STUDY PROTOCOL

HIV self-testing to improve the efficiency of PrEP delivery

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Abbreviations

3TC	Lamivudine
AIDS	Acquired Immunodeficiency Virus
AE	Adverse Event
ART	Antiretroviral Therapy
ARC	AIDS Related Complex
CDC	Centers for Disease Control and Prevention (US)
CHCT	Couples HIV testing and Counseling
DAIDS	Division of AIDS (NIH)
DALY	Disability-Adjusted Life Year
DBS	Dried Blood Spots
EC	Ethics Committee
FDA	Food and Drug Administration (US)
FTC	Emtricitabine
FTC-TP	Emtricitabine-triphosphate
HIV	Human Immunodeficiency Virus
GEE	Generalized Estimating Equations
HTTP	Hypertext Transfer Protocol (presentation of web data)
ICER	Incremental Cost-Effectiveness Ratios
IRB	Institutional Review Board
KEMRI	Kenya Medical Research Institute
NACOSTI	National Council of Science, Technology and Innovation
NIH	National Institutes of Health (US)
PrEP	Pre-exposure prophylaxis
SAS	Statistical Analysis Software
STI	Sexually transmitted infection
TDF	Tenofovir
TFV-DP	Tenofovir diphosphate
UNAIDS	Joint United Nations Program on HIV/AIDS
US	United States
UW	University of Washington
VCT	Voluntary counseling and testing
WHO	World Health Organization

PROTOCOL SUMMARY

Maximizing access and minimizing costs of delivery are key challenges for optimizing the public health impact of pre-exposure prophylaxis (PrEP) for HIV-1 prevention, particularly for resource-constrained settings. PrEP is highly effective and safe when taken as prescribed, and demonstration studies are showing how PrEP can be delivered in clinical settings. In Africa, PrEP will be added to an already-burdened health infrastructure and the ability of public health systems to afford PrEP will necessitate making its delivery cost-effective and time-efficient. PrEP delivery programs will need to be cost-sensitive to staffing needs (e.g., frequent clinic visits); moreover, patients may not continue PrEP if their costs (e.g., travel to / waiting in clinics) are high. HIV-1 testing is central to PrEP: testing must occur prior to initiation and ongoing HIV-1 testing is essential for delivery. Like PrEP, HIV-1 self-testing is a recent innovation and its opportunities to improve HIV-1 prevention have not been fully realized. We hypothesize that HIV-1 self-testing can streamline PrEP delivery – through decreasing the frequency of PrEP clinic visits by having self-tests at home replace clinic-based testing. *Both oral fluid and new finger stick blood-based HIV-1 self-tests could be used, and these two modalities might have different costs or preferences.*

In May 2017, Kenya announced national scale-up of PrEP for persons at risk for HIV-1, prioritizing HIV-1 serodiscordant couples, women at risk, and other priority groups, and also the prioritization of HIV-1 self-testing in the country. This project proposes to address key access and cost of delivery challenges for PrEP by integrating the new modality of HIV-1 self-testing, with the following Aims:

Aim 1: **In a randomized trial, we will test the use of HIV-1 self-testing to decrease the frequency and burden of clinic visits for PrEP while resulting in equivalent adherence and testing.**

Hypothesis: Guidelines recommend HIV-1 testing quarterly on PrEP; we propose HIV-1 self-testing at home could alternate (e.g., Months 3, 9) with clinic-based testing (e.g., Months 6, 12), eliminating half of clinic visits and saving staffing and patient costs. Reducing clinic contact frequency will not result in reductions in PrEP adherence or completion of HIV-1 testing, overall or in subgroups.

Approach: **Design:** We will conduct a randomized trial using a non-inferiority design among 495 women and men at risk for HIV-1 in Kenya initiating PrEP. **Population:** We will enroll men (n=165) and women (n=165) who are HIV-1 uninfected partners in HIV-1 serodiscordant couples and women at risk of HIV-1 (n=165), populations prioritized for PrEP delivery in Kenya and more generally in Africa. **Intervention:** Approximately one month after PrEP initiation, participants will be randomly assigned in a 2:1 fashion to either: six-monthly clinic visits with either oral fluid-based or blood-based HIV-1 self-testing at home for quarters between clinic visits (self-testing arm) or quarterly clinic visits with in-clinic finger stick blood-based rapid HIV-1 testing (standard of care arm). **Follow-up:** PrEP refills will occur at clinic visits – quarterly (standard of care) and 6-monthly (self-testing), outcomes will be measured at Months 6 and 12. **Outcomes:** PrEP adherence (defined by PrEP quantity in dried blood spots and persistence in refilling PrEP), HIV-1 testing, and safety (including side effects and social harm).

Aim 2: **We will conduct mixed-methods work to understand user and provider experiences, preferences, barriers, and facilitators related to HIV-1 self-testing.**

Hypothesis: HIV-1 self-testing will appeal to patients, because of greater self-efficacy and reduced opportunity costs, and providers, for reduced workload. Blood-based tests *may inspire* greater confidence than oral fluid tests. Gender and partner

involvement may influence acceptability of HIV-1 self-testing.

Approach: Triangulating data from structured survey and qualitative interviews, we will assess patient and provider perceived benefits of and concerns about HIV-1 self-testing in the context of PrEP.

Aim 3: We will assess costs and cost-effectiveness of HIV-1 self-testing to optimize PrEP delivery.

Hypothesis: HIV-1 self-testing will decrease the cost of PrEP delivery and improve PrEP cost-effectiveness.

Approach: Using activity-based micro-costing data and outcome information from Aim 1, we will define the costs and model the cost-effectiveness of HIV-1 self-testing for optimized PrEP delivery.

Strategies to decrease the frequency of PrEP follow-up visits would improve its cost-effectiveness, reach, and impact. Combining self-testing and PrEP brings together two cutting-edge interventions, and the simple HIV-1 self-testing strategy in this application could cut the number of PrEP follow-up visits in half.

BACKGROUND/RATIONALE

Importance of the problem

More than two million persons become newly infected with HIV-1 each year, the majority in sub-Saharan Africa [1]. In Kenya, more than 1.4 million people are living with HIV-1 [2], making it the country with the fourth greatest number of persons living with HIV-1. The past five years have witnessed major strides in the development of highly-effective HIV-1 prevention interventions, particularly ones using antiretroviral medications: antiretroviral therapy (ART) for HIV-1 infected persons to decrease infectiousness and pre-exposure prophylaxis (PrEP) for uninfected persons to prevent acquisition. Novel strategies to successfully and efficiently deliver these strategies are needed to achieve maximum impact among populations at the highest risk of HIV-1.

PrEP is an effective and recommended strategy for HIV-1 prevention

PrEP is efficacious and safe for HIV-1 prevention.

PrEP has been demonstrated to be efficacious and safe for reducing HIV-1 risk among men who have sex with men [3], heterosexual men and women [4, 5], and injection drug users [6] in diverse geographic settings. In 2012, the US Food and Drug Administration approved combination tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) as the first medication with a label indication for HIV-1 prevention in adults [7] – an action followed by drug regulatory authorities in a number of other countries including Kenya (in December 2015). In 2015, the World Health Organization issued guidance recommending PrEP as an additional prevention option for all persons at high risk for acquiring HIV-1 [8]. The 2016 Kenyan ART guideline have incorporated Tenofovir/Emtricitabine (TDF/FTC) as the preferred regimen with Tenofovir/Lamivudine (TDF/3TC) and Tenofovir (TDF) alone as recommended options for HIV-1 pre-exposure prophylaxis [58].

Adherence is key to PrEP efficacy.

Like for ART, adherence is essential for PrEP efficacy. PrEP clinical trials had a wide range of results for estimates of PrEP's efficacy for HIV-1 protection – explained by the degree to which the trial populations were adherent to PrEP [9]. Secondary analyses from clinical trials and demonstration studies have shown that PrEP is clearly efficacious when taken as prescribed. At the individual level, HIV-1 protection is on the order of 90-100% in both men who have sex with men and heterosexual populations when PrEP adherence was high, as measured by the presence and quantity of PrEP in blood samples [4, 10, 11]. PrEP adherence and HIV-1 prevention effectiveness have been higher in open-label demonstration projects among HIV-1 serodiscordant couples, men who have sex with men, and young women at risk for HIV-1 than in prior clinical trials [12-14], which has been hypothesized to be a result of offering a strategy with demonstrated safety and effectiveness, and without a placebo. In those PrEP demonstration studies, HIV-1 incidence has been low and visits were generally quarterly and brief, suggesting that many who initiate PrEP in the context of known safety and efficacy may not need frequent or intensive follow-up to achieve high adherence.

Strategies to effectively and efficiently deliver PrEP are needed

PrEP delivery can be expensive, in terms of medication costs, staffing time, laboratory testing, and patient opportunity costs. Multiple analyses from high-income settings have argued that,

while PrEP is cost-effective when delivered to high-risk persons, it is still a costly intervention [15-17]. For developing country settings, the results are similar – even when taking into account lower cost inputs such as generic or discounted medication pricing, lower staff salary costs, and more truncated laboratory testing recommended by WHO and country policies [16, 18]. Thus, costs will be a barrier to PrEP delivery for impact, in all settings.

In costing analyses we have conducted in East Africa, we estimated that adding PrEP to routine public health services using Ministry of Health personnel, drug, and laboratory costs would cost ~US$100 annually per person. Notably, in those models, the greatest proportion of the total costs was not medication costs but was instead personnel (39%) [19]. That finding emphasizes the need for efficiency in PrEP delivery, particularly so given that qualified medical staff in Kenya and similar settings are often highly over-stretched, because of competing priorities in overburdened health systems. Our modeling did not take into account patient costs related to PrEP; however, we have learned through providing PrEP in studies to over 5000 individuals over the past 10 years that travel and time away from work and costs for getting to PrEP clinic visits can be a challenge for persons taking PrEP. Efficient strategies to deliver PrEP could reduce costs, potentially improving patient engagement and allow services to be available to a larger number of people as a result – and this kind of approach would be applicable in a variety of settings worldwide.

HIV-1 testing is central to PrEP; HIV-1 self-testing is a novel approach that could streamline PrEP delivery

Point-of-care HIV-1 testing is a standard component of PrEP delivery.

PrEP requires regular HIV-1 testing – at the time of PrEP initiation and then in an ongoing basis. HIV-1 testing is necessary to reduce the risk of antiretroviral resistance if HIV-1 infection is present prior to PrEP, in which case PrEP will not be started, or occurs while prescribed PrEP, in which case it will be discontinued. PrEP clinical trials were carried out in the context of monthly HIV-1 testing, generally using point-of-care third-generation antibody-based tests, conducted at the clinical trial sites. Although this frequent approach to HIV-1 testing was important for the clinical trials, which were the first evaluations of PrEP use, monthly testing would be logistically impossible for routine public health settings because of excessive costs and burden to PrEP takers and providers. Thus, initial guidance about PrEP delivery from the US FDA and CDC recommended testing every three months, and demonstration projects of PrEP distribution conducted quarterly testing [13, 14, 20]. The safety of this approach has been borne out in analyses of HIV-1 acquisition among persons receiving PrEP, which have repeatedly demonstrated that the risk of HIV-1 during PrEP use is greatest at the start of PrEP (i.e., unrecognized acute infection coincident with PrEP initiation), that HIV-1 acquisition after PrEP initiation is rare except for persons not taking PrEP, and that resistance risk is thus also rare during PrEP follow-up (as either persons take PrEP and do not get HIV-1 or don't take PrEP and thus cannot select for resistance of they acquire HIV-1) [3, 4, 21, 22]. WHO recommends quarterly testing as the global standard in an effort to balance costs, safety, and burden to PrEP takers and providers [8], and US and global guidelines do not restrict either the assay (point-of-care versus laboratory, antibody- vs. antigen/RNA-based) or the location (in-clinic versus laboratory versus home) of HIV-1 testing for persons receiving PrEP follow-up. Nevertheless, to our knowledge, no programs distributing PrEP have attempted to move HIV-1 testing out of clinical settings and into the home with self-testing, and evidence is needed to motivate policy change for this opportunity. As PrEP expands into public health clinical settings there are new opportunities for easier models of HIV-1 testing.

Self-testing offers an innovative way to test for HIV-1

In 2012, the US FDA approved use of the OraQuick In-Home HIV Test as the first self-administered test for HIV-1, opening a new opportunity for evaluating HIV-1 testing directly under the control of an individual [23]. Several other self-testing assays in addition to OraQuick are under development or available. Self-testing offers strong advantages: privacy and convenience, and these may appeal to both patients and providers. HIV-1 self-testing has been proposed as a strategy to increase both first-time HIV-1 testing (i.e., as a general population screening tool) and repeat HIV-1 testing (i.e., for persons with ongoing HIV-1 risk), both of which could be extremely valuable in high-prevalence settings. A study conducted in Malawi demonstrated high use and accuracy: only 8% of subjects chose not to test and self-testing results were 99% concordant with rapid finger-stick tests collected in parallel [24]. In Kenya, a recent population based survey found 74% reported willingness to use HIV-1 self-test kits for first-time HIV-1 testing [2]. Ongoing projects, some at very large scale [25, 26], are evaluating wide-scale distribution of HIV-1 self-tests in Africa. WHO now recommends HIV-1 self-testing as an additional testing option for individuals and countries [27].

No studies have put HIV-1 self-testing and PrEP together.

Evaluating HIV-1 self-testing within a PrEP context has not been evaluated, although our pilot work (detailed below) suggested both feasibility and acceptability. In the present study, we propose that HIV-1 self-testing can reduce facility-based periodical testing and clinics visits among persons receiving PrEP and can do so safely and without detrimentally affecting adherence. Our proposed model has several potential advantages. First, self-testing could provide an efficient method that achieves the objectives of achieving high adherence to PrEP and ensuring HIV-1 testing is done without increasing the delivery costs and participant burden, compared to standard of care. Second, both PrEP and self-testing are new and seeing how they fit together is an incredible new opportunity. Third, efficiency of delivery could be appealing not only to the policy makers (reduced cost) and health providers (reduced work load) but also to the PrEP users (reduced clinic visits).

Summary: unanswered questions and central hypothesis

For persons taking PrEP for HIV-1 prevention, regular HIV-1 testing at fixed-site clinics has been the standard. We hypothesize that HIV-1 self-testing can replace some of the periodic follow-up HIV-1 testing otherwise done at a facility for persons receiving PrEP, reducing clinic and patient burdens. As detailed below, the proposed work will build on and extend our prior work in PrEP and HIV-1 self-testing, by proposing a novel model of delivering PrEP through fewer clinic visits which has the potential to revolutionize PrEP delivery.

The Government of Kenya has proposed a visionary 20-year plan for evidence-based HIV-1 prevention, including prioritizing PrEP and encouraging use of HIV-1 self-testing. In Kenya, the Ministry of Health developed the Kenya HIV Prevention Revolution Road Map: Count Down to 2030, a national plan to drive new HIV-1 infections towards zero between 2013 and 2030 [28]. The approach is based on key concepts in combination prevention: recognition of a heterogeneous epidemic, prioritization of sub-populations for prevention (HIV-1 serodiscordant couples, sex workers, men who have sex with men, and women at risk), and delivery of evidence-based prevention. Kenya was one of the first countries to implement point-of-care testing for HIV-1 [29, 30], and the Ministry of Health has supported research for self-testing. In May 2017, Kenya formally launched PrEP and HIV-1 self-testing as part of this plan (http://www.nation.co.ke/news/Govt-launches-two-approaches-to-fight-HIV-Aids/1056-3914614-8p6ubc/). Our proposed work aligns tightly with the Kenya HIV Prevention Revolution Road Map and our work will be supported by the Kenya Ministry of Health (see

letter of support).

INNOVATION

PrEP is a potent and safe HIV-1 prevention strategy. To maximize impact, optimal approaches are now needed for delivering PrEP effectively and efficiently, particularly for resource-constrained settings. In our recent PrEP demonstration project among HIV-1 serodiscordant couples in East Africa, HIV-1 transmission was virtually eliminated [14]. In that study, we delivered PrEP with quarterly clinic-based visits, and we piloted HIV-1 self-testing at home between quarterly visits, finding that self-testing was acceptable and feasible in the setting. We now propose to extend that work and simplify PrEP delivery further with HIV-1 self-testing as a strategy to reduce the frequency of clinic visits (from quarterly to six-monthly), which we will test through a randomized trial. This approach is highly innovative, in four key ways: integration of HIV-1 self-testing into PrEP, understanding for whom the proposed approach works and does not work (as a model of differentiated care for HIV-1 prevention [31]), testing of blood-based HIV-1 self-tests, and support by the government of Kenya, which makes the probability of impact high.

HIV-1 self-testing in PrEP delivery has not been formally studied

PrEP is a biomedical intervention, and its evaluation in clinical trials and demonstration settings has been clinic based. However, with greater deployment of PrEP in many settings, strategies to simplify its delivery have been a priority. We hypothesize that HIV-1 self-testing can successfully be used to conduct the HIV-1 testing that is a necessary part of PrEP delivery, but which can be done by PrEP patients instead of clinic-based staff. Reducing the frequency of follow-up clinic visits has the potential to reduce staffing costs associated with frequent visits and client-related opportunity costs such travel to the clinic and waiting time which could increase client persistence with PrEP use. While many studies are using HIV-1 self-testing to link people to care and prevention, self-testing use among those taking PrEP has not been done to our knowledge, and has potential to further efficient strategies for PrEP provision.

Differentiated care models of PrEP delivery are needed

In HIV-1 treatment settings, simplified approaches to follow-up care (e.g., 6-monthly visits for those with stable viral suppression) allow human and financial resources to be directed to those individuals needing more attention, a concept known as differentiated care. For PrEP, differentiated care models have not been developed yet, and thus a "one size fits all" approach is being done. It is very likely that many patients receiving PrEP, like those on ART, can achieve high adherence without frequent follow-up. We will conduct subgroup analyses (in Aim 1) and use mixed-methods behavioral science (in Aim 2) to explore how HIV-1 self-testing fits into PrEP provision and for whom this simplified HIV-1 testing and follow-up approach to PrEP works well and for whom it does not work well, including assessment of gender and partner knowledge of PrEP use, as a first approach to defining a differentiated care model for PrEP.

Blood-based HIV-1 self-tests are new

The OraQuick oral fluid-based HIV-1 self-test is an established, FDA-approved product. Blood-based HIV-1 tests are new and have not been tested nearly as widely. However, blood tests are commonly used in clinics for HIV-1 testing, and blood-based testing could offer greater confidence in results to at least some patients (and providers). In Aim 2, we will directly compare acceptability, usability, and confidence for oral fluid versus blood for HIV-1 self-

testing.

PRELIMINARY RESULTS

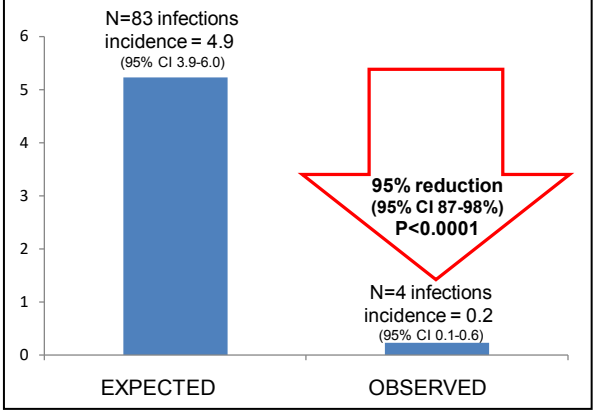
We have conducted randomized trials, behavioral science, implementation science, and mathematical modeling to define the efficacy, acceptability, and cost-effectiveness of PrEP for HIV-1 prevention.

PrEP is effective and safe for prevention

We conducted the Partners PrEP Study, the randomized clinical trial that demonstrated the efficacy of PrEP for HIV-1 prevention in heterosexual populations [4, 32]. Secondary analyses from that trial confirmed that PrEP provided significant protection including in key subgroups: both men and women [33], couples with high-risk characteristics (e.g., those practicing unprotected sex, couples in which the HIV-1 infected partner had a high plasma viral load, those with sexually transmitted infections) [33], and in women using contraception [34]. We also conducted analyses to demonstrate limited selection of antiretroviral resistance [21], safety in women using contraception or who become pregnant [35, 36], and limited renal toxicity [37-39]. Our work has been central to the development of PrEP guidance for populations worldwide [40, 41].

We conducted a large-scale demonstration of integrated ART and PrEP that showed near-elimination of HIV-1 transmission. We conducted the Partners Demonstration Project, an implementation science project delivering PrEP among 1013 HIV-1 serodiscordant couples who attended four HIV-1 research centers in East Africa. The primary goal was to demonstrate a model of PrEP delivery; ART was promoted for all couples for clinical and prevention benefits, and PrEP offered until 6 months after ART initiation by the infected partner, permitting time to achieve viral suppression, a pragmatic strategy we called "PrEP as a bridge to ART", which has directly influenced Kenya's PrEP guidelines for couples; in this study, the majority of couples used PrEP for at least 12 months, because many HIV-1 infected partners delayed ART initiation for at least 3 months or more. We found high adherence (85% of blood samples had PrEP detected) and near-elimination of HIV-1 transmission: only 4 infections observed (all among persons not using PrEP) compared to 83 in a simulated counterfactual cohort (**Figure 1**).

Figure 1. Near-elimination of HIV-1 transmission using an integrated delivery strategy for ART and PrEP: the Partners Demonstration Project



Pilot study: *HIV-1 self-testing is highly acceptable in the context of PrEP*. Within the Partners Demonstration Project, we completed a pilot evaluation of HIV-1 self-testing at the Thika site [42]. OraQuick HIV-1 oral fluid self-test kits were provided for use, at home, in the two-month interval between scheduled quarterly clinic visits. We found 222 of 226 (98%) persons on PrEP offered self-testing accepted and nearly all (96.8%) reported using the self-testing kit was easy. Many reported that HIV-1 self-testing was empowering (**Table 1**); there was a range of opinions about oral fluid versus blood tests for HIV-1, with some participants voicing greater confidence in blood (which we also heard anecdotally from providers working as part of that pilot). Across all visits, a total of 1225 HIV-1 self-testing kits (95.6% of 1282 dispensed) were reported to have been used, 253 (98.1%) and 972 (94.9%) among HIV-1 uninfected women and men, respectively. A total of 17 calls were made to the 24-hour helpline in relation to challenges in performing or interpreting the test results; one was a positive test, not confirmed on follow-up testing, and no participants seroconverted to HIV-1. Other studies in Kenya have demonstrated that HIV-1 self-testing at home is acceptable for women at risk of HIV-1, including women at risk not in known HIV-1 serodiscordant couples [43, 44]

Table 1. Experiences with HIV-1 self-testing and PrEP: pilot study

Reduced anxiety
- "Every day, every time thinking, "How will it be when I go back there [clinic]? When you test yourself, you know your status, you relax"

Testing alone versus with others:
- "Sometimes I call my husband. Like the last time I tested, I called my husband and told him "Come you see mine is okay until now."
- "Like me, I hide myself… [Participants laugh] I go to the bedroom."

Preferences of HIV-1 self-tests:
- "You know … to many people…they know blood is the accurate one. But you know this [oral self-test kit] doesn't have any blood.
- "You know sometimes for blood draw it can happen you [referring to himself] prick yourself wrongly. And you have nothing to prevent germs from getting in… But this one [oral kit] is easy…."

Costing studies and cost-effectiveness modeling.

We have extensive experience with cost and cost-effectiveness studies to understand the deliverability of prevention interventions. Within the Partners Demonstration Project, we conducted micro-costing and time and motion analyses in Uganda [19]. The cost of PrEP (and ART) was assessed, with and without research components. Then, using Ministry of Health data, the costs within a government program were estimated. We parameterized an HIV-1 transmission model to estimate the health and economic impacts of the intervention, with incremental cost-effectiveness ratios (ICERs) per HIV-1 infection and disability-adjusted life year (DALY) averted calculated over 10 years. We found that the annual cost of PrEP and ART delivery for couples would be $453 in the government setting, with $92 due to PrEP. Over 10 years, a program of PrEP and ART for couples was projected to cost $1340 per infection averted. By Uganda's gross domestic product per capita of $1681, this intervention thus is cost-effective [19]. At the Thika, Kenya site, we recently completed a similar costing exercise (Irungu, Ngure, Baeten, et al., data presented at R4P conference, October 2016 and submitted). Using Kenya Ministry of Health personnel, drug, and laboratory costs, we estimated that the incremental cost of delivering PrEP in Kenya to be $110 per couple per year, with a total cost of $544 per couple per year for ART plus PrEP. The largest cost was due to personnel (39%) – emphasizing the importance of efficiencies – followed by medication (34%).

METHODS

Taking PrEP to scale will require simplifying models for delivery, for cost savings and patient preference. We have assembled a multidisciplinary team to test a simplifying strategy for PrEP delivery. We hypothesize that alternating home HIV-1 self-testing with clinic based HIV-1 testing – with resulting reductions in clinic visits from quarterly to semiannually – will translate into cost savings for PrEP programs as well as patient related opportunity costs, without

reducing PrEP adherence, and will be feasible, acceptable, preferred, and safe.

Study Aims

Aim 1: In a randomized trial, we will test the use of HIV-1 self-testing to decrease the frequency and burden of clinic visits for PrEP while resulting in equivalent adherence and testing.

Hypothesis. Global guidelines recommend HIV-1 testing quarterly for persons on PrEP; we propose that HIV-1 self-testing could alternate (e.g., Months 3, 9) with clinic-based testing (e.g., Months 6, 12) to cut the frequency of clinic visits in half, saving staffing and patient costs, without reducing PrEP adherence or persistence.

Aim 2: We will conduct mixed-methods work to understand user and provider experiences, preferences, barriers, and facilitators related to HIV-1 self-testing.

Hypothesis. HIV-1 self-testing will appeal to patients, because of greater self-efficacy and reduced opportunity costs, and providers, for reduced workload. Blood-based tests may inspire greater confidence. Understanding for whom self-testing "works" will help define differentiated care models for PrEP delivery.

Aim 3: Assess the cost and cost-effectiveness of HIV-1 self-testing to optimize PrEP delivery.

Hypothesis. HIV-1 self-testing will decrease the cost of PrEP delivery and improve PrEP cost-effectiveness, allowing for greater efficiency, reach, and impact.

Population

At the Thika clinic, we will recruit women and men in HIV-1 serodiscordant relationships (n=165 HIV-1 uninfected women and n=165 HIV-1 uninfected men) and HIV-1 uninfected women at risk (n=165) who have recently initiated PrEP for this project. We will aim to have equal enrollment for the three study groups, but will over-enroll HIV-1 uninifected women at risk if we have difficulties or delays in enrolling men or women in HIV-1 serodiscordant relationships, whom historically have been more difficult to enroll.

Study services

<u>Standard HIV-1 testing arm</u>
Participants will receive baseline and quarterly HIV-1 counseling, condoms, risk reduction counseling, and syndromic management of sexually transmitted infections according to local guidelines.

<u>HIV-1 self-testing arm</u>
Participants will receive baseline and semiannual HIV-1 counseling, condoms, risk reduction counseling, and syndromic management of sexually transmitted infections according to local guidelines.

<u>Both study arms</u>
To ensure as real world assessment of uptake and sustained use of PrEP as possible, tracing of participants will occur only for follow-up of safety issues and for HIV-1 assessment, but not for completion of routine visits and PrEP refills.

Eligibility

Inclusion

- Age ≥18 years HIV-1 uninfected based on negative HIV-1 rapid testing
- Not currently enrolled in an HIV-1 prevention clinical trial
- Taking PrEP and planning to continue
- Willing to be randomized to either clinic based HIV-1 testing or HIV-1 self testing
- Note: Women who are pregnant at screening/enrollment are still eligible

For the HIV-1 serodiscordant couples, HIV-1 infected members of the couple will be enrolled for a single visit at baseline, if:

- Age ≥18
- Able and willing to provide written informed consent

Exclusion

- Unable to provide written informed consent
- Contraindication to use TDF/FTC/3TC

Sample size

A total of 825 individuals will be recruited: 165 HIV-1 uninfected men and their partners in HIV-1 serodiscordant relationships, 165 HIV-1 uninfected women and their partners in HIV-1 serodiscordant relationships, and 165 HIV-1 uninfected women at-risk for HIV-1 who are not in disclosed HIV-1 serodiscordant partnerships. If we have difficulties enrolling HIV-1 uninifected men or women in serodiscordant relationships, we will plan on over-enrolling HIV-1 uninifected women at-risk for HIV-1 who are not in disclosed serodiscordant relatinships to ensure we have sufficient statistical power to determine interventional effectiveness.

Table 2. Sample distribution

Cohort	Number	HIV-1 Infected Partners	Number	
Women in HIV-1 serodiscordant relationships	165	Men	165	
Men in HIV-1 serodiscordant relationships	165	Women	165	
Women	165	n/a	n/a	**TOTAL**
	495		**330**	**825**

PrEP medication

Tenofovir disoproxil fumarate (or TDF, 9-[(R)-2-[[bis [[(isopropoxycarbonyl) oxy] methoxy] phosphinyl] methoxy] propyl] adenine fumarate), emtricitabine (or FTC, 5-fluoro-1-(2R,5S)-[2-(hydroxymethyl)-1,3-oxatholan-5-yl]cytosine), and lamivudine (or 3TC, 2',3'-dideoxy-3'-thiacytidine 4-Amino- 1-[(2R,5S)- 2-(hydroxymethyl)- 1,3-oxathiolan-5-yl]- 1,2-dihydropyrimidin- 2-one) are reverse transcriptase inhibitors that have been approved for the treatment of HIV-1 infection in humans in Kenya and the United States. A fixed-dose, oral co-formulation of FTC/TDF (Truvada®) has also been approved for HIV-1 prevention in

Kenya and the United States. The World Health Organization recommends TDF-containing medications as PrEP, which includes TDF combined with FTC as well as potentially TDF alone and TDF combined with lamivudine (or 3TC, a medication closely related to FTC). Any TDF-containing medications that align with WHO and Kenya national guidelines for PrEP will be used in this study. PrEP will be prescribed for once-daily use. Study medication will be provided by the Kenya Ministry of Health.

The study drug will be stored in accordance with the drug manufacturer's recommendations. The pharmacy and storage facility will have locked, climate-controlled environments, with controlled humidity and temperature to remain within limits allowed by the manufacturer for drug storage. Dispensing will be sufficient to last until the next visit – thus, at enrollment month, a three month and six monthly supply depending on the study arm.

Counseling on the medications being used, their side effect profiles, how to take the study medication, what to do if side effects are experienced, and the importance of not sharing study medication to optimize potential efficacy and to reduce the chances of developing resistance through suboptimal HIV-1 suppression if study medication is shared with others.

HIV-1 self-test kits

The **OraQuick In-Home HIV Test (Figure 2)** is the first FDA approved test (2012) that uses oral fluid to test for antibodies to HIV-1 and HIV-2. The OraQuick In-Home HIV Test is a qualitative test that gives visually read results: preliminary positive, negative, or test not working (invalid) in about 20 minutes and its ease of use makes it ideal as an in-home test kit. The OraQuick oral fluid test has a sensitivity 91.7 percent and a specificity of 99.9 percent and is categorized as a "screening" test, therefore a second test to confirm the results is recommended.

Figure 2. The OraQuick In-Home HIV Test

The **AtomoRapid™ HIV (1&2) Test (Figure 3,** (http://atomodiagnostics.com/ products/atomorapid-hiv/) is an integrated HIV test of blood for the presence of antibodies to HIV-1 and HIV-2. It uses a contact-activated auto-retracting safety lancet, which safeguards against needlestick injuries and cross contamination (all material and waste are within the kit itself). The all-in-one device puts the end user first and makes it easy to test. AtomoRapid's interlocking features ensure each user step is performed in the correct sequence, which helps to reduce user errors. Additionally, its blood collection and delivery is controlled which simplifies test procedures, improves blood volume accuracy and delivers blood to the correct location on the test strip. The AtomoRapid™ HIV (1&2) Test has demonstrated sensitivity 99.8% and a specificity of 100% in laboratory tests conducted by the Institute of Tropical Medicine, Belgium and the German Red Cross. Pilot studies of the AtomoRapid™ HIV (1&2) Test have been done in both Kenya and South Africa. The retail price of the AtomoRapid™ HIV (1&2) Test in Kenya is anticipated to be about 20-40% less than of the current price of the OraQuick In-Home HIV Test in Kenya (personal communication, Atomo Diagnostics).

Figure 3. The AtomoRapid™ HIV (1&2) Test

If there are any issues or interruptions with the procurement of AtomoRapid HIV self-testing kits in country, we will procure and train participants on the use of other HIV self-testing kits that have been prequalified by the WHO, an official observer of the International Medical Device Regulators Forum. We will ensure that all HIV self-testing kits utilized by participants in this study will have a greater than 95% sensitivity and specificity. A list of applicable HIV self-testing kits is available in the UNITAID's HIV Rapid Diagnostic Tests for Self-Testing, 4th Edition. [45]

Recruitment

The Thika site has established local recruitment and screening methods that operationalize protocol-specified requirements for eligibility determination in a manner that is tailored to and most efficient for the local study setting and target study population.

Thika is an urban center, about 40 km outside of Nairobi, and has a large peri-urban and rural population base surrounding it; over the past decade, the Thika site team established a multi-disciplinary site, focused on HIV-1 and sexually transmitted disease prevention research (more than two dozen projects) and on provision of clinical care (HIV-1 testing, HIV-1 comprehensive care, HIV-1 prevention services). Our experienced community outreach team at the Thika site has established successful recruitment strategies, including collaborating with existing HIV-1 testing centers and community-based mobilization for couples and women to engage in HIV-1 prevention. The Thika clinic is a center of excellence for PrEP in Kenya and is leading training of other clinics as part of Kenya national scale-up.

Recruitment strategies will include partnering with existing voluntary counseling and testing (VCT) centers and outreach workers, public promotion of couples VCT by well-known figures and community organizations such as churches, and community mobilization around couples and women's VCT promotion (e.g., around Valentine's Day). Recruitment materials will educate couples and women about PrEP. Individuals on PrEP referred to the Thika clinic or those initiating PrEP at the Thika clinic will then be recruited to this study approximately one month after PrEP initiation.

Screening and enrollment may occur on the same day or may be split across days, depending on the preferences of the potential participant. Informed consent for study participation and enrollment in the study may proceed on the same day when eligibility is determined. For couples, HIV-1 infected partners will provide separate informed consent for a single visit but will not have longitudinal trial follow-up.

Randomization

Randomization will be done in variable-sized blocks using opaque envelopes opened at the time of randomization. Randomization will occur in a 2:1 fashion to alternating HIV-1 testing at home and in-clinic testing, or standard of care (HIV-1 testing at in-clinic follow-up visits every 3 months). Those randomized to the self-testing arm will then be further randomized in a 1:1 fashion to either blood-based or oral fluid-based self-testing kits. Randomization will be stratified by group (HIV-1 uninfected men in serodiscordant couples, HIV-1 uninfected women in serodiscordant couples, and HIV-1 uninfected women at risk). Randomization will be done at the enrollment visit which will occur approximately one month after the participants have begun taking PrEP.

Study procedures

Specific study procedures will take place at screening and enrollment, and then quarterly for the standard testing arm and biannually for the HIV self-testing arm, for up to 12 months.

At screening, eligibility information will be collected. Subjects who meet the eligibility criteria will then be enrolled in the study.

Demographic and behavioral information will be collected at enrollment. As part of PrEP intiation and continuation, several standard of care laboratory tests will be completed including HIV-1 testing, serum creatinine, and a urine pregnancy test. For this study, additional information will be collected on medical history, physical exam findings, and STI syndromic assessment and additional testing will be done as part of standard of care PrEP follow-up. Other laboratory tests will be conducted to measure adherence to PrEP medication by testing drug levels in the collected blood specimen (dried blood spots, blood hemoglobin, and blood plasma).

HIV-1 positive participants will also be assessed at baseline. Assessment will include demographic and sexual-behavior information, ART adherence data, and a brief medical history. Laboratory procedures carried out on HIV positive participants will include standard HIV-1 testing, CD4 count, and plasma HIV-1 viral load.

PrEP delivery will be according to the 2016 Kenya PrEP guidelines [46], including measurement of renal function (estimated creatinine clearance >50 mL/min to start PrEP and periodic monitoring over time, aligned to the visit schedule of the study), standard clinical assessment to avoid initiating PrEP during acute HIV-1 infection, and adherence counseling. Subjects will then be randomized at enrollment (Month 0) in a 2:1 fashion to alternating HIV-1 testing at home (Months 3, 9) with in clinic testing (Months 6, 12), translating to clinic visits every 6 months (the self-testing arm), or in-clinic follow-up visits with HIV-1 testing every 3 months (the standard of care arm). Those randomized to self-testing will be further randomly assigned to half receive oral-fluid tests and half blood-based tests (and will use the same type of test throughout their follow-up). Participants in the self-testing arms will get 6 months of PrEP medication at each visit while only those on the clinic based arm will get 3 months of PrEP, corresponding to enough to last until the next clinic-based visit. Participants in both arms will be counseled on PrEP discontinuation according to Kenya national guidelines (e.g., for HIV-1 uninfected members of HIV-1 serodiscordant couples, 6 months after their partner has begun taking ART, if there are no other HIV-1 risks). Tracing for retention at Months 6 and 12 will be done, particularly to establish PrEP continuation and HIV-1 status. All HIV-1 serodiscordant couples will receive counseling on PrEP as a bridge to ART; infected partners will be encouraged to start ART if not already started **(Tables 2-4).**

As we did in our pilot evaluation (detailed above) those assigned to self-testing will receive training – blood or oral depending on their assignment and will complete one test in clinic on the day of randomization including interpretation of the test result under the guidance of the study staff to increase comfort with the process. Those assigned to HIV-1 self-testing will be provided with two self-testing kits to conduct quarterly testing until their next scheduled visit (i.e., one test kit for the quarterly visit and an extra kit to be used as back-up), and participants will be counseled to use the self-testing kit at a place and time where they will feel comfortable performing the testing (e.g., at home). Participants will also be asked to bring back the used HIV-1 self-test kits to confirm HIV-1 self-testing (though this method has limitations, it will be a proxy measure). As we did for our pilot study, a pictorial information brochure translated into local languages will be provided and a toll-free 24-hour helpline will be provided to call in case of challenges in performing the self-testing or in the event of a positive test result. Participants will be informed that any positive self-test result will need to be confirmed by study staff in accordance with the Kenyan testing algorithm and additional testing as needed (we have used both laboratory-based HIV-1 antigen/antibody enzyme-linked immunoassay testing and HIV-1 RNA PCR to confirm HIV-1 seroconversions in our prior studies and would do so in this project as well, to provide a complete ascertainment of HIV-1 status).

At the final visit (Month 12, for most participants) all participants will be trained on a HIV-1 self-testing method that they had not used and offered an opportunity to self test using the new method, specifically those on the standard arm will be trained on both oral HIV self-testing and blood based HIV self-testing while those on the oral HIV-1 self-testing arm will be trained on the blood based HIV self-testing and those on the blood based HIV-1 self-testing will be trained on the oral HIV-1 self-testing. A HIV-1 testing preference questionnaire will then be administered to assses participants preferences between the three HIV-1 testing methods.

At each study visit, we will offer counseling for participants for HIV-1 testing (pre- and post-testing), HIV-1 infection risk reduction best practices, condom promotion and provision, adherence to HIV-1 medication, adherence to HIV-1 self-testing, and PrEP and ART as HIV-1 prevention strategies.

806 **Table 2. Procedures for HIV-1 uninfected participants: standard of care testing arm**

Procedure	E)	M3	M6	M9	M12/final visit
Obtain informed consent	X				
Apply inclusion/exclusion criteria, including behavioral and lab eligibility	X				
Collect/update locator information	X	X	X	X	X
Collect demographic information	X				
Collect sexual behavioral information	X		X		X
Collect alcohol and substance use data	X		X		X
Collect depression indicators	X		X		X
Collect HIV-1 risk perception data	X		X		X
Collect general self-efficacy indicators	X		X		X
Provide HIV-1 rapid test results	X	X	X	X	X
Medical history / symptoms information	X	X	X	X	X
Perform physical exam	X	[X]	[X]	[X]	[X]
STI syndromic assessment and management	X	[X]	[X]	[X]	[X]
Offer and provide PrEP sufficient until next visit, instructions; discontinue PrEP 6 months after HIV-1 infected partner initiates ART	X	X	X	X	X
Randomization	X				
Risk reduction counseling and condom promotion & provision	X	X	X	X	X
Contraception counseling and provision/referral	X	X	X	X	X
Adherence counseling	X	X	X	X	X
Provide HIV-1 pre and post-test counseling	X	X	X	X	X
Collect PrEP adherence data	X		X		X
HIV-1 self-testing preferences	X		X		X
Collect antiretroviral-based prevention preference data, information on fertility intentions, other sociobehavioral data to inform PrEP and ART preferences and use	X		X		X
Collect blood specimen for HIV-1 testing and other lab tests as defined here	X	X	X	X	X
Measure serum creatinine			X		X
Dried blood spot collection for PrEP adherence	X		X		X
Measure blood hemoglobin to calibrate measures of PrEP adherence	X		X		X
Plasma for PrEP adherence.	X		X		X
HIV-1 serology (rapid test and, if positive, confirmatory testing according to Kenya policies)	X	X	X	X	X
Urine pregnancy test (women only, as clinically indicated or requested by the participant)	[X]	[X]	[X]	[X]	[X]

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808 [ ] as indicated

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Table 3. Procedures for HIV-1 uninfected participants: HIV-1 self-testing arms

Procedure	E	M6	M12/final visit
Obtain informed consent	X		
Apply inclusion/exclusion criteria, including behavioral and lab eligibility	X		
Collect/update locator information	X	X	X
Collect demographic information	X		
Collect sexual behavioral information	X	X	X
Collect alcohol and substance use data	X	X	X
Collect depression indicators	X	X	X
Collect HIV-1 risk perception data	X	X	X
Collect general self-efficacy indicators	X	X	X
Provide HIV-1 rapid test results	X	X	X
Medical history / symptoms information	X	X	X
Perform physical exam	X	[X]	[X]
STI syndromic assessment and management	X	[X]	[X]
Collect used HIV-1 self test kits		X	X
Offer and provide 6 months of PrEP, instructions; discontinue PrEP 6 months after HIV-1 infected partner initiates ART	X	X	X
Randomization (half will be randomized to blood-based test while the other half will receive oral-based test)	X		
Risk reduction counseling and condom promotion & provision	X	X	X
Contraception counseling and provision/referral	X	X	X
Adherence counseling (at M1, by phone, an adherence check-in)	X	X	X
Provide HIV-1 pre and post-test counseling	X	X	X
Collect PrEP adherence data	X	X	X
Collect HIV-1 self-testing data	X	X	X
HIV self-testing preferences		X	X
Collect antiretroviral-based prevention preference data, information on fertility intentions, other sociobehavioral data to inform PrEP and ART preferences and use	X	X	X
Collect blood specimen for HIV-1 testing and other lab tests as defined here	X	X	X
Measure serum creatinine		X	X
Dried blood spot collection for PrEP adherence	X	X	X
Measure blood hemoglobin to calibrate measure of PrEP adherence	X	X	X
Plasma for PrEP adherence.	X	X	X
HIV-1 serology (rapid test and, if positive, confirmatory testing according to Kenya policies)	X	X	X
Urine pregnancy test (women only, as clinically indicated or requested by the participant)	[X]	[X]	[X]

[ ] as indicated

Table 4. Procedures for index (HIV-1 seropositive) participants at the SINGLE study visit

Baseline Procedures
Obtain informed consent
Apply inclusion/exclusion criteria
Collect demographic information
Collect sexual behavior information
Medical history
Risk reduction counseling and condom promotion & provision
Collect ART adherence data
Adherence counseling (if on ART)
Provide HIV-1 pre and post-test counseling
Collect antiretroviral-based prevention preference data, information on fertility intentions, other sociobehavioral data to inform PrEP and ART preferences and use
Laboratory procedures
Conduct standard HIV-1 testing
CD4 count
Plasma HIV-1 viral load

Table 5. Procedures for Qualitative data collection (from both study arms).

Procedure			
	Baseline	**M6**	**M12/final visit/study end**
In-depth interviews	X	X	X
Focus Group Discussions			X
Health provider interview			X

Seroconversion

Seroconversion will be determined by local HIV-1 testing guidelines. For initially HIV-1 uninfected participants who seroconvert, a plasma sample or dried blood spot will be collected and archived for tenofovir levels and resistance testing. Couples and young women in which the initially HIV-1 uninfected participant seroconverts will be exited from the study but will continue with their normal HIV clinic care follow up as usual. A suspected seroconversion will be confirmed per the Kenyan National Testing Algorithm. In addition, suspected seroconverters will have a blood sample drawn that will be sent to laboratory identified by NASCOP for drug resistance testing as per Kenyan National Guidelines. Laboratory testing for suspected seroconverters is done as per standard clinical care and is not considered part of the study procedures.

Participant retention and withdrawal

Thika site will develop retention methods tailored to and most efficient for the local study setting. Retention activities may include explanation of the study visit schedule and procedural requirements during the informed consent process and re-emphasis at each study visit, collection and updating of locator information, and use of appropriate and timely visit reminder mechanisms (including phone calls and text messages). To provide complete information at the end of the study, efforts will be made to have a final follow-up visit for each participant.

Participants may voluntarily withdraw from the study for any reason at any time. The site Investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Reasons for withdrawal will be recorded.

Adherence

High adherence is important for PrEP effectiveness in preventing HIV-1 acquisition. Study staff also will provide brief adherence counseling at each scheduled visit, in accordance with Kenya PrEP counseling guidelines.

Data on adherence to the product use regimen will be collected via standardized interviewer-administered questions to ascertain product use. Finally, adherence will also be assessed through batched drug levels at enrollment and study visits at Months 6 and 12. Dried blood spots and plasma from batched drug levels will be shipped to the University of Washington for processing and analysis for tenofovir drug levels. Dried blood spot data are improved when analyzed with standardization against hemoglobin concentrations.

Discontinuation of PrEP

PrEP continuation will be according to Kenya PrEP guidelines. Use of PrEP may be interrupted by the site Investigator due to safety concerns for the participant, use of concomitant medications that could interfere with PrEP or present a safety concern, or if the participant is unable or unwilling to comply with study procedures. All treatment interruptions will be documented.

SAFETY

Multinational studies including the Thika site conducted Partners PrEP Study and Partners Demonstration Project demonstrated that PrEP (including FTC/TDF) was safe for use in heterosexual men and women from Kenya and Uganda. There were no statistically significant differences in the frequency of deaths, serious adverse events, adverse events overall, or key laboratory adverse events (specifically, creatinine elevation and phosphorus decrease) for those receiving PrEP compared to those receiving placebo in the Partners PrEP study.

For the purposes of this study, only serious adverse events (SAEs), for both index (HIV-1 infected) and partner (HIV-1 uninfected) participants, and adverse events felt related to PrEP or self-testing will be documented. SAEs felt to be related to PrEP will result in temporary hold of PrEP. In the case of temporary holds, the hold will continue until the event is stabilized or resolved. If the event resolves, PrEP may be reinitiated at the discretion of the Investigator, resuming safety monitoring. The severity of clinical symptoms will be scored using the DAIDS Table (July 2017 Version) for Grading the Severity of Adult and Pediatric AEs. Reporting on adverse events to relevant IRBs will be according to relevant regulations.

Pregnancy among partner (HIV-1 uninfected) participants

Animal and human data, including from the Partners PrEP Study and Partners Demonstration Project, suggest safety of FTC/TDF when used by HIV-1 infected women during pregnancy and breastfeeding. Other studies are exploring detailed safety of PrEP use in pregnancy. For this study, PrEP will not be discontinued when pregnancy is detected.

HIV-testing safety

HIV-1 testing is an essential component of PrEP delivery to protect patient safety – specifically, to prevent the initiation of PrEP among persons who have already acquired HIV-1 and to prevent continuation of PrEP if HIV-1 is acquired while receiving PrEP. In clinical trials and delivery projects of PrEP, the greatest risk of HIV-1 infection is at the time of initiation – either because of unrecognized chronic HIV-1 infection prior to HIV-1 testing as part of PrEP start or recent (acute) HIV-1 infection acquired just prior to PrEP initiation. Global and national guidelines for PrEP use do not have a consistent standard for the type of test to be used; Kenya, for example, recommends testing according to the national HIV-1 testing algorithm, which uses third-generation HIV-1 antibody based tests, done in sequence (i.e., if a positive first test, then perform a second test for confirmation, and a third as tie-breaker). Antigen-based tests (and HIV-1 RNA testing) are not in widespread use, although antigen-based options are becoming more available.

For the self-testing arms, there is an inherent difference in sensitivity between the oral fluid- and blood-based tests, as detailed above; we recognize this as a potential risk for undetected infection, and ascertainment of the magnitude of that risk will be part of this evaluation. Incident HIV-1 infections are rare among persons offered PrEP (<0.5% per year in our prior work, and essentially 0% among those taking PrEP) and thus HIV-1 acquisition is expected to be very uncommon in this study.

Social harm considerations for HIV-1 self-testing and PrEP

We have extensively considered the risk of social harm related to both PrEP use and HIV-1 self-testing at home, including risks of depression/anxiety and disclosure and stigma. Our extensive experience with longitudinal follow-up of heterosexual HIV-1 serodiscordant couples and women at risk mitigates some of this risk, and we found very little risk of social harms or anxiety related to HIV-1 self-testing in our pilot evaluation, among couples (detailed above). Low evidence of social harms has been reported in other HIV-1 self-testing studies [47]. The

24-hour helpline that that Thika clinic has, and which we used for our pilot study, will be available in case of anxiety, social harm, depression, or a positive test. Analyses of social harm related to self-testing will be done overall, by sex and by relationship status, given the potential for differential gendered and relationship risks (detailed more in Aim 2). In the event of a clinical need (e.g., side effects, symptoms of a sexually transmitted infection), participants will be requested to return to the clinic for care.

DATA AND ANALYSIS

The primary goal of this project is to address key access and cost of delivery challenges for PrEP by using the new modality of HIV-1 self-testing.

Data collection

We will use structured interviews on HIV-1 testing practices and self-reported PrEP adherence (e.g., frequency, ability, self-rating, missed doses). We will use CommCare, an electronic data capture platform, to collect data at the Thika site.

Qualitative data collection

Qualitative data collection will include serial in-depth interviews using pre-piloted semi-structured guides (n=20 men in couples, n=20 women in couples, and n=20 women at risk, from both self-testing modalities and the standard of care randomization arm) and focus group discussions (n=8, stratified by gender and whether or not in a serodiscordant partnership), conducted by experienced social scientists acting in the roles of facilitator and note taker. The semi-structured qualitative interview guide will provide a general structure for discussion but require participants to share their own barriers and facilitators [48]. The serial in-depth interviews will be conducted soon after enrollment to get information on early experiences, at Month 6, and after Month 12 after participants have tested for a couple of visits. The focus group discussions will be conducted at study exit. Interviews will be conducted using the participants preferred language and by consensus in the focus group discussions. The sampling for the qualitative interviews to include a range of possible perspectives (stratified-purposive sampling), to allow for stratification by study arm, gender, HIV-1 serodiscordant relationship status, and other relevant factors that may emerge during the work.

Qualitative discussions will be recorded, transcribed, and translated into English by the study team. Audio recordings will be destroyed by the qualitative team after being transcribed not later than August 2023. Qualitative work will extend our prior work among couples and women at risk, and we will adapt existing questionnaires and topic guides to focus on questions related to HIV-1 testing in the context of PrEP delivery, specifically to gain a deeper understanding of participants' experiences with HIV-1 self-testing, including challenges, benefits, concerns, risks, preferences (self- versus provider-based testing) and intention to use in the future, if available.

Health provider barriers and facilitators to HIV-1 self-testing

Health providers are key to PrEP delivery [49]. Therefore, in addition to self-testing users, we will study operational delivery at the level of providers. We will conduct key informant interviews (n=6-8) with providers at the research clinic (counselors, nurses, clinicians) to understand acceptance, barriers, facilitators, and confidence regarding HIV-1 self-testing in

the context of PrEP. Interviews will be conducted at the end of the study. We will document suggestions on how to optimize PrEP delivery through the use of HIV-1 self-testing. We will use similar interview and analysis methods detailed above.

Outcomes

Trial outcomes will be PrEP adherence (PrEP quantity in dried blood spots and PrEP refills), HIV-1 testing completion, and safety (including accuracy of HIV-1 testing, management of side effects, and social harm). **Timing.** All outcomes will be assessed at the Month 6 and 12 clinic visits. The study is powered against a single measurement of adherence (Month 6, see calculations below). **Adherence outcome.** Adherence by PrEP in dried blood spots is defined as the primary trial outcome for the purposes of sample size calculations. Cumulative and recent adherence to PrEP will be measured by concentrations of tenofovir diphosphate (TFV-DP) and emtricitabine triphosphate (FTC-TP), respectively, in a 3 mm punch from a dried blood spot in the laboratory of Dr. Anderson. TFV-DP and FTC-TP are measured by validated liquid chromatography tandem mass spectrometry (LC-MS/MS), which has become the gold standard for research evaluations of PrEP adherence [10, 11]. High TFV-DP levels will define good adherence. In recent studies, levels ≥1250 fmol/punch (=the median among persons taking 7 doses/week) and ≥700 (=≥4 doses/week, associated with high HIV-1 protection in some studies) have been used. FTC-TP detection with low TFV-DP will distinguish those with only recent (e.g., "white coat dosing") adherence [10, 11, 50]. In addition, we will be standardizing drug levels in dried blood spots by collecting whole blood to measure levels of hemoglobin, which has been validated as a more accurate means of interpretating drug levels.PrEP refills will be measured through data from the clinic's electronic pharmacy system. **Testing and safety outcomes.** HIV-1 testing will be measured as the combination of in-clinic tests and home tests, recorded by self-report and by requesting that completed self-test cartridges be returned to the clinic for validation of self-report. HIV-1 incidence will be measured but is expected to be low (0.2% per year in the Partners Demonstration Project, and 0% for those taking PrEP) and the study would need to be considerably larger to be powered to assess incident HIV-1 (and unnecessary, given the established relationship between PrEP adherence and efficacy); we will assess genotypic HIV-1 resistance among any seroconverters. **PrEP duration.** In our recently-completed Partners Demonstration Project, most couples used PrEP for 9-12 months, justifying our 12 months of follow-up for the couples; those who are established on ART by 6 months will be recommended to discontinue PrEP and their follow-up thereafter for the purposes of PrEP adherence and continuation will be censored. All individuals requiring PrEP for longer than 12 months will continue to receive PrEP through the clinic's services. Analyses for Aim 1, and Aim 2, will be done overall (total population of n=495), separately for serodiscordant couples (n=330) and for women (n=330, half in serodiscordant relationships) – each of these separate subgroups (i.e., couples and women) is well-powered for adherence assessment.

Self-testing to standard of care clinic testing, powered for the PrEP adherence outcome; we hypothesize that HIV-1 self-testing at home will not substantially undermine PrEP use, and thus a non-inferiority design is most appropriate. Most individuals will continue to be eligible for PrEP for 12 months (minus those with a clinical hold, expected to be rare, and those in the couples who for whom the HIV-1 infected partner immediately began ART at baseline and has continued with high adherence); we have powered the study for a single adherence assessment (e.g., Month 6) and increased power will result from repeated measurement of most participants at Month 12. **Primary comparison.** The primary comparison will be self-testing versus clinic testing; the two self-testing modalities will be analyzed together (versus clinic testing) because we hypothesize that the effect on adherence and other outcomes relates to the use of self-tests and frequency of follow-up, not the self-test modality; Aim 2 and 3 are designed to explore potential differences in acceptability and cost between self-testing modalities. **Power.** The trial will be powered for the adherence outcome (measured by

detection of PrEP in dried blood spots). Based on our prior work in couples, and published work for women at risk, we estimate ~80% among those seeking to initiate PrEP will achieve blood levels consistent with high PrEP adherence [51, 52]. Thus, if PrEP adherence is 80% in both the standard of care and self-testing arms, with 80% power, 10% loss-to-follow-up, a one-sided 95% confidence interval (common for non-inferiority trials), and a 10% non-inferiority margin, a sample size of n=495 is needed (n=330 self-testing, n=165 standard of care). A 10% non-inferiority margin has been chosen as an important reduction in PrEP use that might be tolerated in order to gain programmatic efficiency through HIV-1 self-testing. We have planned for two sub-analyses with sample sizes of n=330: those in HIV-1 serodiscordant relationships (which will include 165 men and 165 women) and women (which will include the 165 in serodiscordant relationships pus an additional 165 women at risk). These primary sub-analyses will have 80% power to rule out a 12% decrease in adherence (i.e., a slightly greater non-inferiority margin). We have considered whether enrolling n=330 women at risk (rather than n=165, alone or in addition to n=330 couples) would be warranted but feel we can gain important information about both of these populations through the hybrid design, with greater efficiency, in time and in costs. However, we recognize that women outside of serodiscordant relationships may face unique adherence challenges and less frequent follow-up could be truly inferior to quarterly follow-up; thus, among the n=165 women at risk, we will also plan a superiority analysis, for which we will have 80% power to detect a decline in adherence from 80% to 66% (14% lower) with self-testing. For the HIV-1 testing outcome, utilization of self-test kits will be compared between arms; assuming 95% of participants test, we have 80% power to detect a difference of 5% in use of consistent use of self-testing kits (90% vs. 95%). Also, if we end up having to over-enroll HIV-1 uninfected women at HIV-1 risk not in disclosed HIV-1 serodiscordant relationships to compensate for difficulties or delays in enrolling HIV-1 uninfected men and women in HIV-1 serodiscordant relationships, we will have more power to detect outcomes in this important sub-group.

Costing. The costs for a PrEP delivery program that uses HIV-1 self-testing with 6-monthly visits compared to quarterly visits with standard testing will be estimated. Activity-based micro-costing will be conducted and compared by study arm for costs incurred (start-up activities, recruitment, service delivery, monitoring costs, and adherence support) and costs averted (personnel, lab monitoring, incident HIV-1 cases, social, and health benefits). Time and motion studies will be conducted by observing clinic visits, and staff time spent on training on use of home HIV-1 self-testing, counseling clinical procedures, cost of the three types of HIV-1 self-testing kits (blood based provider kit, blood based HIV-1 self-testing kit and oral based HIV-1 self-testing kit) and ART and PrEP delivery. Adjusting for time spent on research activities (e.g., informed consent, research questionnaires), the total time required for PrEP delivery will be estimated. Estimates of cost using the activity-based approach will be compared with the top down (dividing the budget by the number of clients) approach to support scalable estimates of cost. Costs incurred by clients for clinic visits (which contribute to the societal perspective) will be estimated with standard questionnaires that we have used previously.

Model. Mathematical models will be used to simulate health outcomes from a combination of study data and the literature, allowing us to consider clinical outcomes beyond the scope of the prospective cohort. We will adapt our existing compartmental dynamic transmission models (programmed in Matlab) to estimate and compare the impact of each of the interventions on HIV-1 incidence [19, 53, 54]. The model explicitly includes patterns of risk behavior and can account for risk compensation. Our simulation model of HIV-1 progression, transmission, and treatment in HIV-1 serodiscordant couples includes the composition of couples (by sex, age, and CD4 counts), aging, use of ART, conception and pregnancies, variations in coital frequency within stable partnerships and partner change rate. To adapt and parameterize the model, we will use data from our prior studies including the Partners Demonstration Project and the Kenya AIDS Indicator Survey [2, 14]. An alternative modeling

approach would be adapting our individual-based HIV-1 model to include PrEP [55]. Assumptions will be as published previously, including our publication on micro-costing work within the Partners Demonstration Project [19].

For key delivery informants

Health providers are key to PrEP delivery [49]. Therefore, in addition to self-testing users, we will study operational delivery at the level of providers. We will conduct key informant interviews (n=6-8) with healthcare providers at the research clinic (counselors, nurses, clinicians) to understand acceptance, barriers, facilitators, and confidence regarding HIV-1 self-testing in the context of PrEP. Interviews will be conducted at the end of the study. We will document suggestions on how to optimize PrEP delivery through the use of HIV-1 self-testing. We will use similar interview and analysis methods detailed above.

Quantitative Analysis

Analyses will be intention-to-treat. HIV-1 testing and PrEP detection in blood will be compared between arms using repeated measures analysis of proportions (e.g., generalized estimating equations [GEE]); PrEP continuation, defined as not missing any refill, will be analyzed as a time-to-event outcome using Cox proportional hazards regression. As noted above, for the couples, those in which the HIV-1 uninfected partner completes PrEP use because the infected partner has initiated and sustained ART for >6 months (the Kenya standard for discontinuing PrEP) will be considered to have successfully used PrEP and will be counted as adherent; similarly, if PrEP is discontinued by the treating clinician for safety reasons (but not adherence reasons), follow-up thereafter will be censored, since the subject will not be able to be assessed for adherence to PrEP. Adjusted analyses will be done as needed, controlling for potential confounders based on our prior work assessing correlates of PrEP use: demographics (e.g., gender, age, educational level), sexual behaviors (e.g., condom use, outside partnerships), medical status (e.g., depression), and beliefs (e.g., risk perception, PrEP efficacy). SAS or R will be used.

For quantitative data, descriptive analyses will be done at baseline and over time, and GEE will be used to test associations between facilitators/barriers and testing preferences outcomes. Analyses will be done to test effect modification by gender and, within women, by serodiscordant couple status

Qualitative Analysis

The transcripts will be reviewed separately by two investigators for completeness and initial theme generation. Coding and analysis will be performed with Atlas.ti, using inductive approach informed by grounded theory [56]. We will then review the results of our coding for consistency of text segmentation and code application with continued inter-coder agreement, and inconsistent results will be reviewed by the coders until consensus is reached and then codes will be grouped together into themes through consensus among coders [57, 58]. We have extensive experience with in-depth interviews with purposefully sampled individuals and couples; for couples we have found dyadic interviews to be a powerful tool to explore joint decision-making and power/gender dynamics [49]. Analyses of the qualitative data will assess how both individuals and dyads respond to HIV-1 self-testing in the context of PrEP, with areas of focus such as gender roles, sexual negotiation, trust, and power. In addition, we will probe delivery, including preference of quarterly versus 6-monthly visit schedule, confidence in HIV-1 self-testing, confidence in blood versus oral fluid, and confidence in HIV-1 testing and PrEP more broadly.

HUMAN SUBJECTS CONSIDERATIONS

The protocol, informed consent forms (for cohort participation and for interviews of providers), and patient education and recruitment materials will be reviewed and approved by the institutional review boards at the University of Washington and at KEMRI. All participants will provide written informed consent before participation in the quantitative and qualitative interviews. Participants will be informed the purpose of the study, the procedures to be followed and the risks and benefits of participation. The consents forms will be translated into Kiswahili. Specifically the participants will be informed that this novel study will answer a critical questions on acceptability, performance and barriers of HIV-1 self testing in the context of implementation of PrEP. Participants will also be informed that the counselors may conduct a home visit to provide additional support after a positive test result if required.

Study oversight

This study will be subject to oversight by an independent data monitoring committee that will periodically review data from the study, including study execution, adherence, HIV-1 incidence, HIV-1 drug resistance, and serious adverse events. Review will be in an unblinded fashion, consistent with the open-label, randomized, unblinded nature of the study. The independent data monitoring committee will provide recommendations to the study team as part of six-monthly reviews. Reports from all reviews will be provided for submission to overseeing IRBs/ECs.

Risks

Partner participants may feel pain or discomfort from phlebotomy if selected for a blood sample archive. Participants may become embarrassed, worried, or anxious when answering behavioral or demographic questions. We have trained counselors who are available through the study to help participants deal with any feelings or questions they may have. The study staff will make every effort to protect participant privacy and confidentiality while you are in the study. However it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as participating in a trial involving HIV-1 infected persons). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

Benefits

Participants will benefit from ongoing access to this prevention package.

This study aims to provide HIV-1 prevention policy makers with information on how to best implement antiretroviral-based HIV-1 prevention. In addition to the provision of this biomedical method, the study site will provide CHCT, and routine adherence counseling. The outcome of the study will be evidence upon which to based policy guidelines for scaling up HIV-1 prevention centers in Kenya and nearby countries with similar HIV-1 prevention needs. The HIV-1 treatment centers that serve as sites for this study will be models upon which future centers can be based. Summary outcomes from this study will be submitted to overseeing regulatory bodies and will be especially important for the development of normative guidance.

Care for persons identified as HIV-1 infected

This study will identify persons who are infected with HIV-1, either as part of the study screening process or during follow-up of enrolled participants. Study staff will provide participants with their HIV-1 test results in the context of post-test counseling. Persons identified as HIV-1 infected will be referred for care.

Treatment for injury

Participants will be asked to inform the clinic staff if they feel they have been injured because of taking part in the study. Injuries may also be identified during laboratory testing, medical histories, and physical examinations. Treatment for adverse events related to study participation will be provided by the treatment clinic. If treatment is required that is beyond the capacity of the clinic, the clinic staff will refer the participant to appropriate services or organizations that can provide care for the injury.

Study records

Implementation investigators will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. Study records include administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the cohort, including informed consent forms, data forms, notations of all contacts with the participant, and all other source documents.

Biometric Identification

Thika site will use a biometric system (fingerprint scanner) to identify participants during follow-up visits. Participants will be offered an informed consent form with the option to accept or decline to have their fingerprint taken. Participants who decline to have their finger print taken will not be excluded from taking part in the study. The finger print database will be destroyed after completion of active follow-up in the study.

Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent possible. Personal identifying information will be retained at the local study site

Dissemination Plan

The study team for this award is committed to public dissemination of results of clinical trial, to trial participants, local stakeholders in Kenya, the global scientific community, and US, Kenyan, and global policymakers. Dissemination of study results will follow principles of good participatory practice. The clinical trial will be registered with Clinicaltrials.gov prior to initiation and results will be updated there in a timely fashion. Results will be published in conference abstracts and peer-reviewed journals. Study results will be disseminated through presentations to local stakeholders and policymakers in Kenya, including the Ministry of Health.

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Appendix I: Enrollment informed Consent – HIV uninfected

Study Title: HIV self-testing to improve the efficiency of PrEP delivery

Protocol version 1.7
18 April, 2019

INVESTIGATORS

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INFORMED CONSENT

We are asking you to volunteer in a research study. This study is sponsored by the University of Washington and funded by the National Institutes of Health which are located in the USA.

If you decide to take part in this study you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web stie will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

PURPOSE OF THE STUDY

Studies have shown that the medications used to treat HIV infection can also be used to prevent passing the virus. This concept is called pre-exposure prophylaxis, or PrEP. These studies have also learned that PrEP is safe (meaning that it does not produce significant health problems in persons who take them) when taken by HIV-uninfected men and women. Studies have also shown that women and men are able to test themselves for HIV using special types of HIV-self test kits and that HIV uninfected persons taking PrEP are able to use HIV self-tests safely and correctly at home.

Both HIV self-testing and PrEP have been recently endorsed and launched by the Kenyan Ministry of Health.

The purpose of this study therefore is to find out more about how PrEP could be delivered more efficiently to HIV uninfected men and women with some of the participants testing for HIV at home for some of the visits.

Through a method similar to tossing a coin the you will be assigned to a group that: (1) comes to the clinic every three months and gets tested by a health provider, (2) comes to the clinic every

six months and tests at home between clinic visits for HIV using an oral fluid HIV self-test kit, (3) comes to the clinic every six months and tests at home between clinic visits for HIV using a blood based HIV self-test kit.

Approximately 495 participants who are using PrEP will be enrolled in this study and will be in the study for up to 12 months.

YOUR PARTICIPATION IS VOLUNTARY

Before you learn about this study, it is important that you know the following:

- You do not have to be in this study if you do not want to.
- You may decide not to be in the study, or to being in the study at any time, without losing your regular medical care.
- If you decide not to be in the study, you can still join other research studies later, if available and you qualify.
- You may be asked about joining other studies. Due to the time commitment from being in this study, you may not be eligible to join this study if you are in other studies. If you do not agree to join these other studies, you may still take part in this study.
- If you decide to enroll in this study, after your enrollment visit you will be in the study up to 12 months.
- You will receive the results of the HIV related tests.
- The answers you provide to survey questions will remain confidential and identifying information about you will not be shared.

ENROLLMENT PROCEDURES

The enrollment tests for this study will include questions and tests done from samples of blood. The enrollment procedures will include the following:

- The study staff will ask you where you live and other questions about you and your sexual practices.
- We will counsel you about HIV and other infections passed during sex, and how to avoid these infections including the use of condoms and other contraceptives. We will provide you with free condoms at your screening visit as well as at each visit throughout the study.
- Even if you have recently been tested for HIV, we will need to repeat the HIV test today as part of the study. The study staff will talk with you about the HIV test, what it may mean to know your HIV test results, including issues for partners when one partner is HIV-infected and the other is HIV-uninfected. You must receive your HIV test results to be in the research study.
- We will ask you questions about your medical history, you will have a physical examination, and you will undergo an STI assessment.

- You will be asked to give us permission to obtain a blood sample for laboratory tests. No more than 10 ml (about two teaspoons) will be collected for all the enrollment tests, including the HIV test. We will use the blood to test for PrEP drug levels and hemoglobin levels in your blood. We will also test your blood for PrEP drug levels and hemoglobin levels at six months and at the final study visit.

- In this research study, some of you will come to the clinic every 3 months for 12 months for HIV testing, while others will be offered two oral-fluid or blood-based HIV self-tests to test themselves at home instead of coming back to the clinic on month 3 and month 9 visits. The self-test group will only come to the clinic on month 6 and month 12. We will also provide advice about when it might be best to use the self-tests. We may also visit you at home after a positive test result to provide additional support if required. More training on the use of the self-testswill be done the 6-month visit. Please note that the HIV self-tests provided to you will only be for your own use and should not be used to test others.

- Additionally, you will continue to be offered PrEP to be taken as one pill once each day to prevent HIV infection. The PrEP medication will be provided by this clinic, free of charge.

FOLLOW-UP PROCEDURES

- You will be asked questions about your health and medical history, including whether you have any clinical symptoms, your sexual practices and other behaviors, and your feelings about taking medications for HIV prevention.

- Talk with study staff about ways to avoid HIV and other infections passed during sex. We encourage you to have this counseling with your partner, but you can have it by yourself if you wish. You will be offered condoms.

- Get medical care or referrals for medical care and other services if you need them.

- Give updated information on where you live and how to keep in contact with you. The study staff will use this information to remind you of scheduled visits. If you miss a visit, the study staff will try to contact you by telephone. They may try to reach you through the contact people that you list. If they talk to these people, they will not tell them why they are trying to reach you. The study staff may also visit you at your home, however if they visit they will visit you as 'friends' so that your neighbors and other community members will not know why they are visiting.

- Women will be asked whether they think they may be pregnant. A urine pregnancy test may be done if unsure about being pregnant. Women who are pregnant will not be excluded from the study.

- If your HIV test is negative you can continue to receive PrEP medication. You will be asked to answer questions about the pills you took during the previous month and be counseled about methods for not forgetting to take your pills during the following month. The pharmacy staff will provide you with new bottles with pills to last until your next visit.

- At the sixth month after starting PrEP and then at 12 months, you will have a blood sample to check the safety of PrEP for your kidneys. If at any time you have an abnormal result, we will contact you so that you will know.

Those in the HIV self testing arms will be requested to bring back used HIV self-tests (if available) at their month 6 and month 12 visits.

At any time in the study:

- If you or the study staff thinks you may have any health problems, you may need to undergo a physical exam and may need to provide blood or other samples for testing.

- You can have extra counseling and testing for HIV if needed between scheduled visits, either with your partner or by yourself.

- If you decide to leave the study before your last scheduled study visit, we will ask you to have a final study visit with all the exams and tests listed above.

- If you test positive in the clinic for HIV, we will take additional blood samples amounting to no more than 15 mL (about three teaspoons) to confirm your test, measure your CD4 count and viral load, and send a sample to the Kenyan Ministry of Health laboratories to test for drug resistance.

At month 12 visit:

- You will be provided with an opportunity to experience either a blood based or oral fluid-based HIV self-testing kit or both if you had not used them during the study.

After experiencing the kit/s we will request you to complete a brief questionnaire on your testing experiences.

Long interviews

At some point during the study, the staff may invite you to answer more questions about your opinions on HIV self-testing, including perceptions, preferences, challenges, and concerns. An interview will take no more than two hours. Some interviews will be done individually and some will be done as a group session with other people who are participating in the study. We will record the interviews so we can write them down later. This recording will then be destroyed not later than August 2023.

Pregnancy

If you become pregnant at any time during this study you will be referred for antenatal care and will have the option to continue in the study.

IF YOU BECOME HIV INFECTED

During the course of the study we will provide you with condoms, PrEP, and other materials to help prevent getting HIV. However, it is possible to become HIV infected.

If you have a positive HIV test during the study:

- The study staff will talk with you about this test result and what this means for you.
- You will stop taking the PrEP medication.
- The staff will ask your permission to obtain a second blood test [no more than 15 ml / about 3 teaspoons] that will be used to confirm the initial positive test, measure of your immune function (CD4 count) and viral load, and test for drug resistance.
- You will undergo a physical exam
- Women will be asked to provide a urine sample for a pregnancy test.
- You will then be asked to return for another visit within about 2 weeks. At that visit, results from the confirmatory HIV test will be available. If those results confirm that you have become infected with HIV, you will be referred to an HIV care clinic.

IMPORTANCE OF NOT SHARING THE STUDY MEDICATION

It is very important that you do not share HIV medications medication with your partner or with anyone else. Although the PrEP medication is used to treat HIV infection, it is only effective for treating people who already have HIV infection if they are used in combination with other medications. Thus, PrEP by itself is only for HIV uninfected people. Similarly, HIV medications for treatment are only for HIV infected people, and must be used every day.

IMPORTANCE OF NOT SHARING THE STUDY HIV SELF-TESTING KITS

It is very important that you do not share HIV self-test kits with anyone else. This is because the persons you share the kits with have not been trained to conduct the tests and have do not have linkage system established for them. However, if for any reason your HIV self-testing kit is used by someone else please inform the study staff during the next visit or by phone so that the staff can offer the support if necessary.

SPECIMEN STORAGE AND USE OF SAMPLES AND DATA FOR FUTURE STUDIES

Some of the blood taken at study visits will be shipped to University of Washington in the United States for testing of tenofovir. We would also like to save data from this study and samples of your blood at Thika site and at the University of Washington for future research by us and by other researchers. We will use these samples only for research related to HIV, HIV-related diseases, and sexually-transmitted infections. Before your samples leave the clinic, they will be assigned a code and your name will not be on them. Your name will be linked to the code only at this clinic and only for five years after the study is completed. After that time, the link between your name and the code on your data and samples will be destroyed. An Institutional Review Board or Independent Ethics Committee, which watches over the safety and rights of research participants, must approve any future research studies using your data and samples. If you agree to store your samples, we will keep them for as long as sample remains that can be used for future research. If you do not want to have your samples saved for future research, you can still be in this study and your samples will be destroyed once testing for this study is completed. If you agree to store your samples now, but change your mind before the end of the study, let the study staff know and we will make sure that your samples do not get stored for future research. We will not sell your

data or samples. Tests done on your samples may lead to a new invention or discovery. We have no plans to share any money or other benefits resulting from this invention or discovery with you.

RISKS AND/OR DISCOMFORTS

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise where the needle goes into your arm.

You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against HIV and other infections passed during sex, and your HIV test results. You may become worried or anxious while waiting for your test results. If you become infected with HIV, knowing this could make you worried or anxious. Talking about HIV and finding out your test results could cause problems between you and your partner. Trained counselors will help you and your partner deal with any feelings or questions you may have.

The study staff will make every effort to protect your privacy and confidentiality while you are having the study procedures. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

You may experience discomfort when performing the oral HIV self-test. You may feel worried when interpreting HIV results - please call the 24-hour toll free line on the front of this form for any result that appears positive or for any result that you have difficulties in interpreting. You should also call this line in case of a positive test result. We will record all the main content of our conversations with you and others in a book in the clinic, this will enable us to make our training and counseling to be more responsive to your needs. You may feel embarrassed, worried, or anxious when talking about your experiences with HIV self-testing or when discussing the results of your self-testing. Counselors are available through the study that will help you deal with any feelings or questions you have. The study staff will make every effort to protect your privacy and confidentiality while you are answering the questions. However, it is possible that others will learn of your answers and, because of this, may treat you unfairly or discriminate against you. In the group discussions, even though all participants will promise to not talk about the group discussion outside of the discussion, anything you say will not be fully confidential since all members of the group discussion will hear it.

For more information about risks of this study, ask your study clinician.

BENEFITS

You will be receiving PrEP, which is known to help keep HIV-uninfected individuals who have HIV-infected partners from getting HIV. You will get counseling and testing for HIV. You will get free condoms. If you or your partner have health problems that may be due to infections passed during sex, you will get medicine to treat them, if needed. For other health problems, the study staff will give you care and treatment that is available at the clinic. For care and treatment that is not available at the clinic, study staff will tell you about other places where care and treatment may be available.

HIV self-testing has the potential of capturing a positive HIV test before your scheduled clinic visit and there are medical benefits to identifying an HIV infection sooner. Your participation in this study will contribute to understanding about HIV self-testing among couples in Kenya, which will help others in the future.

NEW FINDINGS

You will be told any new information learned during this study that is important for your health or might cause you to change your mind about staying in the study. You will be told when the results of the study may be available, and how to learn about them.

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you from the study will be given free of charge.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY

You may be removed from the study without your consent for the following reasons:

- The study is stopped or canceled.
- The study staff feel that staying in the study would be harmful to you.

ALTERNATIVES TO PARTICIPATION

There may be other studies going on here or in the community that you or your partner may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.

REIMBURSEMENT

You will receive transportation reimbursement and an additional 200 Kshs for your time and effort spent at the clinic.

BIOMETRIC FINGERPRINT SCAN

To help us keep track of who is enrolled in our clinic and who is coming for follow up visits, we will ask you to put either your right or left index finger on a small machine that will scan your finger print. This scan will be linked to a unique identification number and will be accessible only to study staff. We will take your fingerprint at each study visit. You are free to refuse to have your fingerprint taken and this will not affect your participation in the study. The finger print database will be destroyed after completion of active follow up in the study.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any sample from you or information about you will be identified only by code. The link between your name and code will be kept in a secure location at the clinic only. We will not discuss any information about you with your partner unless you give written permission, and will encourage you to be present during the discussion. Any publication of this study will not use your name or identify you personally.

Your study records may be reviewed by study staff and representatives of:

- the University of Washington, including study monitors
- The United States National Institutes of Health
- Kenya Medical Research Institute (KEMRI)

- National Council of Science and Technology (NACOSTI)

RESEARCH-RELATED INJURY

The study staff will monitor your health and the health of your partner while you are in this study.

If you or your partner has any health problems between visits, or if you have a medical emergency that requires immediate care, please contact the study staff.

If you are injured from participating in this study, you will be offered care at the study clinic, free of charge. It is important that you tell the members of the team of researchers at this clinic if you feel that you have been injured because of taking part in this study. There is not a program of monetary compensation through this institution. If you require medical care that the study clinic cannot provide, the study clinicians will refer you to the appropriate services or organizations that can provide care for the injury. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, you should contact Dr. Kenneth Ngure at the Thika Study clinic at Tel 06721305/22561. For research related injury, please call the 24-hour emergency number: 0736464299.

If you have questions about your rights as a participant, contact the secretary of the KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi, Telephone number 020272-2541, 0722205901, 0733-400003. Email address: seru@kemri.org.

STATEMENT OF CONSENT AND SIGNATURES

I have read this form or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the study is voluntary. I understand that if I decide to join the study I may withdraw at any time. By signing this form, I do not give up any rights that I have as a research participant.

_____	_____	_____
Participant Name (print)	Participant Signature/Thumbprint	Date
_____	_____	_____
Study Staff Conducting Study Consent Discussion (print)	Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

SPECIMEN STORAGE AND USE OF YOUR DATA AND SAMPLES FOR FUTURE STUDIES:

Please initial and date one option:

_____ I DO agree to store my data and samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

_____ I DO NOT agree to store my data and samples for future research into HIV, HIV-related diseases, and other sexually transmitted diseases.

_____	_____	_____
Participant Name (print)	Participant Signature/Thumbprint	Date
_____	_____	_____
Study Staff Conducting Study Consent Discussion (print)	Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

SPECIMEN SHIPMENT TO UNIVERSITY OF WASHINGTON

Please initial and date one option:

_____ I DO agree to allow my biological samples to be shipped to University of Washington for specialized tests and used for future research tests

_____ I DO NOT agree to allow my biological samples to be shipped to University of Washington for specialized tests and used for future research tests

_____	_____	_____
Participant Name (print)	Participant Signature/Thumbprint	Date
_____	_____	_____
Study Staff Conducting Study Consent Discussion (print)	Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

STATEMENT OF CONSENT: BIOMETRIC FINGERPRINT

Please initial and date one option

_____ I DO agree to have my finger print taken

_____I DO NOT agree to have my fingerprint taken

Participant Name (print)	Participant Signature/Thumbprint	Date
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

PERMISSION FOR AUDIO RECORDING

Please initial and date one option:

_____ I give permission for the interviews that I participate in to be recorded.

_____ I DO NOT give permission for the interviews that I participate in to be recorded.

Participant Name	Participant Signature	Date
Study Staff Conducting Consent (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

Copies to: 1. Investigators
2. Study participant

Appendix II. Enrollment informed Consent – HIV infected

Study Title: HIV self-testing to improve the efficiency of PrEP delivery

Protocol version 1.7
18 April, 2019

INVESTIGATORS

Investigator	Title	Institution	Telephone
Kenneth Ngure	MPH, PhD	Jomo Kenyatta University of Agriculture and Technology	067 22561
Nelly Mugo	MBChB, MMed, MPH	Kenya Medical Research Institute	020 2736744
Elizabeth Irungu	MD, MPH	Jomo Kenyatta University of Agriculture and Technology	067 22561
Jared Baeten	MD, PhD	University of Washington	001 206-520-3808

24 HOUR EMERGENCY TELEPHONE NUMBER: Tel: 0736464299

INFORMED CONSENT

We are asking you to volunteer to for a research study. This study is sponsored by the University of Washington and funded by the National Institutes of Health which are located in the USA.

If you decide to take part in this study you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

PURPOSE OF THE STUDY

Studies have shown that the medications used to treat HIV infection can also be used to prevent passing the virus. This concept is called pre-exposure prophylaxis, or PrEP. These studies have also learned that PrEP is safe (meaning that it does not produce significant health problems in persons who take them) when taken by HIV-uninfected men and women. Studies have also shown that women and men are able to test themselves for HIV using special types of HIV-self test kits and that HIV uninfected persons taking PrEP are able to use HIV self-tests safely and correctly at home.

Both HIV self-testing and PrEP have been recently endorsed and launched by the Kenyan Ministry of Health.

The purpose of this study, therefore, is to find out more about how PrEP could be delivered more efficiently to HIV uninfected men and women with some of the participants testing for HIV at home for some of the visits

Approximately 495 participants weill be enrolled in this study and will be in the study for up to 12 months. 330 HIV uninfected individiuals, whose partner is HIV positive, will be enrolled in this study and followed up for up to 12 months, while their HIV infected partners will have a single visit.

YOUR PARTICIPATION IS VOLUNTARY

Before you learn about this study, it is important that you know the following:

- You do not have to be in this study if you do not want to.
- If you decide not to participate in this study , you can still join other research studies later, if available and you qualify.
- You will receive the results of the HIV related tests.
- The answers you provide to survey questions will remain confidential and identifying information about you will not be shared.

STUDY PROCEDURES

The procedures for this visit will include questions and tests done from samples of blood. These procedures will include the following:

- The study staff will ask basic questions about yourself your sexual practices, and your ART adherence (if applicable).
- We will counsel you about HIV and other infections passed during sex, and how to avoid these infections including the use of condoms and other contraceptives. We will provide you with free condoms if you need them
- Even if you have recently been tested for HIV, we will need to repeat the HIV test today. The study staff will talk with you about the HIV test, what it may mean to know your HIV test results, including issues for partners when one partner is HIV-infected and the other is HIV-uninfected. We will then ask your partner and you whether you are ready to be tested today and receive your HIV test results. You must receive your HIV test results to be in the research study.
- We will ask you questions about your medical history. As part of these questions, you will be asked about symptoms of AIDS.
- You will be asked to give us permission to obtain a blood sample for laboratory tests. No more than 10 mL (about two teaspoons) will be collected for all the screening tests, including the HIV test. Some of the blood sample will be used for a test called a CD4 cell count. The CD4 count is a measure of how well your immune system is functioning. The lower the CD4 count in persons who are HIV-infected, the more at risk they are for having problems from AIDS. Some of the blood sample will be used to test for the amount of HIV virus in your blood, called ‘viral load.’
- Be asked questions about your health and medical history, including whether you have any clinical symptoms, your sexual practices and other behaviors,and your feelings about taking medications for HIV prevention.

Your partner

- Your partner may be assigned to one of two groups. One group will come to the clinic every 3 months for HIV testing for 12 months, while the other group will be offered two oral-fluid or blood-based HIV self-test kits to test themselves at home instead of coming back to the clinic on month 3 and month 9 visits. Therefore, if your partner is randomized to the second group, they will only come to the clinic on month 6 and month 12 for testing.

- Additionally your partner will be offered PrEP to be taken as one pill once each day, as pre-exposure prophylaxis to prevent HIV infection. The PrEP medication will be provided by this clinic, free of charge.

RISKS AND/OR DISCOMFORTS

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise where the needle goes into your arm.

You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against other infections passed during sex, and your HIV test results. You may become worried or anxious while waiting for your test results. Talking about HIV and finding out your test results could cause problems between you and your partner. Trained counselors will help you and your partner deal with any feelings or questions you may have.

The study staff will make every effort to protect your privacy and confidentiality while you are having the study procedures. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

For more information about risks of this study, ask your study clinician.

BENEFITS

Your HIV uninfected partner will be receiving PrEP, which is known to help keep HIV-uninfected individuals who have HIV-infected partners from getting HIV. You will get counseling and testing for HIV. You will get free condoms.

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you from the study will be given free of charge.

ALTERNATIVES TO PARTICIPATION

There may be other studies going on here or in the community that you or your partner may be eligible for. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling and testing. We will tell you about those places if you wish.

REIMBURSEMENT

You will receive transportation reimbursement and an additional 200 Kshs for your time and effort spent at the clinic.

BIOMETRIC FINGERPRINT SCAN

To help us keep track of who is enrolled in our clinic and who is coming for follow up visits, we will ask you to put either your right or left index finger on a small machine that will scan your finger print. This scan will be linked to a unique identification number and will be accessible only to study staff. We will take your fingerprint at each study visit. You are free to refuse to have your fingerprint taken and this will not affect your participation in the study. The finger print database will be destroyed after completion of active follow up in the study.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any sample from you or information about you will be identified only by code. The link between your name and code will be kept in a secure location at the clinic only. We will not discuss any information about you with your partner unless you give written permission, and will encourage you to be present during the discussion. Any publication of this study will not use your name or identify you personally.

Your study records may be reviewed by study staff and representatives of:

- the University of Washington, including study monitors
- The United States National Institutes of Health
- Kenya Medical Research Institute (KEMRI)
- National Council of Science and Technology (NACOSTI)

RESEARCH-RELATED INJURY

The study staff will monitor your health and the health of your partner while you are in this study. If you or your partner has any health problems between visits, or if you have a medical emergency that requires immediate care, please contact the study staff.

If you are injured from participating in this study, you will be offered care at the study clinic, free of charge. It is important that you tell the members of the team of researchers at this clinic if you feel that you have been injured because of taking part in this study. There is not a program of monetary compensation through this institution. If you require medical care that the study clinic cannot provide, the study clinicians will refer you to the appropriate services or organizations that can provide care for the injury. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, you should contact Dr. Kenneth Ngure at the Thika Study clinic at Tel 06721305/22561. For research related injury, please call the 24-hour emergency number: 0736464299.

If you have questions about your rights as a participant, contact the secretary of the KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi, Telephone number 020272-2541, 0722205901, 0733-400003. Email address: seru@kemri.org.

STATEMENT OF CONSENT AND SIGNATURES

I have read this form or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the study is voluntary. I understand that if I decide to join the study I may withdraw at any time. By signing this form, I do not give up any rights that I have as a research participant.

_____	_____	_____
Participant Name (print)	Participant Signature/Thumbprint	Date
_____	_____	_____
Study Staff Conducting Study Consent Discussion (print)	Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

Statement of Consent: Biometric fingerprint

Please initial and date one option

_____ I DO agree to have my finger print taken

_____I DO NOT agree to have my fingerprint taken

_____	_____	_____
Participant Name (print)	Participant Signature/Thumbprint	Date
_____	_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

Copies to: 1. Investigators
2. Study participant

Appendix III: Provider Interview - Consent Form

Study Title: HIV Self-Testing to Improve the Efficiency of PrEP Delivery
Protocol Version 1.7
18 April 2019

INVESTIGATORS

Investigator	Title	Institution	Telephone
Kenneth Ngure	MPH, PhD	Jomo Kenyatta University of Agriculture and Technology	067 22561
Nelly Mugo	MBChB, MMed, MPH	Kenya Medical Research Institute	020 2736744
Elizabeth Irungu	MD, MPH	Jomo Kenyatta University of Agriculture and Technology	067 22561
Jared Baeten	MD, PhD	University of Washington	001 206-520-3808

24 HOUR EMERGENCY TELEPHONE NUMBER: Tel: 0736464299

INFORMED CONSENT

We are asking you to volunteer for a study to answer questions about your experiences providing HIV prevention and Self-Testing services to participants. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, and what would be expected of you if you agree to participate. This study is sponsored by the University of Washington with funding from the National Institutes of Health which are located in the USA.

If you decide to participate in this study, you will be asked to sign this consent form. We will give you a copy of this form. Please ask us to explain anything you may not understand.

PURPOSE OF THE STUDY

Studies have shown that the medications used to treat HIV infection can also be used to prevent passing the virus. This concept is called pre-exposure prophylaxis, or PrEP. These studies have also learned that PrEP is safe (meaning that it does not produce significant health problems in persons who take them) when taken by HIV-uninfected men and women. Studies have also shown that women and men are able to test themselves for HIV using special types of HIV-self test kits and that HIV uninfected persons taking PrEP are able to use HIV self-tests safely and correctly at home.

Both HIV self-testing and PrEP have been recently endorsed and launched by the Kenyan Ministry of Health.

The purpose of this study therefore is to find out more about how PrEP could be delivered more efficiently to HIV uninfected men and women with some of the participants testing for HIV at home for some of the visits.

Through a method similar to tossing a coin participants will be assigned to a group that: (1) comes to the clinic every three months and gets tested by a health care provider, (2) comes to the clinic every six months and tests at home between clinic visits for HIV using an oral fluid HIV self-test kit, (3) comes to the clinic every six months and tests at home between clinic visits for HIV using a blood based HIV self-test kit.

Approximately 495 participants who are using PrEP will be enrolled in this study and will be in the study for up to 12 months. In addition to self-testing users, we will study operational delivery at the level of the providers by conducting key informant interviews with 6-8 providers at the research clinic (counselors, nurses, clinicians).

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that we will discuss with you. Once you understand the study, and if you agree to take part, we will ask you to sign your name or make your mark on this form. We will offer you a copy to keep.

Before you learn about the study procedures, it is important that you know the following:

- You do not have to be in this study if you do not want to.
- The answers you provide to survey questions will remain confidential and identifying information about you will not be shared.
- You may decide not to take part in this study, or to withdraw from the study at any time, without any repercussions to your job.
- If you decide not to take part in this study, you can still provide clinical guidance to our research studies later, if available and you qualify.

STUDY PROCEDURES

After you read, discuss, and sign or make your mark on this form, we will set up a time for your interview. During your interview(s), the interview staff will invite you to answer questions about your experience working with participants in the HIV self-testing study. You should not identify any of the study participants that you know by their names. The interview will take approximately one hour. We will make sure that the space where the interview takes place is private and the conversation cannot be overheard. During the interviews, the research staff member will ask for your permission to record what you say, so we can write it down later. These recordings will be destroyed immediately after. If you do not want to answer any of the questions, that is okay. Just let the research staff member know and we will move on to another question.

RISKS AND/OR DISCOMFORTS

You may feel uncomfortable when talking about your experiences working with study participants and their partners. Counselors are available through our research clinic in Thika who will help you deal with any feelings or questions you may have. The study staff will make every effort to protect your privacy and confidentiality during the interview. However, it is possible that others will learn of your answers and, because of this, may treat you unfairly or discriminate against you.

If you become tired or uncomfortable during the long interview, we can: (a) discuss the situation, (b) take a break, or (c) stop. If you choose to stop, we can either finish the interview another day or you can end your participation in the study.

For more information about risks of this study, ask your study clinician.

BENEFITS

You may get no direct benefit from answering the questions. However, you will contribute to understanding about HIV prevention in Africa, which will help others in the future.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled
- You are not able to complete the study interview process
- The study staff feel that the interview questions in this study would be harmful to you

COSTS TO YOU

There is no cost to you for the answering the questions.

REIMBURSEMENT

You will be reimbursed for any transport costs incurred in order to meet with the study staff for your interview, if the interview occurs out of your usual work place. You will receive these reimbursements at the end of your individual interview.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. However, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. Any information about you will be identified only by code and not by name. The link between your name and code will be kept in a secure location at the clinic only. Any publication of this study will not use your name or identify you personally.

Your responses to the questions may be reviewed by study staff and representatives of:

- The University of Washington, including study monitors
- The United States National Institutes of Health
- Kenya Medical Research Institute (KEMRI)
- National Council of Science and Technology (NACOSTI)

RESEARCH-RELATED INJURY

If you are injured from participating in this study, the study staff will give you immediate necessary treatment for your injuries until complete cure or stabilization. If you require medical care that the study clinic cannot provide, the study clinician will refer you to the

appropriate services or organizations that can provide care for the injury and care for you until the injury resolves.. There is not a program of monetary compensation through this institution. If you require medical care that the study clinic cannot provide, the study clinicians will refer you to the appropriate services or organizations that can provide care for the injury. You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, you should contact Dr. Kenneth Ngure at the Thika Study clinic at Tel 06721305/22561. For research related injury, please call the 24-hour emergency number: 0736464299.

If you have questions about your rights as a participant, contact the secretary of the KEMRI Scientific and Ethics Review Unit, P.O. Box 54840-00200, Nairobi, Telephone number 020272-2541, 0722205901, 0733-400003. Email address: seru@kemri.org.

STATEMENT OF CONSENT AND SIGNATURES

I have read this consent form or had it read to me. I have discussed the information with study staff. My questions have been answered. It is clear to me that my decision whether or not to take part in this study is voluntary. It is also clear to me that if I decide to answer the questions, I may withdraw at any time. By signing this form, I do not give up any rights that I have as a research participant.

Participant Name (print)	Participant Signature	Date
Study Staff Conducting Consent (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

PERMISSION FOR AUDIO RECORDING

Please initial and date one option:

_____ I give permission for the interviews that I participate in to be recorded.

_____ I DO NOT give permission for the interviews that I participate in to be recorded.

Participant Name	Participant Signature	Date
Study Staff Conducting Consent (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

Copies to: 1. Investigators
2. Study participant

Appendix IV: In-depth qualitative guide

Qualitative component: Exploring HIV self-testing experiences among HIV-1 uninfected men and women.

Target group: HIV uninfected partners enrolled in the Partners HIV Self-testing Project in Thika

Objectives:

1. Learn opinions of HIV uninfected partners on HIV self-testing.
2. Gain an understanding of how participants performed the HIV self-test including any challenges experienced.

Approach:

Focus group discussions: Three different groups of participants: HIV-uninfected women in serodiscordant relationship, HIV-uninfected men in serodiscordant relationship and young women, enrolled in the study. Two focus group discussions of 5-8 participants will be conducted with each type of group (6 focus groups total) to strengthen comparisons made across groups.

In-depth Interview Guide

INTRODUCTION

Ice breaker

What kinds of HIV tests are you aware of?

Probe:

- Clinic based HIV testing and HIV self testing

- How is HIV self testing performed?

Topic 1: **Acceptability**

What do you think about HIV Self Testing? What are the advantages? What are the disadvantages?

Possible probes:

- What would be the advantages or benefits? What would motivate you to take / do a HIV self test?
- What would be the challenges or disadvantages?
- Are there any reasons that would make you not perform a HIV self test?
- Possible concerns with HIV self testing?
- How did your partner feel about you performing a HIV self test?

Topic 2: **Usability**

How was your experience in using the HIV self test?

Possible probes:

- How (easy/difficult) was it to perform a HIV self test?
- What challenges did you experience in performing the HIV self test?
- How was the training provided at the clinic?
- Have you shared your results with others?
- Have you tested others with your HIV self test kits?
- Have you used the 24 hour helpline?

Topic 3: **HIV testing preferences**

What would you prefer self testing at home or clinic based testing?

Possible probes:

- What would you prefer, oral HIV self testing at home or clinic based testing? What are your reasons?

- What are the things that would make you prefer self testing?
- What are the things that would make you prefer clinic based testing?
- How did you find the monthly testing schedule?

Topic 4: **Disclosure**

Possible probes:

- How was it like to tell someone that you used an HIV self test?
- Was there any difference disclosing results from a self test than disclosing results from clinic based tests

Topic 5: **Sexual Behavior**

Possible probes:

- How does sexual behavior change after HIV test results? Condom use? The number of partners?

Topic 6: **Closing discussion**

Possible probes:

- When people self-test and get a positive result, what are some ways to help them?
- Probe about helping via the phone calls, packaging inserts that could provide helpful messages, what kind of preparation should people have before they self-test to prepare for the results, etc.
- What would make it easier for you or others to perform self testing?
- Any other thoughts or suggestions or questions on HIV self testing that you would like to share?

Appendix V: Participant Information sheet with oral HIV self-test Instructions

Participant information sheet: HIV-1 self-testing

OraQuick® HIV1/2 is a qualitative, in vitro immunoassay. It detects antibodies to the human immunodeficiency virus types 1 and 2 (HIV1/2) in human oral fluid. The assay is read visually and is intended for the detection of such antibodies from individuals infected by HIV-1 or HIV-2.

Summary and explanation of the test.

Clinical evidence of HIV infection may be obtained by testing for HIV antibodies in oral fluid of individuals who may be at risk for HIV infection. OraQuick® HIV1/2 detects antibodies to HIV-1 and HIV-2 present in oral fluid.

Accessories.

No accessories are required to run the oral fluid test. However, a timer or watch is needed to determine when to read the result.

Warning and precautions

- Dispose of all potentially contaminated materials in accordance with local regulations for disposal of dangerous materials.
- If an oral fluid test must be repeated (following the gum-swab procedure), start the process over using a new test device, and use the blood test procedure.
- Use adequate lighting to visually check a test result. If two lines are present at any visible intensity, the test result is interpreted as positive.
- Do not cover or otherwise obstruct the two small holes on the back of the test device. The flow of fluid can be impaired.

Storage.

Store unused OraQuick® HIV1/2 tests unopened at 2-30°C. Do not open the foil pouch until you are ready to perform a test. If stored refrigerated, allow the pouch to come to room temperature before opening it.

Specimen collection and test procedure.

The administrator of the test should first instruct the subject about the test and how to collect an oral fluid sample. The test device is then offered to the subject. Instruct the subject to collect a sample, as outlined below:

1. Set the reusable stand on a flat, level surface.
2. Tear open the foil pouch containing the test device and developer vial. Remove the developer vial
3. Carefully uncap the vial gently rocking the cap back and forth.
4. Place the uncapped vial into the stand.
5. Have the subject grasp the test device and remove it from foil pouch without touching the collection pad. **Check to see if desiccant pack is present. If no desiccant is present, discard the unit**.
6. Instruct the subject to swab completely around the outer gums with the test device, by gently wiping the porous flat pad completely across the upper and lower gums, one time around.

7. When the subject has finished swabbing the gums, have the subject insert the pad end of the test device all the way down into the vial.
8. Be sure the result window faces forward so it can be read.
9. Start the timer, or note the time.
10. Read test result in 20 to 40 minutes. Record the test result seen in the result window, then dispose of the device and vial in a dangerous waste container.

Interpretation of results.

Negative test result – only the control line appears.
If a single line appears on the test strip in the area adjacent to the triangle labeled 'C', the result is **negative**. This suggests the **absence** of anti-HIV antibodies in the specimen.
Positive test result – two lines appear
If two lines appear on the test strip, adjacent to the 'T' and 'C' triangles, respectively, the result is considered reactive. One of these lines may be darker than the other. This suggests **presence** of anti-HIV antibodies in the specimen. Please call our Thika clinic on 0736464299.
Invalid – no line present in 'C' area of the window
If there is no line in the area labeled 'C', the result is **invalid**. An invalid test should be repeated with a new test device. If the invalid test was obtained with an oral fluid specimen, use the blood test procedure for repeat testing.

For any challenges in conducting or interpreting the test results please call our Thika Clinic on 0736464299.

Quality control.

A control line in the 'C' area of the result window indicates a valid result. A valid result indicates a suitable sample was collected and the test functioned properly. The control line will appear on all valid tests, whether or not the result is reactive.
Kit control reagents are available separately. These are used to verify adequate test performance. Kit controls should be run once per shift by the test administrator, and whenever changing to a different lot of tests. Refer to the Kit control product insert when using these reagents.

Limitations of the procedure.

1. The OraQuick® HIV1/2 test kit must be used in accordance with these instructions to obtain an accurate result.
2. Oral fluid specimens for OraQuick® HIV1/2 testing must be freshly collected, as detailed in the procedure.
3. The test is not for use with body fluids not specified here, with oral fluid collected by other methods or with other commercially available oral fluid collectors, or with pooled specimens.
4. Clinical data has not been collected to demonstrate the performance of OraQuick® HIV1/2 in persons under 13 years of age.
5. Do not use this test as the sole basis for a diagnosis of AIDS, ARC or HIV infection. **Any reactive result should be confirmed.** Please call our Thika Clinic on 0736464299.
6. For a reactive result, the intensity of the test line does not necessarily correlate to

the titer of antibody in the specimen.

7. **A non-reactive result does not preclude the possibility of exposure to HIV or infection by HIV. An antibody response to recent exposure may take some time to reach detectable levels.**
8. If a red background in the result window makes it difficult to read the test at 20 minutes, wait until the background clears to read the result (but not more than 40 minutes total time).

Appendix VI: Participant Information sheet with bloodbased HIV self-test Instructions

[attached as supplement]

Appendix VII-Focus Group Discussion Guide

Qualitative component: Exploring HIV self-testing experiences among HIV-1 uninfected men and women with HIV-1 infected partners.

Objectives:

1. Learn opinions of HIV uninfected partners in on HIV self testing.
2. Gain an understanding of how participants performed the HIV self test including any challenges experienced.
3. To explore preferences for HIV testing

Approach:

Focus group discussions: Two focus group discussions of 5-8 participants will be conducted with each type of group (6 focus groups total) to strengthen comparisons made across groups.

Focus Group Discussion Guide

INTRODUCTION

Topic 1: **Community Perceptions**

What does your community think about HIV Self Testing? What are the advantages? What are the disadvantages?

Possible probes:

- What are the advantages or benefits?
- What would be the challenges or disadvantages?
- Any reasons they would not want to perform a HIV self test?
- Possible concerns with HIV self tests?

Topic 2: **Acceptability**

What do you think about HIV Self Testing? What are the advantages? What are the disadvantages?

Possible probes:

- What would be the advantages or benefits? What would motivate you to take do a HIV self test?
- What would be the challenges or disadvantages?
- Any reasons why you would not want to perform a HIV self test?
- Possible concerns with HIV self tests?
- How did your partner feel about you performing a self test

Topic 3: **Usability**

How was your experience in using the HIV self test?

Possible probes:

- How (easy/difficult) was it to perform a HIV self test?
- Any challenges in performing the HIV self test?
- How was the training provided at the clinic?
- Have you shared your results with others?
- Have you tested others with your test kits?

Topic 4: **HIV testing preferences**

What would you prefer self testing at home or clinic based testing?

Possible probes:

- What would you prefer, oral HIV self testing at home or clinic based testing? Why?
- What are the things that would make you prefer self testing?
- What are the things that would make you prefer clinic based testing?
- How did you find the monthly testing schedule?

Topic 5: **Disclosure**

Possible probes:

- What was it like to tell someone that you used an HIV self test?
- Was there any difference disclosing results from a self test than disclosing results from clinic based tests

Topic 6: **Sexual Behavior**

Possible probes:

- How does sexual behavior change after HIV test results? Negative test results? Condom use?

Topic 7: **Closing discussion**

Possible probes:

- When people self-test and get a positive result, what are some ways to help them?
- Probe about helping via the phone calls, packaging inserts that could provide helpful messages, what kind of preparation should people have before they self-test to prepare for the results, etc.
- What would make it easier for you or others to perform self testing?
- Any other thoughts or suggestions on self testing that you would like to share?