70)	Decliners (n=132)	p-value
Item	N (%)	N (%)	N (%)	
Ever self-tested for HIV in the past				
yes	22 (13.8)	14 (20.0)	25 (18.9)	0.871
no	138 (86.2)	56 (80.0)	107 (81.1)	
Where got self-test kit				
research study	13 (59.1)	8 (57.1)	13 (52.0)	0.943
facility	6 (27.3)	3 (21.4)	5 (20.0)	
Pharmacy/friend/family	3 (13.6)	3 (21.4)	7 (28.0)	
Would consider (or repeat) HIVST in the future				
yes	138 (86.2)	67 (95.7)	100 (75.8)	<0.001
no	22 (13.8)	3 (4.3)	32 (24.2)	
Main reason to consider HIV ST in future				
privacy / confidentiality	30 (21.7)	NA	26 (26.0)	NA
personal empowerment / taking charge of my own health	72 (52.2)	NA	51 (51.0)	
no pricking / painless	16 (11.6)	NA	8 (8.0)	
saves time / no waiting in queues	18 (13.0)	NA	11 (11.0)	
other	2 (1.4)	NA	4 (4.0)	
Main reason not want to self-test again				
testing difficult to do	NA	0 (0.0)	NA	NA
I made mistakes when doing the test	NA	0 (0.0)	NA	
I did not understand the results	NA	1 (33.3)	NA	
I don't believe the results/still have to go for confirmatory testing	NA	0 (0.0)	NA	
afraid/prefer to have counselor with me	NA	2 (66.7)	NA	
Main reason why declined HIVST				
I was afraid the test would be difficult to do	NA	NA	22 (16.7)	NA
I was not comfortable testing alone	NA	NA	44 (33.3)	
the HTS queue was not long	NA	NA	2 (1.5)	
I did not trust self-testing	NA	NA	18 (13.6)	
I did not know how to use HIVST kit	NA	NA	15 (11.4)	

I am used to PITC	NA	NA	13 (9.8)	
PITC is faster	NA	NA	9 (6.8)	
other	NA	NA	9 (6.8)	
How easy HIV testing experience / conducting HIVST†				
very difficult	0 (0.0)	1 (1.4)	0 (0.0)	
difficult	6 (3.8)	3 (4.3)	2 (1.5)	
undecided	2 (1.2)	2 (2.9)	1 (0.8)	
easy	97 (60.6)	36 (51.4)	92 (69.7)	
very easy	55 (34.4)	28 (40.0)	37 (28.0)	0.061
How easy to understand test results†				
very difficult	0 (0.0)	0 (0.0)	0 (0.0)	
difficult	7 (4.4)	6 (8.7)	1 (0.8)	
undecided	5 (3.1)	1 (1.4)	3 (2.3)	
easy	93 (58.1)	37 (53.6)	87 (65.9)	
very easy	55 (34.4)	25 (36.2)	41 (31.1)	0.129
What like most about provider-initiated HIV testing				
having someone with me during the test	34 (21.2)	NA	23 (17.4)	NA
getting counseling during the testing	73 (45.6)	NA	83 (62.9)	
getting help understanding my test results	45 (28.1)	NA	17 (12.9)	
other	8 (5.0)	NA	9 (6.8)	
What like most about HIV self-testing				
privacy / confidentiality	NA	24 (34.3)	NA	NA
personal empowerment / taking charge of my own health	NA	17 (24.3)	NA	
no pricking / painless	NA	17 (24.3)	NA	
saves time / no waiting in queues	NA	8 (11.4)	NA	
other	NA	4 (5.7)	NA	
How long waited for HIV testing or HIVST kit				
0-15 minutes	133 (83.1)	54 (77.1)	118 (89.4)	
16-30 minutes	17 (10.6)	16 (22.9)	14 (10.6)	
>30 minutes	10 (6.2)	0 (0.0)	0 (0.0)	0.081
Would you recommend HIV self-testing				
yes	NA	67 (95.7)	NA	

no	NA	3 (4.3)	NA	NA
How happy with overall testing experience[‡]				
very unhappy	0 (0.0)	1 (1.4)	0 (0.0)	
unhappy	1 (0.6)	1 (1.4)	1 (0.8)	
undecided	1 (0.6)	1 (1.4)	2 (1.5)	
happy	44 (27.5)	16 (22.9)	66 (50.0)	
very happy	114 (71.2)	51 (72.9)	63 (47.4)	0.003

[†]For HIVST period comparisons, collapsed into 3 categories: very difficult/difficult/undecided, easy, and very easy
[‡]For HIVST period comparisons, collapsed into 3 categories: very unhappy/unhappy/undecided, happy, and very happy
HTS=HIV testing services; PITC=provider-initiated testing and counseling

Table 6. Clinic experience and satisfaction

		HIVST period		
	Standard of care (n=160)	Acceptors (n=70)	Decliners (n=132)	p-value
Item	N (%)	N (%)	N (%)	
How happy with way you were treated†				
very unhappy	0 (0.0)	1 (1.4)	4 (3.0)	
unhappy	1 (0.6)	0 (0.0)	0 (0.0)	
undecided	0 (0.0)	0 (0.0)	0 (0.0)	
happy	47 (29.4)	19 (27.1)	51 (38.6)	
very happy	112 (70.0)	50 (71.4)	77 (58.3)	0.187
How happy with clarity of explanation†				
very unhappy	0 (0.0)	1 (1.4)	0 (0.0)	
unhappy	1 (0.6)	1 (1.4)	0 (0.0)	
undecided	1 (0.6)	0 (0.0)	1 (0.8)	
happy	53 (33.1)	24 (34.3)	60 (45.5)	
very happy	105 (65.6)	44 (62.9)	71 (53.8)	0.276
How happy with time to ask questions†				
very unhappy	0 (0.0)	1 (1.4)	2 (1.5)	
unhappy	3 (1.9)	1 (1.4)	0 (0.0)	
undecided	4 (2.5)	1 (1.4)	2 (1.5)	
happy	80 (50.0)	35 (50.0)	68 (51.5)	
very happy	73 (45.6)	32 (45.7)	60 (45.5)	0.965
How happy with involvement in making decisions about PrEP use†				
very unhappy	0 (0.0)	1 (1.4)	0 (0.0)	
unhappy	0 (0.0)	1 (1.4)	1 (0.8)	
undecided	6 (3.8)	1 (1.4)	5 (3.8)	
happy	55 (34.4)	22 (31.4)	54 (40.9)	
very happy	99 (61.9)	45 (64.3)	72 (54.5)	0.491
How happy with how long had to wait in clinic†				
very unhappy	3 (1.9)	1 (1.4)	0 (0.0)	
unhappy	9 (5.6)	3 (4.3)	6 (4.5)	
undecided	2 (1.2)	0 (0.0)	2 (1.5)	
happy	73 (45.6)	25 (35.7)	68 (51.5)	

very happy	73 (45.6)	41 (58.6)	56 (42.4)	0.079
How would rate overall experience at clinic‡				
poor	0 (0.0)	0 (0.0)	0 (0.0)	
fair	2 (2.9)	6 (4.5)	6 (4.5)	
good	28 (40.0)	60 (45.1)	59 (44.7)	
excellent	40 (57.1)	67 (50.4)	67 (50.8)	0.637

†For HIVST period comparisons, collapsed into 3 categories: very unhappy/unhappy/undecided, happy, and very happy
‡For HIVST period comparisons, collapsed into 3 categories: poor/fair, good, and excellent

Table 7. Duration (minutes) of PrEP delivery procedures

	Acceptors†	Decliners†	p-value
HIV testing	27.0 [26.0, 30.0]	15.0 [13.0, 17.5]	0.001
Counseling‡	8.5 [5.0, 10.0]	8.0 [5.3, 9.5]	0.892
PrEP dispensing	2.5 [1.0, 3.0]	4.0 [3.3, 4.0]	0.010
Other§	7.0 [5.0, 9.0]	6.0 [4.5, 12.5]	0.646
Client waiting time	2.0 [1.0, 6.0]	11.0 [0.5, 25.0]	0.301
Total visit time	33.0 [32.0, 38.0]	54.0 [41.5, 81.0]	0.003

†Median [IQR]; ‡Counseling on PrEP (adherence, side effects), risk reduction, family planning, sexually transmitted infections; §Other procedures include confirmation of client ID, taking vitals (blood pressure, pulse, height, and weight) and scheduling next appointment date

Chapter 4. Cost of pre-exposure prophylaxis delivery in family planning clinics to prevent HIV acquisition among young women in Kisumu, Kenya

TITLE PAGE

Cost of pre-exposure prophylaxis delivery in family planning clinics to prevent HIV acquisition among young women in Kisumu, Kenya

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Running head: Cost of PrEP delivery for young women in Kenya

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ABSTRACT

Background: Oral pre-exposure prophylaxis (PrEP) is increasingly being implemented in sub-Saharan African countries. Evidence on the cost of PrEP in real-world implementation is needed to inform the budget impact, cost-effectiveness, and financial sustainability of these programs.

Methods: Using micro-costing methods, we estimated the incremental cost of delivering PrEP to adolescent girls and young women (AGYW) enrolled in a PrEP implementation study in two family planning clinics in Kisumu county, located in western Kenya. We derived total annual costs and the average cost per client-month of PrEP by input type (variable or fixed) and visit type (initiation or follow-up). We estimated all costs as implemented in the study, and as would be incurred under implementation by the Kenyan Ministry of Health (MoH), both at the program volume observed and if the facilities were delivering PrEP at full capacity (scaled-MoH).

Results: For the costing period between March 2018 and March 2019, 615 HIV-negative women contributed 1,128 (502 initiation and 626 follow-up) visits. The average cost per client-month of PrEP dispensed in the MoH scenario was $14.52. If the MoH scaled the program so that facilities could see PrEP clients at capacity, the average cost per client-month of PrEP was $10.88. Medication costs accounted for the largest proportion of the total annual costs (48% in MoH scenario and 65% in the scaled-MoH scenario).

Conclusions: Using data from a PrEP implementation program, we found that the cost per client-month of PrEP dispensed is reduced by 62% if PrEP is scaled up at a national level. Our findings are valuable for informing local resource allocation and budgetary cost projections for scale-up of PrEP delivery to young women. Additionally, previous cost-effectiveness studies have been limited by the use of fixed assumptions of the cost of PrEP per person-month. Our study provides cost estimates from practical data which will better inform cost-effectiveness and budget impact analyses.

Key words: Cost; Input; Pre-exposure prophylaxis; Sexually transmitted infections

BACKGROUND

In 2015, the World Health Organization (WHO) expanded its recommendation on the use antiretroviral therapy as pre-exposure prophylaxis (PrEP) for the prevention of HIV transmission [42]. Since then, 35 countries have issued guidelines indicating PrEP as an additional HIV combination prevention to priority populations including adolescent girls and young women aged 15-24 years, who account for a disproportionate number of new infections [91]. There is a need to identify the cost of delivering PrEP to young women in order to inform the most cost-effective ways of PrEP delivery.

Health facilities are the most common platforms for PrEP delivery for young women in sub-Saharan Africa [14]. These platforms offer the benefit of reaching individuals who are using other services such as HIV testing and family planning, but the incremental cost of PrEP delivery in these settings remains unknown. Moreover, low- and middle-income countries (LMICs) still rely on donor funding for their HIV response, with an estimated 44% of the total resources for HIV in LMIC reported to have come from external sources in 2018 [92]. In the context of limited funding for HIV response, uncertainty about PrEP delivery costs leaves decision-makers unable to determine if PrEP is affordable or cost-effective within a given budget. Cost estimates from PrEP implementation projects are needed to provide actionable insights on the financial implications of PrEP delivery to at-risk populations.

Evidence from mathematical modelling of PrEP in sub-Saharan Africa suggest that compared to no PrEP, PrEP can be a cost-saving intervention for young women if implemented in combination with other HIV prevention strategies [31-33]. However, these models had fixed assumptions about the cost of PrEP per person-year and did not use data from real-world implementation settings. To date, only one study has reported the cost of delivering PrEP to young women in sub-Saharan Africa using practical data from implementation [34], and more evidence is needed on the cost of delivering PrEP to this population.

The objective of this study was to evaluate the cost of delivering daily oral PrEP to young women in two family planning clinics in Kisumu, one of the three high-HIV incidence counties in western Kenya [93]. We estimated the total annual cost and average cost per client-month of PrEP dispensed (1) as implemented in the study setting and (2) as would be incurred by the Kenyan Ministry of Health (MoH) if it were to implement PrEP delivery to the same population in the same facilities.

METHODS

Study setting and population

Prevention Options for Women Evaluation Research (POWER) is an ongoing implementation science study evaluating PrEP delivery to adolescent girls and young women aged 16-25 years in Kenya and South Africa [14]. This costing study was conducted for the two POWER study sites in Kisumu, Kenya (Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH), a public facility and Kisumu Medical Education Trust (KMET), a youth-friendly private facility). Study enrollment started in August 2017 at KMET and in October 2017 at JOOTRH. Young women were eligible for enrollment in the study if they were 16-25 years old, able and willing to provide written informed consent, recently sexually active (defined as having had vaginal intercourse at least once in the previous three months) and HIV-uninfected at enrollment. Scheduled follow-up visits in the study were one month post-enrollment, three months post-enrollment and quarterly thereafter, per the Kenyan national guidelines [81].

Data collection

We collected PrEP delivery costs of programmatic activities including 1) direct service delivery activities: counseling, HIV testing, laboratory testing (creatinine clearance, hepatitis B surface antigen, *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT)), PrEP prescribing and dispensing; 2) ancillary activities: demand creation (flyers, posters, t-shirts, and quarterly support groups for POWER clients) and adherence support through appointment reminder calls; and 3)

site-level activities: initial PrEP training, annual refresher trainings, and supervision and administration (monthly reporting of PrEP uptake and continuation, monthly PrEP accounting). Additionally, we collected costs of capital inputs (vehicle, clinical equipment, stationery) and overhead (building, utilities, fuel, maintenance, internet).

We obtained personnel salaries, startup costs (e.g., training, capital), and recurrent costs (e.g., clinical supplies, rent, utilities) from study salary records, expense reports and receipts. We obtained facility staff and ministry of health (MoH) salaries from communication with site staff and publicly-available information on job groups and basic allowances (housing and commuter) per job cadre [94]. Public sector cost per bottle of tenofovir disoproxil fumarate/emtricitabine (TDF/FTC, $6.25 in 2017 US dollars) was obtained from recently published data from Kenya [34]. We conducted time-and-motion observations to record the time spent by providers during each direct PrEP delivery activity. Through interviews with study personnel, we also collected data on the proportion of time spent on ancillary PrEP activities by each staff. Study data was used to determine the number of initiation and follow-up visits and the number of PrEP months dispensed in the one-year costing period. We collected all costs in Kenyan shillings (KES) and converted them to U.S. dollars at the market exchange rate (1 USD = 100.7 KES) on August 30, 2018, the mid-point of the costing period.

Cost analysis

Using the Global Health Cost Consortium Reference Case (GHCC) principles [95], we evaluated the economic costs associated with PrEP services from a provider perspective for the period between March 1, 2018 and March 1, 2019. We used methods similar to Roberts et.al., [34] to derive total annual costs and average cost per client-month of PrEP (defined as total annual cost divided by the months of PrEP dispensed in a year) by input type (variable or fixed) and visit type (initiation or follow-up). All costs were estimated 1) as implemented in the study (as-implemented scenario); 2) as would be incurred by the MoH if it were to implement the program (MoH scenario) and 3) as would be incurred by the MoH if the program were at scale (scaled-MoH scenario). We

estimated the total number of daily visits in the scaled-MoH scenario as the weighted average of the total time of initiation and follow-up visits, with weights assigned as the proportion of visits of each type observed in the costing period.

Clinical personnel, medication (TDF/FTC) and laboratory testing were categorized as variable inputs, while fixed inputs included training (start-up and refresher), demand creation, personnel (supervision and administration), capital and overhead. To calculate personnel costs, we used total salary per staff (including allowances) and assumed each staff worked eight hours per day for 260 week days per year after excluding standard holidays and leave/vacation. We used the average time clinical staff spent on PrEP delivery activities to estimate unit labor costs per activity. To estimate fixed costs by visit type, we calculated the proportion of total average visit time contributed by each visit type, and multiplied each proportion by the total cost of fixed inputs.

We added the shipping cost per bottle of PrEP ($2.18) to the public sector cost per bottle ($6.25) to estimate a drug cost of $8.43 per bottle for the program; costs of drug storage were included in building and utility costs. For MoH and scaled-MoH scenarios, we added 8% central storage and distribution fees per Roberts et.al., [34] to the public sector cost per bottle for a total cost of $6.75 per bottle. Total medication costs were determined by multiplying the unit price by the number of months of PrEP dispensed during the costing period. The total cost of laboratory and HIV testing was estimated as the unit cost of tests and clinical supplies multiplied by the number of tests done during the costing period.

For most inputs, we used as-implemented costs to derive MoH and scaled-MoH costs. Key differences in the MoH scenarios, per consultation with site staff, were: 1) we used MoH salaries and allowances for personnel costs; 2) start-up training would only take one day instead of two days; 3) annual POWER refresher trainings would be similar to weekly, hour-long continuous medical education (CMEs) and that PrEP would be discussed at CMEs once a month; 4) demand creation would only be done through flyers and posters; 5) no vehicle would be

purchased since costs of drug transportation (what the vehicle was mainly used for in the study) are already included in the drug price; thus, there would be no fuel, maintenance and insurance costs; 6) only one laptop per facility would be purchased for PrEP use at the health records department; 6) at JOOTRH, StatSensor Xpress [34] creatinine machine (unit cost of KES 10000) would be purchased instead of the machine used for the study (unit cost of KES 450,000); 7) only one room per facility would be used for PrEP activities; and 8) for sexually-transmitted infection (STI) testing costs, we used a unit cost of $16 per dual NG/CT GeneXpert test cartridge (T. Elvira, personal communication), and assumed, given the number of people living with HIV (1.5 million [93]), relative to the number of PrEP enrollees in Kenya (55,500-56,500 [91]), that the cost of GeneXpert machine use (if already procured for TB and HIV viral load testing) attributable to PrEP would be negligible.

Per POWER study protocol, all study participants were tested for HIV at each visit, and for creatinine clearance (CrCl), Hepatitis B surface antigen (HBsAg) and STIs (NG and CT) at PrEP initiation. Per the national PrEP guidelines in Kenya, testing for CrCl, HBsAg and STIs is recommended but not required at PrEP initiation [81]. Furthermore, in Kenya, as in almost all parts of Africa, etiologic STI testing using nucleic acid amplification is not routinely done in facilities, and STI diagnoses and treatment are made using syndromic assessment [96]. Therefore, in our primary analyses, we estimated costs without CrCl, HBsAg or STI testing. For secondary analyses, we explored the incremental cost of 1) CrCl, HBsAg and STI testing; 2) MoH-recommended CrCl and HBsAg testing but no STI testing and 3) only STI testing, since STI prevalence is considerably higher in this population [97-99] than kidney issues revealed through CrCl [34, 100].

We excluded all research-related costs and visits by clients who never initiated PrEP (7.5% of all visits). Start-up and capital costs were annualized using a discount rate of 3% [95] over the expected useful life of three (e.g., t-shirts) to five (e.g., vehicle) years. All cost estimates are reported in 2019 USD with adjustment for inflation from 2017 [101], the year POWER study

was initiated. Program data extraction was done using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and cost data analysis was done using Excel 2016 (Microsoft, Redmond, WA, USA).

RESULTS

Program volume summary

Between March 2018 and March 2019, 615 HIV-negative women (310 at JOOTRH and 305 at KMET) contributed 1,128 (502 initiation and 626 follow-up) visits, with a range of one to six visits per woman. PrEP was dispensed at 75% (N=471) of all follow-up visits in this period. There were 1,554 (499 at initiation visits, 995 at follow-up visits) months of PrEP dispensed during the one-year period. We conducted 36 time-and-motion observations (13 initiation and 23 follow-up visits), and on average, initiation visits and follow-up visits took 50 minutes and 24 minutes of providers (nurses, HIV testing counselors, laboratory technicians and pharmacy technicians) time, respectively.

Of the visits included in the one-year costing period, 44.5% were initiation visits (all with PrEP dispensed), 19.8% were month one (PrEP dispensed in 82%) visits and 35.7% were quarterly (PrEP dispensed in 72%) visits. Based on the total time providers worked per day at each facility (450 minutes), the proportion of initiation and follow-up visits seen in the costing period and the average time per initiation and follow-up visit from time-and-motion data, we estimated that at full capacity, 14 PrEP visits could be seen per day per facility (i.e., initiation visits per day = 0.45 × 450/50 = 4, follow-up visits per day = 0.55 × 450/24 = 10). For 260 work days a year, we estimated that 7,280 (3,240 initiation and 4,040 follow-up) visits would occur in the scaled-MoH scenario in a year, during which 7,645 months of PrEP would be dispensed.

PrEP delivery costs (without creatinine, hepatitis B or STI testing)

In the MoH scenario, (if MoH implemented the program), the total annual cost of PrEP delivery was $22,566 and the cost per client-month of PrEP dispensed was $14.42, representing half the as-implemented costs (Table 1); medication was the main driver of the total annual cost (48%),

followed by overhead costs (25%), while demand creation contributed only a small proportion (1%) to total annual costs (Figure 1). In the scaled-MoH scenario, the cost per client-month of PrEP dispensed was $10.88, with medication, personnel and overhead contributing 65%, 19% and 9% of total costs, respectively (Figure 1).

Assessing costs by visit type, we found that the total cost per initiation visit was $46.85 in the as-implemented scenario, $20.23 in the MoH scenario and $11.84 in the scaled-MoH scenario. Follow-up visits cost less, at a total cost per visit of $33.38, $19.16 and $10.70 in the as-implemented, MoH and scaled-MoH scenario, respectively. Compared to the total cost per initiation visit, the total cost per follow-up visit was 1.4, 1.1 and 1.1 times higher in the as-implemented, MoH and scaled-MoH scenarios, respectively (Table 2). For all scenarios, the total annual cost of PrEP delivery and the cost per client-month of PrEP dispensed were comparable between the public and private facility (results not shown).

Added costs of creatinine, hepatitis B and STI testing

In a scenario with CrCl, HBsAg and STI testing at initiation, most of the total annual cost came from laboratory and HIV testing; 33% in MoH scenario and 47% in scaled-MoH scenario. Adding these three tests at initiation notably increased the cost per client-month of PrEP dispensed to $21.12 (45% increase) in the MoH scenario and $19.39 (78% increase) in the scaled-MoH scenario (Table 3).

Excluding STI testing while performing guidelines-recommended CrCl and HBsAg testing at initiation resulted in minimal increases in total annual cost of PrEP delivery (8% in MoH scenario and 13% in scaled-MoH scenario). In comparison, when testing for STIs only, the average cost per client-month of PrEP dispensed was $19.90 (37% higher) and $17.93 (65% higher) in the MoH and scaled-MoH scenario, respectively (Table 3).

DISCUSSION

In this economic analysis among young women attending family planning clinics, we estimated the cost of Ministry of Health PrEP delivery in this setting to be $14.52 per client-month of PrEP dispensed. Under a scaled-MoH scenario, assuming 14 clients were seen at each facility per day, fixed costs would be distributed over a larger proportion of PrEP visits, significantly lowering the cost per client-month of PrEP to $10.88. Consistent with other costing studies of PrEP implementation, [34, 102, 103] medication costs accounted for the majority of the total annual cost in both the MoH and scaled-MoH scenarios, highlighting the need to identify ways to further lower medication costs in PrEP delivery.

At PrEP initiation, the Kenyan MoH recommends STI assessment (usually syndromic) and if available, laboratory evaluation of CrCl and HBsAg [81]. When we included costs of testing for CrCl, HBsAg and STIs (NG/CT (by nucleic acid amplification)) at initiation visits, laboratory costs contributed the majority of total annual costs and increased cost per client-month of PrEP by 45% in the MoH scenario (to $21.21) and 70% in the scaled-MoH scenario (to $19.39). Of the 502 women who initiated PrEP in the costing period, 7% and 17% tested positive for N. gonorrhoeae and C. trachomatis, respectively. Other studies have also shown high rates of NG and CT among young people, with even higher rates among women compared to men [104]. In PrEP users, high rates of STIs have been reported at baseline mostly among MSM populations [97] but also in young African women [105]. Because PrEP does not confer protection against STIs, and those at high risk of HIV are also usually at high risk of bacterial STIs which confers risk of infertility and other adverse reproductive health outcomes for women, there is a unique opportunity for PrEP programs to integrate STI testing and treatment with PrEP delivery. Still, the high unit cost of lab testing in this study ($58.53 per test as implemented and $16.00 per test in the MoH scenario) may not be sustainable in resource-limited settings. Furthermore, existing STI testing systems are inefficient due to long waiting times for laboratory results and the requirement that patients return to the clinic for treatment. Reliable, low-cost point-of-care testing for STIs are needed to address the high burden of STIs in young women in sub-Saharan Africa [98, 99].

Although we assumed that demand creation would happen only through posters and flyers in the MoH scenarios, research findings suggest that stigma remains a barrier to PrEP implementation at individual, community and provider levels [70, 71]. In the POWER cohort in Kisumu, additional demand creation was done through giving out t-shirts and having quarterly support groups with PrEP educational sessions for the women; with these additional components, demand creation contributed to 26% of total annual costs. Though we were unable to quantify the direct impact of these demand creation activities, study staff reported increased knowledge and awareness about PrEP among study participants and their friends who accompanied them to the support groups. Other studies have also demonstrated that demand creation, when framing PrEP as a way to stay empowered and healthy (rather than as a way to prevent HIV acquisition), could encourage PrEP uptake among young women [69, 106, 107]. It is also expected that as PrEP awareness increases, the need for demand creation, and its associated incremental cost, will decline.

Our study did not follow screening procedures that would be done in a MoH setting. Therefore, we excluded screening costs, likely underestimating the cost of PrEP delivery. A recently published PrEP study in young women attending maternal and child health and family planning clinics in Kenya reported a total unit cost (in 2017 USD) of $2.91 for a screening encounter [34]. Future research should evaluate the real-world costs of a comprehensive PrEP program that includes screening, initiation and follow-up visits.

Though we only estimated costs from a provider perspective, costs to clients can be a barrier to PrEP implementation due to inadequate transportation or inability to take time off work or school [70, 71]. In the POWER study, after careful consideration, special accommodations were made for women who were at ongoing risk of HIV acquisition but expressed an inability to return to the facility for a scheduled visit. Specifically, in the costing period, 25 women were given two months of PrEP within the month of PrEP initiation, and during quarterly follow-up visits, one woman was given four months of PrEP and another was given five months of PrEP. This example

of a differentiated PrEP delivery model, in addition to non-clinic-based service delivery, could reduce costs for PrEP clients and minimize PrEP discontinuation among those indicated for PrEP. Improving access to PrEP through better referral systems can also help reduce costs for PrEP clients, especially during long periods of travel away from the facility of PrEP initiation.

In our study, PrEP visits were scheduled per the Kenyan national guidelines allowing us to estimate costs as they would occur in the MoH scenario. Additionally, though study staff performed the majority of PrEP delivery tasks, some PrEP delivery procedures were performed by facility staff, allowing for their real-world assessment. Specifically, at the private facility (KMET), CrCl, and HBsAg testing and PrEP dispensing were fully conducted by facility staff, while at the public facility (JOOTRH), HIV testing was fully done by facility staff. Costing PrEP delivery procedures as they are performed by facility staff bolsters the usability of our findings to project the local cost of PrEP delivery under MoH implementation.

CONCLUSIONS

In a practical implementation setting, we estimated the cost of PrEP delivery among young women in family planning clinics, providing valuable data to inform budget impact and cost-effectiveness studies and resource allocation for PrEP. In all scenarios, medication was the main contributor of total annual costs, highlighting the need to find ways to lower the price of drugs used in PrEP. Other approaches to minimize costs such as task-shifting, differentiated delivery and prioritization of those at high risk of HIV for PrEP will also need to be evaluated.

LIST OF ABBREVIATIONS

AGYW	Adolescent girls and young women
CrCl	Creatinine clearance
CT	*Chlamydia trachomatis*
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
JOOTRH	Jaramogi Oginga Odinga Teaching and Referral Hospital
KMET	Kisumu Medical Education Trust
MoH	Ministry of Health
NG	*Neisseria gonorrhoeae*
POWER	Prevention Options for Women Evaluation Research
PrEP	Pre-exposure prophylaxis
STIs	Sexually transmitted infections
TDF/FTC	Tenofovir disoproxil fumarate/emtricitabine

DECLARATIONS

Ethics approval and consent to participate

The POWER study protocol was reviewed and approved by the Institutional Review Boards (IRBs) at the University of Washington and the Human Subjects Review Committees at each clinical site. The study included women of ages 16-25, and we followed local guidelines for consent for those under 18 years of age.

Consent for publication

Not applicable.

Availability of data and materials

The data used and/or analyzed during the current study are included in the supplementary information files.

Competing interests

All authors declare no conflict of interest related to this work.

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Authors' contributions

VW contributed to time-and-motion data collection and data analysis. VW and KP contributed to data analysis and drafting of the manuscript. VW, AO, FM and VO contributed to data collection, data extraction and informing MoH scenario cost allocations. VW contributed to data extraction for program volume. JFM contributed to data extraction to inform study PrEP costs. CC contributed to informing STI costs under MoH scenario. VW, KP, AO, FM, VO, JBO, JFM, EAB, CC, JMB and RVB contributed to critical revision of the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Figure 3. Proportion of total annual cost (2019 USD) by input type

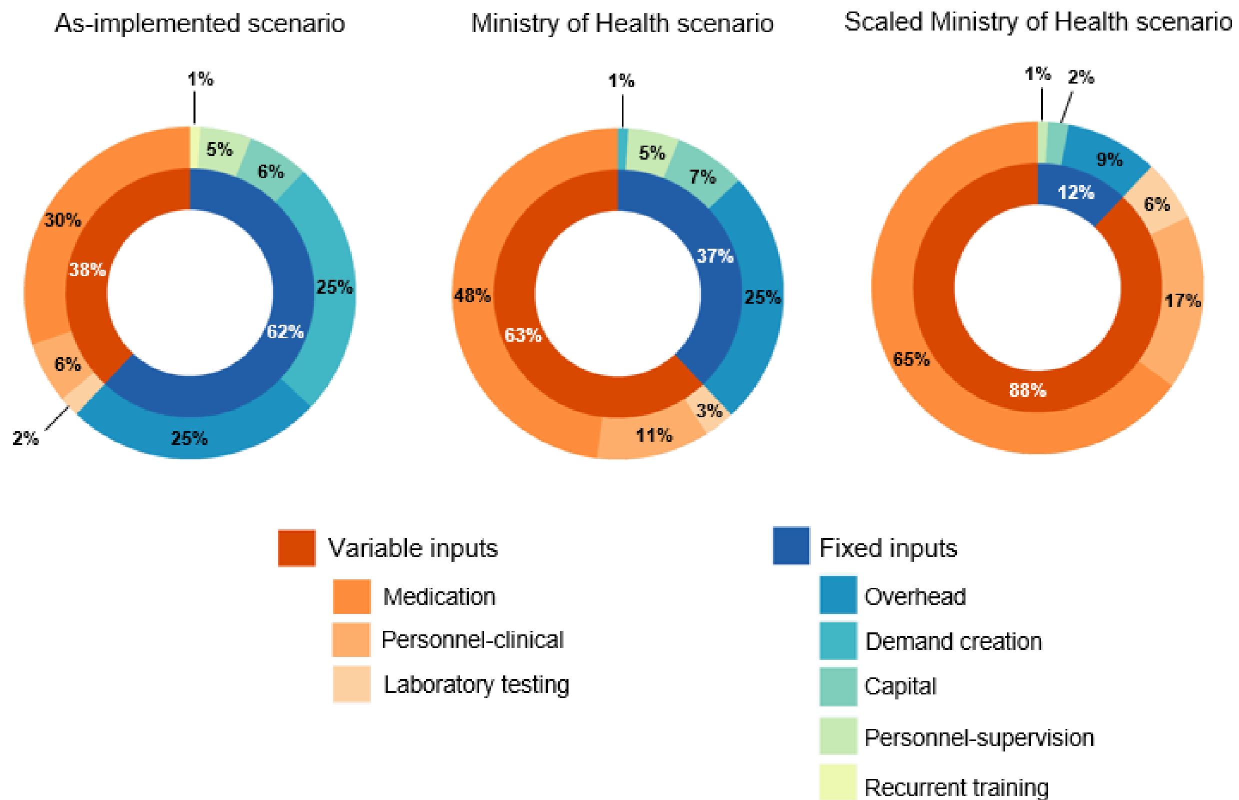

Table 8. Estimated total and average economic costs (2019 USD)

	As-implemented scenario		MoH scenario		Scaled-MoH scenario	
	Annual cost	Cost/client-month of PrEP	Annual cost	Cost/client-month of PrEP	Annual cost	Cost/client-month of PrEP
Variable inputs						
Personnel (clinical staff)	2705	1.74	2562	1.65	14536	1.90
Medication	13620	8.77	10907	7.02	53670	7.02
Laboratory and HIV testing	782	0.50	782	0.50	5044	0.66
Variable total	17107	11.01	14251	9.17	73250	9.58
Fixed inputs						
Training (start-up)	97	0.06	52	0.03	52	0.01
Training (refresher)	257	0.17	6	0.00	6	0.00
Demand creation	11436	7.36	125	0.08	125	0.02
Personnel (supervision and administration)	2391	1.54	1089	0.70	1089	0.14
Capital (vehicle, stationery, furniture, clinical equipment)	2513	1.62	1478	0.95	1478	0.19
Overhead (building, utilities, fuel, maintenance, internet)	11133	7.16	5566	3.58	7198	0.94
Fixed Total	27826	17.91	8315	5.35	9946	1.30
Total variable and fixed costs	44933	28.92	22566	14.52	83196	10.88

MOH=Ministry of Health

Table 9. Economic costs by visit type (2019 USD)

	As-implemented scenario		MoH scenario		Scaled-MoH scenario	
Visit type	Annual cost	cost per client-month of PrEP	Annual cost	cost per client-month of PrEP	Annual cost	cost per client-month of PrEP
Initiation						
Variable costs	6327	12.67	5149	10.31	33346	10.29
Fixed costs	17194	34.42	5007	10.02	5007	1.55
Total variable and fixed	23520	47.09	10156	20.33	38352	11.84
Follow-up						
Variable costs	10264	10.31	8689	8.73	39905	9.06
Fixed costs	10633	10.68	3308	3.32	3308	0.75
Total variable and fixed costs	20896	20.99	11997	12.05	43213	9.81

MOH=Ministry of Health

Table 10. Economic costs by lab testing at initiation visit (2019 USD)

	As-implemented scenario		MoH scenario		Scaled-MoH scenario	
	Annual cost	Cost/client-month of PrEP	Annual cost	Cost/client-month of PrEP	Annual cost	Cost/client-month of PrEP
CrCl, HBsAg and STI testing						
Laboratory and HIV testing (% of total cost)	31,936 (41%)	20.55	10,830 (33%)	6.97	59,911 (47%)	9.14
Total cost	77,275	49.73	32,810	21.12	148,245	19.39
CrCl and HBsAg testing only						
Laboratory and HIV testing (% of total cost)	2,477 (5%)	1.59	2,477 (10%)	1.59	13,702 (17%)	2.09
Total cost	47,817	30.77	24,457	15.74	94,333	12.34
STI testing only						
Laboratory and HIV testing (% of total cost)	30,240 (41%)	19.46	9,135 (30%)	5.88	50,533 (43%)	7.71
Total cost	74,392	47.88	30,919	19.90	137,107	17.93

CrCl=Creatinine clearance; HBsAg=Hepatitis B surface antigen; STI=*N. gonorrhoeae* and *C. trachomatis* MOH=Ministry of Health

Chapter 5. Discussion

The work in this dissertation has addressed important questions concerning PrEP delivery for young women in sub-Saharan Africa. Chapter 2 contributes to the literature on factors that influence PrEP uptake and continuation and suggests that HIV-negative individuals at high risk of HIV can recognize their risk based on their sexual behavior. Our study in Chapter 3 illustrates the feasibility of adding HIVST in PrEP delivery, not only as a screening tool, but also as a tool to streamline PrEP delivery for young women. Lastly, the costing analysis in Chapter 4 demonstrates the cost of PrEP delivery by type of input, highlighting medication as a main contributor of PrEP delivery costs, and draws attention to the urgent need to address STIs in PrEP delivery. Collectively, this dissertation informs research, practice and policy around strategies for PrEP provision for young women.

INTERPRETATIONS AND IMPLICATIONS FOR RESEARCH AND POLICY

Risk perception, sexual behavior and PrEP adherence (Chapter 2)

We found strong associations between sexual behavior and risk perception. Compared to those who reported no condomless sex, individuals who reported any condomless sex had fivefold, fourfold and threefold higher odds of reporting themselves to be at “high risk”, “moderate risk” and “low risk”, respectively, of acquiring HIV. There was no evidence of effect modification by gender, but these associations were stronger among women than men. Moreover, men tended to report that they perceived no risk of HIV more often than women. Our findings are consistent with those from other studies that have also shown that those who report riskier sexual behaviors also tend to perceive some risk of HIV [19] and men perceive low risk of HIV infection more often than women [16, 37, 108].

We also examined how risk perception influences PrEP adherence, and though not statistically significant, reporting a “high risk” perception was associated with lower odds of having high PrEP adherence, yet reporting “moderate” and “low risk” were both associated with increased odds of high PrEP adherence. Individuals enrolled in the Partners Demonstration Project had high PrEP adherence (by MEMS caps data) and received comprehensive risk reduction counseling

throughout the study; this could explain why risk perception had minimal impact on PrEP adherence. Additionally, HIV-negative individuals reported few outside partnerships, and knowing their primary partner's HIV-positive status could explain why there was high adherence to PrEP regardless of perceived HIV risk. Nevertheless, other studies have found that risk perception influences PrEP adherence [19, 48, 51] and PrEP acceptance among men who have sex with men [109, 110]. Our null findings highlight the need to longitudinally evaluate how risk perception influences adherence among individuals who may not know the HIV-status of their partners.

Together with other published findings, our study shows evidence that sexual behavior and risk perception both influence PrEP uptake and continuation. Like other studies of risk perception, we used a single-item question to measure risk perception, which does not fully capture other social and cultural factors that influence an individual's perceived risk. More complete measurement of risk perception is crucial, especially among young people whose relationships are likely to change over time. Assessment of risk perception more comprehensively by incorporating external factors such as behaviors of partners, may help in identifying seasons when PrEP could be most beneficial. Some tools that are being evaluated currently among young women such as a decision support tool (POWER study) and participant-empowered visual narratives of sexual history timeline (HPTN082 study) [14] could help individuals to more accurately align their perceived and true risk of HIV. Future studies will be needed to elucidate optimal ways to incorporate these tools into real-world delivery settings.

Risk assessment tools are widely used in PrEP programs to screen for PrEP candidacy. Researchers have developed risk scores that could be also used to prioritize PrEP delivery to those at most risk of HIV infection [111-113]. These tools are valuable, particularly in instances where providers are uncertain about ideal PrEP candidates and, more so, when there is misalignment between perceived and actual risk; poor agreement between perceived risk and objectively calculated risk has been found among men who have sex with men [114] and serodiscordant couples [108]. Still, risk scoring tools rely on accurate responses to questions such

as condom use and number of sexual partners and may exclude individuals who need PrEP but are unwilling to disclose behaviors that put them at risk. Furthermore, there are limited data on the applicability of these tools to broader populations, including young women, and additional research is needed on the joint application of self-perceived risk and objective risk scores in screening for PrEP in order to optimize uptake of PrEP by those who need it most.

Risk and risk perception change over time for each individual, and it is essential for PrEP programs to improve efforts to support individuals in making informed choices about when to start or stop PrEP, evaluate reasons for PrEP discontinuation and develop strategies to minimize loss to follow-up among those at ongoing risk of HIV. Finally, there is a population-level benefit of PrEP provision regardless of risk behavior in averting HIV infections over time [115]. This, together with our findings that risk perception aligned with sexual behavior, emphasize the usefulness of allowing individuals to self-select for PrEP.

HIVST in PrEP delivery (Chapter 3)

Although integrating PrEP delivery with other reproductive and sexual health services for young women could promote PrEP screening, uptake and counseling, it could subsequently add delivery challenges to providers and clients if not simplified or combined with additional capacity and resources. For providers, adding PrEP increases the number of people who need to be tested for HIV (since HIV testing is required at each PrEP visit) and the amount of time needed to screen and counsel clients, which could result in less time per patient and lower quality of care. In a qualitative study among HIV care providers in Western Kenya, providers reported high strain due to high patient volume, lack of control in their professional roles (e.g., a lab tech not being able to run lab tests because the facility is out of lab supplies or a HTS counselor being asked to do community mobilization, a task that is outside his/her specialization) and low personal and professional support as barriers to providing high quality patient care [116]. For clients, long waiting times in clinics could discourage PrEP continuation and utilization of other prevention services; long waiting times have been cited as a barrier to using HIV services among people

living with HIV [117, 118], and for PrEP clients who are not sick to begin with, this could be an even bigger deterrent to seeking care. Collectively, these issues underscore the need to identify approaches to deliver PrEP without adding burden to health systems.

In Chapter 3, we evaluated HIVST as a strategy to simplify PrEP delivery, and we found that young women were willing to use HIVST during their follow-up PrEP visits. Using HIVST also significantly reduced the overall time clients spent at the clinic (median total time: 33 minutes for acceptors and 54 minutes for decliners of HIVST). Privacy/confidentiality was reported as the main reason for accepting HIVST, while not being comfortable testing alone was the main reason reported for preferring PITC. Both HIVST acceptors and decliners were satisfied with their overall clinic experience and found it easy to understand their test results, but HIVST acceptors tended to be very happy with their overall testing experience than HIVST decliners. Coupled with a HIVST uptake of 34.7% across all visits in the HIVST period, our results demonstrate that adding HIVST in PrEP delivery is feasible and can be a solution to make PrEP delivery more efficient.

The current WHO guidelines do not recommend the use of HIVST by people taking PrEP [119] due to concerns about false negative results. Continuing to take PrEP with undetected HIV could lead to drug resistance, but a recent review of PrEP studies found that resistance selection for TDF and FTC with PrEP use is infrequent [120]. Evaluations of HIV rapid diagnostic tests (RDTs) among PrEP users have found variable sensitivities and specificities, with reported specificities >98% [121-125]. In particular, an evaluation of OraQuick ADVANCE® Rapid HIV-1/2, the test kit we used in our study, found that it had high specificity (99.99%) and high negative predictive value (99.94%) [124]. Still, considerations about the performance of RDTs and drug resistance with undiagnosed HIV infection necessitate additional evidence on the safety and utility of HIVST for those initiating, restarting or continuing PrEP. Our study in Chapter 3 is an initial stride towards informing guidance on the use HIVST in PrEP delivery.

There is increasing advocacy to provide young women in sub-Saharan Africa with choices of prevention products that meet their individual needs and preferences, centered on promoting

the right of women to independent decision-making. The rationale behind this is that with more choices, young women will feel empowered in their decision-making, which could facilitate uptake of prevention products. In the majority of standard of care visits (52%) in our Chapter 3 study, women expressed that they would consider HIVST in the future because of personal empowerment/taking charge of own health. Among those who accepted HIVST, following privacy/confidentiality (34% of visits), personal empowerment/taking charge of own health was the second aspect of HIVST that was liked most (24% of visits). Beyond evaluating the utility of HIVST to streamline PrEP delivery, our findings highlight the value of considering HIVST as a means to promote young women's empowerment and autonomous decision-making about HIV testing while on PrEP.

Cost of PrEP delivery for young women (Chapter 4)

To date, only few studies such as PrIYA [34] have reported on the costs of delivering PrEP through maternal and child health and family planning (FP) clinics in Kenya. Our study in Chapter 4 presents additional data of the incremental cost of delivering PrEP to young women through FP clinics. We found that the cost (in 2019 USD) per client-month of PrEP dispensed was $28.92 as implemented by the study, $14.52 if the MoH were to implement the study (MoH scenario) and $10.88 if the MoH were to scale delivery so that the maximum number of PrEP clients (14 per clinic based on time-and-motion observations) are seen per day (scaled-MoH scenario). Our estimates were comparable to those of the PrIYA study, which found a cost (in 2017 USD) per client-month of PrEP dispensed of $26.52 as implemented and $18.00 in the MoH scenario [34]. While these estimates may not be generalizable to broader FP settings due to the heterogeneity in health systems and populations, they are a first step towards elucidating the financial implications of PrEP delivery to young women.

In our analyses, we also evaluated the costs of testing (at PrEP initiation) for creatinine clearance (CrCl) and Hepatitis B surface antigen (HBsAg) as recommended by the Kenyan national PrEP guidelines [81], and STI (NG/CT) testing as was implemented in the POWER study.

As anticipated, conducting all three tests (CrCl, HBsAg and STI) substantially increased the cost per-client month of PrEP dispensed to: $49.73 as implemented, $21.12 in the MoH scenario and $19.39 in the scaled-MoH scenario. Excluding STI testing but testing for CrCl and HBsAg only minimally increased costs to $30.77, $15.74 and $12.34 in the as-implemented, MoH and scaled-MoH scenarios, respectively. Given the high rates of STIs among individuals using PrEP [97], and the generally high rates of STIs among young women in sub-Saharan Africa [98, 99, 104], excluding STI testing in PrEP results in a missed opportunity to diagnose and treat incident STI infections. Our findings that STI testing significantly drives up the cost of implementing PrEP highlight the need to accelerate the development and accessibility of low cost point-of-care STI tests in low-resource settings in order to simultaneously tackle HIV and STIs. In the guidelines for PrEP implementation for adolescents and young adults, the WHO recommends initiating PrEP without CrCl results on the basis that TDF renal toxicity risk is small in this population [100]. Thus, PrEP programs could prioritize STI testing over CrCl testing among young women.

In the primary analyses excluding CrCl, HBsAg and STI testing, we found that medication (TDF/FTC) was a major driver of PrEP delivery costs. Considerable progress has been made in improving procurement practices and achieving better prices for ARVs [126]. However, medication costs are still expected to contribute a significant portion of overall PrEP delivery costs. Research is needed to evaluate approaches to reduce other PrEP delivery costs. Task-shifting and differentiated delivery models have been used successfully in HIV treatment and care and there is a potential role for them in reducing costs of PrEP delivery [86]. HIVST could also allow providers to spend more time on specialized tasks thereby reducing personnel costs, but the additional costs of self-test kits will need to be evaluated. Lastly, prioritization of PrEP delivery to high-risk individuals, if they can be identified, could also be used as a strategy to reduce PrEP delivery costs [34, 115].

Conclusion

Using data from demonstration and implementation studies in eastern Africa, this dissertation has

provided insight into practical approaches to improve PrEP delivery for young women. First, our finding that individuals can accurately assess their HIV risk supports the idea that individuals should be empowered to self-select for PrEP. Although this finding was among mutually-disclosed HIV serodiscordant couples and it may not be fully generalizable to young women with partners of unknown HIV status, it sets the stage for additional work linking sexual behavior, risk perception and PrEP-taking behavior. Second, our finding that integrating HIVST in PrEP delivery was feasible, and that giving a HIV testing choice can be empowering to young women, underscores the value of considering and evaluating HIVST in PrEP delivery, not only as an instrument to screen for HIV and improve clinic flow, but also as a strategy to promote autonomous decision-making about HIV testing method. Third, in Chapter 4, we found that scaling up PrEP delivery significantly reduces the cost per client-month of PrEP dispensed due to the distribution of fixed costs across more people, underscoring the need to increase PrEP awareness and facilitate uptake and retention among those at risk of HIV. We also found that the prevalence of STIs among young women is very high. However, including STI testing at initiation significantly drives up the cost of PrEP delivery, presenting a prioritization conundrum for programs with competing prevention interventions and constrained budgets. Reliable low-cost point-of care STI tests are urgently needed to minimize the financial burden of laboratory-based STI testing, and to take advantage of the opportunity to address STIs in PrEP programs for young women. Finally, in addition to lowering the cost of STI testing, it is necessary to evaluate other strategies to simplify PrEP delivery and minimize costs of delivering PrEP to young women, such as task-shifting, differentiated delivery and prioritization of high-risk individuals for PrEP delivery. The availability of national guidelines and policies for those delivering PrEP is only the first step in PrEP implementation. To realize the maximum benefit of PrEP for HIV prevention among young women, more work is needed to promote risk awareness among those at ongoing risk of HIV, facilitate PrEP access, uptake and retention, and identify and evaluate optimal approaches to streamline PrEP delivery in a cost-effective manner.

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