Protocol

MPYA: Monitoring Pre-exposure Prophylaxis for Young Adult women

Mpya means "new" in Swahili

(Official title: Next generation real-time monitoring for PrEP adherence in young Kenyan women)

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Abbreviations

ADAPT	Alternative Dosing to Augment Pre-Exposure Prophylaxis Pill Taking
AIDS	acquired immunodeficiency virus
AE	adverse event
ART	antiretroviral therapy
CAG	community advisory group
CBO	community based organization
CDC	Centers for Disease Control and Prevention (US)
DAIDS	Division of AIDS (NIH)
DMC	data monitoring committee
DBS	dried blood spots
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration (US)
FTC	emtricitabine
FTC-TP	emtricitabine-triphosphate
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HPTN	HIV Prevention Trials Network
HTTP	hypertext transfer protocol (presentation of web data)
iPrEx	Pre-exposure Prophylaxis Initiative
IQR	interquartile range
IRB	institutional review board
KEMRI	Kenya Medical Research Institute
MEMS	medication event monitoring system
MGH	Massachusetts General Hospital
MPYA	monitoring pre-exposure prophylaxis for young adult women
MSM	men who have sex with men
NACOSTI	National Council of Science, Technology and Innovation
NIH	National Institutes of Health (US)
NIMH	National Institute of Mental Health (US)
PEPFAR	President's Emergency Plan for AIDS Relief
PIN	personal identification number
PPB	Pharmacy and Poisons Board of the Ministry of Health (Kenya)
PrEP	pre-exposure prophylaxis
PROUD	PRe-exposure Option for reducing HIV
RedCAP	Research Electronic Data Capture
SMS	short message service (text messaging)
STI	sexually transmitted infection
TCP/IP	transmission control protocol/internet protocol (internet programming code)
TDF	tenofovir
TFV-DP	tenofovir diphosphate
UNAIDS	Joint United Nations Program on HIV/AIDS
UPenn	University of Pennsylvania
US	United States
UTAUT	Unified theory on acceptance and use of technology
UW	University of Washington
VCT	voluntary counseling and testing
VOICE	Vaginal and Oral Interventions to Control the Epidemic (study)
WHO	World Health Organization

Summary

Real-time electronic monitoring is the optimal approach for understanding patterns of adherence, which is critical for determining if adherence to daily oral pre-exposure prophylaxis (PrEP) aligns with an individual's risk for human immunodeficiency virus (HIV) acquisition. Compared with earlier adherence measurement devices, next generation Wisepill technology offers significant innovations in data storage and transmission reliability, cost, and usability and is ready for implementation in resource-limited settings. Coupling Wisepill monitoring to short message service (SMS) adherence reminders has great potential to support adherence at the precise time it is needed. Real-time strategies may be particularly important for young women- a population in need of self-controlled HIV prevention strategies, but one that has previously struggled with PrEP adherence. Triangulating weekly SMS measurement of sexual behavior with adherence may explain how PrEP can be used most effectively for HIV prevention (i.e., prevention-effective adherence).

This protocol describes a longitudinal study of young Kenyan women at high risk for HIV who will be offered PrEP for up to two years. Adherence will be monitored in all women with the next generation Wisepill; half will be randomized to receive SMS reminders. The technical function, acceptability, cost, and validity of the next generation Wisepill device coupled to SMS reminders will be determined among this cohort of young Kenyan women. Additionally, SMS will be used for longitudinal assessment of risk perception and its alignment with PrEP adherence.

Design: Prospective study of open-label PrEP
Randomization (1:1) of SMS reminders on PrEP adherence
Periodic surveys of risk behavior and perception, including by weekly SMS
Two years of follow-up per participant

Population: Young women at high risk for HIV infection who are interested in taking PrEP; HIV infected male partners of up to 30 (HIV uninfected) young women enrolled in MPYA

Study sites:

- Thika, Kenya
- Kisumu, Kenya

Approach:

Overview
We will prospectively enroll up to 380 young women who choose to initiate PrEP at two clinical sites in Kenya. We will also interview up to 30 male partners of study participants who report being in serodiscordant relationships. We will use wireless adherence monitoring to understand PrEP adherence behavior, as well as patterns of PrEP discontinuation (and re-initiation), in this cohort. We will randomize half of the women to SMS reminders to determine its impact on adherence. We will assess the technical function, acceptability, cost, and validity of the next generation Wisepill device coupled to SMS reminders, thus helping to determining the potential for this technology to assess and support PrEP adherence in future studies and potentially clinical care. Additionally, we will longitudinally assess HIV risk behaviors and perceptions using SMS in all women to determine how well risk for HIV infection is aligned with adherence (a concept called prevention-effective adherence). The study will involve a combination of quantitative and qualitative methods. The specific aims are as follows:

Aim 1. Use the next generation Wisepill device in a cohort of young HIV-uninfected Kenyan women initiating PrEP to a) measure real-time adherence and b) determine the impact of

SMS reminders on adherence. We will monitor adherence among all women with Wisepill. We will randomize half to receive daily SMS reminders with the option of switching to SMS reminders only as triggered by missed doses; the other half will receive no SMS reminders. There will be two primary outcomes for this aim. First, we will determine enacted adherence (i.e., pill taking) and persistence (i.e., continuation of PrEP over time) as determined by Wisepill from initiation of PrEP use (when adherence patterns are often established) through 24 months of use, comparing those randomized or not to SMS reminders. Second, we will compare dried blood spot (DBS) tenofovir-diphosphate levels between the two groups at multiple time points. With both outcomes, we will be assessing the synergy of SMS reminders coupled to real-time monitoring.

Aim 2. Determine the technical function, acceptability, cost, and validity of the next generation Wisepill device coupled to SMS reminders. We will measure data transmission reliability, battery life, and other technical features through the two-year cohort study. We will assess acceptability and usability of our strategy via quantitative surveys in all women, as well as qualitative interviews in about 50 women. We will additionally assess costs and ease of use with a time and motion study. Using these cost estimates and adapting an existing mathematical model of HIV transmission, we will estimate the cost-effectiveness of Wisepill plus the SMS reminders per HIV case averted. Adherence validity will be determined by comparing the Wisepill data with DBS tenofovir levels as measured in Aim 1. Discrepancies between the two measures will be explored through qualitative interviews at the conclusion of the study.

Aim 3. Triangulate Wisepill adherence data with weekly assessment of HIV risk behaviors and perceptions, to measure prevention-effective adherence. After the first 6 months of PrEP use (i.e., when initial decisions about PrEP may start to change), we will send all women a weekly SMS survey asking about recent sexual behavior, use of alternate HIV prevention tools, subjective HIV risk, and perception of their PrEP adherence. We will explore the overlap of perceptions and behaviors and PrEP adherence, through quantitative surveys in all women and qualitative interviews in about 50 women. Our goal is to measure dynamic changes in HIV risk and perception of risk or other motivators for HIV prevention that may lead to PrEP discontinuation (appropriately or inappropriately). We will use these SMS surveys to quantify prevention-effective adherence in young women at risk for HIV infection (individually and for the cohort overall). At exit from the study, we will administer a short questionnaire to understand future plans to use PrEP and experiences related to PrEP during the study.

Aim 4. To qualitatively determine why young women in Kenya who are at risk for HIV acquisition may choose not to enroll in a PrEP study or initiate PrEP as it relates to views on PrEP and the impact of technology on study involvement. We will interview up to 60 women who met eligibility criteria at screening but do not return for enrollment. We will also conduct at least 10 and up to 12 focus groups among five key populations across the two sites. These focus groups will include: key community leaders, male parents, female parents, young women (ages 18-24 who are not participating in the larger study), and young men (ages 18-24) from the community, assuming one focus group with each population at each site. We are allowing for one additional focus group per site in case of technical difficulties with the digital recorders or other data collection difficulties. Inquiry will be guided by domains from a prior conceptual model we have developed focused on understanding decision-making related to uptake of HIV treatment for prevention, as well as prior research on PrEP uptake and adherence. We will use an iterative approach over the course of data collection.

Aim 5. Evaluate a novel adherence measure in which the amount of emtricitabine is quantified along strands of hair. We will compare the emtricitabine concentration patterns in hair with other measures of adherence in the study, including Wisepill, dried blood spots, and self-reported adherence. Analysis will include correlation and categorical comparisons among the measures. Additionally, preliminary evidence from women who have used PrEP early in pregnancy has not shown risks to pregnancy or baby. Studies on breast milk exposure show that only minimal amount of drug is present in breast milk and even less is transmitted to the baby. We will therefore allow women who are breastfeeding to enroll in the study. In addition, we will offer participants the option to continue PrEP should they become pregnant during the course of the study or choose to continue PrEP while breastfeeding. Data on pregnancy outcomes will be added to that of other studies involving PrEP and young women, which will collectively contribute to understanding the safety of PrEP during pregnancy.

Aim 6. To explore the acceptability and feasibility of assessing patterns and content of SMS and/or WhatsApp messages as a means of identifying risk for HIV acquisition and/or PrEP adherence**.** We are proposing a sentiment analysis (i.e., the use of language processing to systematically identify, quantify, and study affective states and subjective information). First, we will ask participants for permission to download their SMS and/or WhatsApp message history from the prior 90 days. We will also ask participants to identify the type of relationship (e.g., family member, peer, sexual partner) for up to 20 of the most commonly used numbers. We will then explore the number and patterns of SMS and/or WhatsApp messages sent by the participant to map her social networks, as well as assess for word or phrase frequency potentially related to HIV risk (e.g., sex, HIV) and adherence (e.g., pill, PrEP). We will additionally determine any correlations of this data with other reported risk and adherence assessments already collected in the study. All mobile communication data will be de-identified once it is linked to other MPYA study data to protect confidentiality.

Approach: To accomplish Aim 6, we will approach participants currently enrolled in the study, as well as contact those who have 1) already exited the study and 2) indicated on their primary study consent form that they are willing to be contacted for future studies. We aim to contact as many participants as possible before the study ends (April 2020). Because this aim is exploratory, we do not have specific targets for participation.

We will then obtain separate informed consent specifically for collection and analysis of mobile communication data. We will download this data directly from the participant's phone. We will not seek any mobile communication data stored with the participant's mobile network provider (e.g., Safaricom). We will use a SIM card reader to download SMS; The data will then be transferred to a Word document or Excel spreadsheet, which will be encrypted to ensure privacy using the in-built file encryption feature in Microsoft Office. WhatsApp messages (if the user has a smartphone) will be downloaded to a .txt file using the WhatsApp export functionality. The file will be converted to a Word or Excel file using Microsoft Office and encrypted, as described above.

We will also ask participants to list their most commonly used phone numbers (up to 20) and describe their relationships to each number (e.g., family member, friend, sexual partner, other); we will not ask for that person's name or other identifying information. We will additionally ask a few questions about the acceptability of accessing their mobile communication data.

Analysis: The analysis of the mobile communication data is exploratory in nature and is unlikely to be powered for significant effects. The primary goals are therefore to determine the following:

- *Acceptability*: Acceptability will be defined by a summary of the participants' willingness (or not) to provide the requested data. We will assess their level of comfort with this activity on a Likert scale.
- *Feasibility*:
  - We will assess data availability on the participant's phones (e.g., extent of missing or incomplete data).
  - We will determine our ability to map social networks from the mobile communication data by identifying the frequency of SMS and/or WhatsApp sent by the participant to each provided phone number and exploring patterns of contact (e.g., the number of times a participant contacts a "friend" within a given time frame).
  - We will determine the feasibility of assessing risk of HIV acquisition with the mobile communication data by using a combination of computational linguistic software and manual review of the mobile communication content. We will identify the most frequently used words or phrases in the SMS and/or WhatsApp messages that may be related to risk of HIV acquisition, accounting for the relationship of the person to whom the SMS and/or WhatsApp was sent (e.g., "sex" sent to a sexual partner) and potential use of multiple and/or mixed languages (e.g., a combination of English and Swahili with phonetic spelling).
  - We will use similar techniques to determine the feasibility of assessing PrEP adherence with the SMS and/or WhatsApp data. We will identify the most frequently used of words or phrases potentially related to adherence (e.g., "taking", "PrEP", "pill"), again considering use of multiple and/or mixed languages.
- *Preliminary correlations of SMS and/or WhatsApp data with other HIV risk and adherence data*: To explore the potential for identifying individuals at risk for HIV acquisition and/or poor adherence, we will correlate the social networks and linguistic data with risk assessments obtained earlier in the study through the weekly SMS surveys or quarterly study visits (e.g., self-reported risk, number of sexual partners, use of alcohol), as well as overall and patterns of adherence as measured by pharmacy records, Wisepill data, self-reported data, and (if provided) hair samples. We will also consider any seroconversion events.
- *Security*. Privacy is of utmost concern with these procedures. All data will be stored in an encrypted manner as described above. We will additionally de-identify the social media data as soon it is linked to the participant's other study data (typically within one business day of collection).

Background and rationale

Real-time electronic monitoring is the optimal approach for understanding patterns of adherence to daily pill taking and offers novel opportunities for effective intervention.

Multiple approaches have been studied to measure daily pill adherence, but few provide the rigor of electronic monitoring. Self-reports are often inaccurate due to social desirability and recall bias. Pill counts are subject to manipulation (e.g., pill dumping) and unannounced pill counts are costly. Pharmacy refill is feasible, but insensitive in that it provides only the maximum predicted adherence (i.e., individuals do not necessarily take the pills picked up from the pharmacy). Plasma drug levels and other biomarkers document drug ingestion yet are impractical for frequent collection and are expensive. None of these other measures assess patterns of adherence, which are critical for knowing if day-to-day adherence is adequate for achieving the desired clinical outcomes (e.g., viral suppression in the case of antiretroviral therapy [ART] [1-3] or avoidance of HIV seroconversion in the case of PrEP).

Many electronic adherence measurement tools, including the most commonly used device, the Medication Event Monitoring System (or MEMS), require individuals to return to the clinic for measurement, which may be weeks to months after adherence challenges arise. In such cases, the opportunity for providing adherence intervention may thus be missed, allowing clinical consequences to occur. Instead, monitoring with real-time measurement that can be coupled to real-time adherence intervention is needed [4]. In essence, good adherence measurement is most useful when it is timely and can be coupled to real-time interventions that address the contextual moment in which the adherence challenges arise.

Wisepill is an electronic adherence pill container monitor that transmits the time-and-date stamp of each opening, using cellular technology, thus enabling real-time measurement of day-to-day adherence patterns. It is manufactured by Wisepill Technologies in Cape Town, South Africa. Because of its timely data transmission, Wisepill can be coupled to real-time interventions for individuals in need of support, precisely when they need them. Wisepill is discrete – 6x13 cm – and easy to use. Our group has extensive experience with the first generation Wisepill device, starting in 2009 [5]. In a pilot study among 49 adults taking ART in rural Uganda, Wisepill adherence was found to be 89.5% (interquartile range [IQR] 83.9–92.3%) [6]. All but two participants (97.9%) reported it was 'easy/very easy' to use, and all stated they 'liked/really liked' being monitored. Higher Wisepill adherence was significantly associated with protection against viral rebound (OR 0.58 for each 10% increase in adherence, 95%CI 0.34–0.98; p=0.04). We have used Wisepill to monitor ART adherence among >500 individuals in the same setting. A next generation Wisepill device has recently become available, addressing technical limitations of the first-generation Wisepill and readying the technology for wide-scale use (described below).

In resource-limited settings, cell phones are common and have great potential for adherence intervention when coupled to real-time adherence monitoring. In Kenya, ~30 million people (70% of the population) own cell phones, and mobile technology for health (mHealth) is rapidly developing [7]. Two landmark randomized controlled trials of SMS reminders in Kenya showed significant increases in ART adherence and one showed an increase in viral suppression [8, 9]. We are studying SMS linked to Wisepill for ART adherence support in Uganda; studies assessing real-time adherence interventions are needed for PrEP.

There is equipoise for randomization of SMS reminders, because the evidence for the effectiveness of SMS reminders generally is mixed and there is no evidence that reminders are effective for PrEP adherence. The two randomized controlled trials (RCT) noted above [8,9] did show improvement in antiretroviral adherence; however, another RCT did not [10]. Studies of SMS reminders linked to real-time adherence monitoring have similarly been mixed. Two RCTs found increased adherence [11,12], while a third did not [13]. The Orrell study did find a decrease in treatment interruptions, but none of these studies found an improvement in viral suppression. Importantly, these studies were all conducted within the context of HIV treatment, not prevention. Factors influencing adherence to HIV prevention may be quite different. Additionally, none of these prior studies focused on the proposed study population (young women) and few were conducted in recent years when individuals are inundated with social media, even in resource-limited settings. SMS reminders may or may not have a strong impact in the context of so many other electronic input. For these reasons, there is equipoise and a study like this will help determine the need for such an intervention, and if needed, whether daily or as needed messages have the better impact.
The next generation Wisepill technology offers significant innovations compared with the first generation and has the potential for ready implementation in resource-limited settings, for both research and clinical use.

Wisepill (Figure 1) is a promising emerging technology poised for high impact in understanding adherence through real-time day-to-day measurements of pill taking behavior. A beta-development form of Wisepill has been available for several years; initial limitations included unreliable data transmission, limited battery life, and a challenging user interface in diverse settings (personal communication from Dr. Rivet Amico and Dr. Mirjam Kempf-Collette). Through our prior experience with this device, we are well positioned to test the newly refined next generation technology such that it is "plug and play" and ready for widespread use in research and potentially clinical care. Table 1 below presents the innovations in the Wisepill technology.

Fig 1. Wisepill device

Table 1. Wisepill technology innovations

Functionality	First generation	Next generation
Battery life	2 months	>6 months; a new long-life mode may extend to 12
Data storage capacity	30 events	1,000 events
Data transmission	2G-compatible	2G and 3G-compatible
Data transmission	Simple modem that is required to run device software	Advanced modem with separate processor such that device software can run independently (provides more powerful, reliable communication)
User interface	Oriented to engineers	User friendly display and data organization
Cost (including hosting)	>$200 per person	<$150 per person
Enhanced "heartbeat" (positive control for device functionality)	Not stored on the device or guaranteed	Stored on the device and server; may be sent multiple times per day if desired
Geo-position tracking	N/A	Enables device location (optional)*
SMS packing	Only TCP/IP communication	HTTP POST allows easier integration with the device, enabling use of client servers directly
Magnetic switch (triggered on device opening)	Magnetic reed switch	Chip-based solid state magnetic switch greatly increases reliability
Electronic components	Multiple components	All are now solid state (no moving parts) and are highly reliable, especially in rugged environments

TCP/IP=transmission control protocol/internet protocol (internet programming code)
HTTP=hypertext transfer protocol

**This feature will not be used in this study.*
Oral PrEP requires daily pill taking. Adherence is key to the effectiveness of daily oral tenofovir-based PrEP for HIV prevention, yet has been challenging for women. Intervention through SMS adherence reminders may be an effective and acceptable intervention for this population.

Six randomized placebo-controlled clinical trials explored the efficacy of daily oral tenofovir-based PrEP against HIV infection [14-19], with PrEP efficacy results ranging from 0 to 75% [20]. The variation across trials (and across individuals) in HIV protection can largely be explained by differences in PrEP adherence [21], with tight correlations between trial results and the levels of objective adherence measures in those studies and HIV protection estimates between 90-100%

in individuals with high adherence [15, 22, 23]. Oral PrEP is clearly efficacious, and highly so, when taken.

In the FEM-PrEP and Vaginal and Oral Interventions to Control the Epidemic (VOICE) trials (which involved at-risk women in Kenya, South Africa, Tanzania, Uganda, and Zimbabwe), <30% of participants had objective evidence of PrEP adherence, and no efficacy of PrEP against HIV found as a result. Those data have made some question whether PrEP works for women. However, in the Partners PrEP (KNH/UoN ERC ref. # P286/05/2012 and ref. # SCC 1336) and TDF2 (Tenofovir 2) trials (which involved serodiscordant couples in Kenya and Uganda and heterosexual men and women in Botswana, respectively), women did adhere well to PrEP, and PrEP prevented HIV in subgroups of young, high-risk women, proving that PrEP is efficacious for women when taken [24]. Work done after the VOICE trial suggests that multiple factors contributed to low adherence in that study, including complex perceptions of self-efficacy against HIV risk, HIV and HIV prevention stigma, and components of the clinical trial itself (e.g., blinding, uncertainty about efficacy).

Daily oral PrEP is supported for women by US Food and Drug Administration (FDA) labelling, US Centers for Disease Control and Prevention (CDC) guidance, recent President's Emergency Plan for AIDS Relief (PEPFAR) goals, and World Health Organization (WHO) guidelines [25-28], and the recent Alternative Dosing to Augment Pre-exposure Prophylaxis Pill Taking (ADAPT) trial of multiple dosing regimens for PrEP found that women in South Africa were able to adhere well to a daily regimen (79% overall) [29]. For women wanting PrEP, adherence may be different now that efficacy is proven (unlike during the clinical trials), in an analogous way to the improvements in PrEP adherence and impact seen for men who have sex with men (MSM) between the blinded Pre-exposure Prophylaxis Initiative (iPrEx) trial (44% efficacy) and the open-label PRe-exposure Option for reducing HIV (PROUD) study (86% efficacy) [30, 31].

As noted above, SMS reminders have been shown to be effective for ART adherence when sent on a scheduled basis [8, 9], as well as when tied to real-time adherence monitoring [11]; however, they have not yet been tested for PrEP adherence. Daily reminders may be important to support habit formation at PrEP initiation, given that non-adherence was already well established by the first quarterly tenofovir measurement in the VOICE trial [32]. Because daily SMS may result in habitutation (i.e., annoyance and decreased impact that may result from frequent reminders) with time [9], this study will test the use of daily SMS reminders, followed by SMS reminders only when triggered by misses doses. The approach follows a novel paradigm in healthcare delivery called "just-in-time", which refers to the provision of information and/or services in the moment they are needed. It has been shown to be highly effective in other aspects of healthcare delivery, such as home health care [33-35], and has great potential to be applied to PrEP adherence.

Risk for HIV acquisition depends, in large part, on dynamic sexual behaviors and decisions to use HIV prevention tools. Risk perceptions and attitudes may change over time, influencing PrEP adherence. Understanding the interface of dynamic risk and adherence over time is therefore essential for achieving prevention-effective adherence.

HIV risk is dynamic over time, changing with sexual behaviors, partners, and use of prevention options. For instance, risk is high for a woman who has unprotected sex with an HIV-infected partner who is not taking ART, and risk is low for a woman who does not have sex for a sustained period of time. The combination of these factors at any given time may depend on perceptions and attitudes toward risk. Risk perception plays a central role in multiple theories of health behavior, with the hypothesis that individuals who perceive risk of acquiring a disease will

be more likely to engage in risk reducing behaviors [36, 37]. Attitudes towards risk represent the extent to which individuals are willing to take on risk and are considered to be an important predictor of behavior [38-40].

Measurement of HIV risk behaviors, perceptions and attitudes has been challenging, as recall of behavior and perceptions is typically limited and self-report may be subject to social desirability bias. SMS may be an ideal means for collecting this type of data, given the ability to administer SMS frequently and the relative anonymity of digital data collection. Our group has used SMS to assess sexual behavior, as well as explored assessment of risk perception and attitude, in multiple projects in Kenya [41, 42]. Importantly, dynamic risk behavior and perception should be tracked longitudinally, as PrEP is not forever once started (unlike ART). Assessments of when and how it can be discontinued are needed. PrEP is not an on-and-off-again prevention strategy and decisions regarding its use should not be made on a daily or weekly basis (although risk may change this frequently), particularly for women. Pharmacokinetic studies suggest high adherence and weeks of lead-in may be needed for protection in vaginal tissue (in contrast more rapid protection rectal tissue for MSM) [43, 44]. Thus, decisions to discontinue (and potentially later re-initiate) PrEP should be driven by aggregated risk patterns. No such data are currently available, but are key for developing evidenced-based guidance.

Making the best use of prevention tools during periods of high risk is the ideal– a concept we have termed prevention-effective adherence [3]. High PrEP adherence in the absence of risk for HIV acquisition is not advantageous to the PrEP user (because of potential side effects and other costs such as time away from work to get refills) or society (because of the cost of unnecessary medication, which could have gone to other HIV prevention and/or treatment efforts). These factors are particularly important in resource-limited settings, like Kenya. Moreover, PrEP non-use in the absence of risk is logical and reflects what people do; in the Partners PrEP Study, lack of sexual activity in a month was associated with a four-fold increase in PrEP non-use [23]. Concurrent weekly measurements of risk behavior, risk perception, and adherence over time will improve our understanding of the relationship among these factors and help determine when adherence interventions are needed for women relying on PrEP for HIV prevention.

Based on the FEM-PrEP and VOICE trials, one could argue that women have trouble aligning their risk behaviors and perceptions with adherence to achieve HIV protection. However, women routinely make this type of decision in another area of health prevention - family planning. Women often successfully choose when to use (or not use) a given contraceptive option. While their choices are not always perfect, many more pregnancies have been prevented through family planning than would have been prevented otherwise and family planning is a global public health imperative. This grant proposes the foundational science necessary to help guide women with these vitally important choices for PrEP for HIV prevention. *Advancement of Wisepill for PrEP adherence monitoring and intervention is needed now, as PrEP is being rolled out and implemented in different cultural and economic settings.*

Following demonstrated efficacy in PrEP clinical trials [14, 16], the US FDA approval for use of tenofovir/emtricitabine for HIV prevention [27], and publication of US CDC and WHO guidelines [25, 28], preparations to roll out PrEP have begun. More than two dozen demonstration projects of PrEP are planned or underway worldwide, and PrEP is being prescribed in some clinical care settings [45]. While adherence is known to be a critical issue for PrEP adherence, it is poorly understood and few tools exist to support it. This study will help fill that void.

Importantly, the Kenyan Ministry of Health has included PrEP and has named young women

(among whom 20% of all new infections in Kenya occur) as a priority population in its Prevention Revolution Road Map 2030 [46]. Given the challenges with this population in some PrEP clinical trials, a better understanding of adherence and adherence support is urgently needed for this specific population.

With the proposed administrative supplement, we will assess factors driving decision-making both at the point prior to PrEP uptake, and immediately after PrEP initiation, among high-risk young women in Kenya. In the context of this trial that is technologically intensive for participants, we will also seek to discern the impact of direct monitoring (using Wisepill and SMS feedback) on study engagement, distinguishing it from treatment-related decision-making. Our findings will inform messaging and other interventions to promote PrEP scale-up as a core component of combination prevention for this key population. These issues are critical because our prior research has shown that decision-making related to HIV treatment and prevention often reflects a tension between perceived risks and social costs incurred when taking medication. Specifically, adults living with HIV report that "feeling healthy" is a critical deterrent to ART initiation. It therefore remains unclear whether young women who are at risk for HIV acquisition, but are otherwise healthy, will want to initiate PrEP.

Methods

Overall design
We propose a prospective study to follow up to 380 young women who choose to initiate PrEP at two clinical sites in Kenya; all 3 Aims will involve this cohort. Study visits will occur at baseline, 1 month (to address PrEP start-up symptoms and initial adherence challenges), and every 3 months thereafter for 24 total months per participant. At baseline, we will determine if PrEP is clinically safe to prescribe for each participant, confirm HIV-negative status, and measure socio-behavioral factors that may influence PrEP use. Longitudinal study visits will involve PrEP distribution (if desired), adherence counseling, clinical monitoring (including HIV testing), storage of dried blood spots, and (at some visits) questionnaires. SMS reminders will be sent to half of the participants. Additional data will be collected through the Wisepill device, SMS surveys, time and motion studies, and qualitative interviews.

- **Aim 1**: Use the next generation Wisepill device in a cohort of young HIV-uninfected Kenyan women initiating PrEP to a) measure real-time adherence and b) determine the impact of SMS reminders on adherence. We will monitor adherence among all women with Wisepill. We will randomize half to receive daily SMS reminders with the option at each study visit to switch to SMS reminders only triggered by missed doses; the other half will receive no SMS reminders. Blood will be collected at each study visit as DBS for tenofovir concentration determination.
    - Outcomes:
        - Wisepill adherence (enacted adherence and persistence)
        - Tenofovir concentration as a marker of adherence

- **Aim 2:** Determine the technical function, acceptability, cost, and validity of the next generation Wisepill device coupled to SMS reminders. Data will be collected in an on-going manner for technical function assessment and via questionnaire for acceptability. Time and motion studies will gather data for ease of use and cost. Validity will be evaluated based on data collected in Aim 1.
    - Outcomes:
        - Feasibility of Wisepill monitoring and SMS reminders
        - Acceptability of Wisepill monitoring and SMS reminders

        - Ease of use, health care associated costs, and cost-effectiveness of Wisepill monitoring and SMS reminders
        - Validity of Wisepill monitoring compared to tenofovir concentration in DBS

- **Aim 3:** Triangulate Wisepill adherence data with weekly assessment of HIV risk behaviors and perceptions, to measure prevention-effective adherence. We will determine risk perception and motivations for HIV prevention through weekly SMS surveys, as well as through qualitative interviews. Analysis will involve the SMS data in comparison with Wisepill adherence data collected in Aim 1. At exit from the study, we will administer a short questionnaire to understand future plans to use PrEP and experiences related to PrEP during the study.
    - Outcome: Quantified prevention-effective adherence (defined as adherence during periods of risk for HIV acquisition without other forms of HIV protection)
- **Aim 4**: To qualitatively determine why young women in Kenya who are at risk for HIV acquisition may choose not to enroll in a PrEP study or initiate PrEP as it relates to views on PrEP and the impact of technology on study involvement. We will interview up to 60 women who met eligibility criteria at screening but do not return for enrollment.
    - We will also conduct at least 10 and up to 12 focus groups among five key populations, assuming one focus group with each population at each site. We anticipate having 10 focus groups between the two sites, but are allowing for two additional focus groups if necessary due to technical difficulties, lack of data, etc. Inquiry will be guided by domains from a prior conceptual model we have developed focused on understanding decision-making related to uptake of HIV treatment for prevention, as well as prior research on PrEP uptake and adherence. We will use an iterative approach over the course of data collection.

      For the additional phase of this study, we intend to recruit five potential groups for focus groups:
        1) Key community leaders
        2) Male parents
        3) Female parents
        4) Young women (18-24 years) but are not otherwise participating in the study
        5) Young men (18-24 years) from the community

      All potential participants must be adults, but otherwise, there are no additional exclusion criteria other than those previously noted.
    - Outcomes:
        - Understanding of decision-making in the uptake of PrEP and impact of technology in this study (total n=60 semi-structured interviews and up to n=120 across the anticipated 10 focus groups)
- **Aim 5. Evaluate a novel adherence measure in which the amount of emtricitabine is quantified along strands of hair.** We will compare the emtricitabine concentration patterns in hair with other measures of adherence in the study, including Wisepill, dried blood spots, and self-reported adherence. Analysis will include correlation and categorical comparisons among the measures.
- **Aim 6. To explore the acceptability and feasibility of assessing patterns and content of SMS and/or WhatsApp messages as a means of identifying risk for HIV acquisition and/or PrEP adherence.** We will download this data in a secure manner and then perform a sentiment analysis. Data will also be compared with other reported risk and adherence assessments in the study.
    - Outcomes:

- Acceptability
- Feasibility
- Preliminary correlations

Population

This study will enroll young Kenyan women in the communities near the study sites who are at high risk for HIV infection who are interested in taking PrEP. For women not known to be in an HIV serodiscordant relationship, we define high risk according to the following risk score (Table 2), which was developed from women enrolled into several prior prospective studies (VOICE, HIV Prevention Trials Network [HPTN] 035 and FEM-PrEP [47]. A score ≥5 was associated with HIV incidence >5 per 100 person-years and will therefore be used for an enrollment criteria for this study. Alternatively, a woman will be considered as high risk if she is in a known serodiscordant relationship (i.e., she has a sexual partner with known HIV infection); in these cases, the risk score will not be used.

Table 2. HIV risk score

Participant age		
Less than 25 years	2	X*
25 years or more	0	
Married or living with husband /primary partner		
No	2	
Yes	0	
Partner provides financial/material support		
No	1	
Yes	0	
Partner has other partners		
Yes	2	
Don't know	2	
No	0	
Any alcohol use in the past 3 months		
Yes	1	
No	0	
Total score		

*For this study everyone will be <25 years

PrEP counseling

We will provide PrEP to all participants in accordance with CDC and WHO guidance [25, 28]. At enrollment, participants will be fully informed of the benefits and risks of PrEP, as well as the need for daily adherence to achieve maximal protection against HIV acquisition. Adherence strategies will be discussed as recommended by the CDC guidelines (e.g., tailoring doses to daily routines) by trained counseling staff. Brief follow-up adherence counseling will be offered at each visit and may be intensified if requested by the participant or deemed necessary by the study staff. Additionally, starting at the 6-month follow-up visit, we will reassess each participant's risk for HIV during counseling sessions per the above criteria. If she is no longer at high risk for HIV acquisition, we will discuss whether PrEP continues to be a good prevention option for her; this strategy is consistent with the goal prevention-effective adherence. Participants will be able to access PrEP throughout the 24-month study period, if desired, and will be offered guidance in making this decision during the counseling sessions. Participants will be encouraged to only consider PrEP discontinuation during these sessions and not in between visits. They will, however, be

offered the option of returning to the study site off schedule if they are considering PrEP discontinuation. PrEP re-initiation will similarly be offered at study visits following discontinuation or in between visits if desired by the participant. Staff providing counseling will be distinct from those assessing adherence or dispensing PrEP to limit potential manipulation of the Wisepill device (e.g., opening the device without dosing to increase the appearance of adherence).

PrEP delivery
Tenofovir disoproxil fumarate (or TDF) and emtricitabine (or FTC) are reverse transcriptase inhibitors that have been approved for the treatment of HIV infection in humans in Kenya and the United States, among other settings. A fixed-dose, oral co-formulation of FTC/TDF (Truvada®) will be used in this study. PrEP will be prescribed for once-daily use. PrEP medication will be obtained through a donation from Gilead Sciences.

Participants will receive PrEP through prescription by clinician and distribution through the study pharmacy. PrEP will be provided in the context of a comprehensive HIV prevention package, including treatment for sexually transmitted infections, offer of HIV testing for sexual partners, and provisions of condoms.

Eligibility criteria
The following inclusion and exclusion criteria will be used to identify potential study participants. These criteria reflect the target population, as well as the availability of a cell phone, which is critical to the adherence monitoring and intervention strategy under evaluation.

Inclusion

- Female
- HIV-uninfected (as determined by Kenya national testing algorithms)
- Age 18-24 years
- Wanting to start PrEP with an initial recommendation of 6 months of use
- Clinically safe to receive PrEP, in accordance with CDC guidelines:
    - Creatinine clearance >60 mL/min
    - Not infected with hepatitis B
    - No other medical condition that in the discretion of the site investigator would make participation unsafe or complicate the goals of the study
- Sexually active (defined as vaginal or anal sex) within the last 3 months
- At high risk for HIV infection based on a score of $\geq$5 [47] or being in an HIV serodiscordant relationship (each site will enroll at least 15 young women in HIV serodiscordant partnerships)
- Not pregnant
- Owns a personal cell phone (not shared) compatible with the technology used in the study and the ability to charge it
- Ability to send a text message
- Intending to stay in the area for at least the next year
- Willing to use study technology
- Up to 30 HIV-infected male partners (whose HIV uninfected female partners have been enrolled in MPYA study) for the qualitative study

Exclusion

- Unable to provide consent

- Concurrent or prior participation in another research study that may influence adherence to PrEP and/or interfere with the procedures of this study.

Sample size

The study will enroll up to 380 women. The following assumptions were made in determining the sample size for this study:

- An anticipated increase in executed adherence of 10% (e.g., from 70% in those without to 80% in those with reminders) as a result of SMS,
- A standard deviation in adherence of 30%
- Power=80%
- A two-sided alpha=0.05
- 10% loss-to-follow-up

Under these assumptions, each randomized arm for Aim 1 should contain a minimum of 157 women (314 total). This sample size should also be sufficient for reasonable point estimates for Aims 2 and 3.

Recruitment

We will use a community-based recruitment strategy for young women at risk for HIV, drawing from nearby organizations that provide primary health services. At the time of recruitment, participants will be informed about the study and given general information about what PrEP is and for whom it is intended (e.g., high risk of HIV acquisition). While study staff will attempt to identify areas where the technology doesn't function prior to recruitment, if a participant does not have mobile phone reception, we will allow them to participate, but would not enroll them in the randomization aspect of the study.

Thika site

Prior to commencing this study, the Thika team will go through a process of community entry. The first steps of community entry will involve discussions with the community advisory group (CAG) to whom the protocol will be presented. The CAG for this study will include community stakeholders who are involved with this age group as well as at least 2 young women from the community aged 18-24. The CAG will advise on Thika site's recruitment strategies as well as review recruitment materials. After approval by the relevant institutional review boards (IRBs), Thika site will sensitize the National AIDS &STI Control Program (NASCOP) and the County Health Departments about the proposed study and the catchment areas. This will ensure that the community will be engaged and fully informed of this proposed study. This engagement process has been used successfully in previous research projects funded by the National Institutes of Health (NIH) and Bill and Melinda Gates Foundation.

Thika site will recruit the young women through community-based recruitment strategy. Specifically for this study, Thika site plans to recruit young women from the following areas:

- Informal settlements
- Farming communities
- HIV clinics (for young HIV- women in serodiscordant relationships)
- Vocational institutions – these institutions target women who have dropped out of school
- Local organizations working with women at higher risk of HIV such as those involved in sex work
- Organizations that provide primary health care services

Through this study, Thika site shall have an opportunity to educate the community about HIV, other sexually transmitted infections and PrEP. Educational messaging will be done in a culturally sensitive way with initial approval sought from community opinion leaders.

Kisumu site
The CAG will facilitate entry into the community. The CAG is comprised of seven members who will help us identify the potential study participant. Kisumu site will employ the following recruitment strategies:

1. Liaison with Voluntary Counseling and Testing (VCT)/ Sexually Transmitted Infection (STI) clinics
   We will collaborate with the VCT counselors and STI clinics and distribute study referral forms to refer HIV negative women to the study for pre-screening. We will also identify and encourage those who have referrals from post-test clubs, HIV care and various STI clinics within the seven sub-counties in Kisumu County. The study will also focus on support and promotion from important opinion leaders in the community, such as Sub-County Health Management Team and the Medical Officers of Health, the Provincial and Hospital Superintendents, and other Heads of Departments in both the County and National Government. These links will be used to demystify the study and help arrest any rumors and bad publicity that may arise in the course of the study.

2. Referrals
   The study staff will keep a log of key contacts and partners within the catchment area. HIV Testing and Counseling counselors will refer potential participants to our clinic for screening and possible enrolment. They will also rely on word-of-mouth of participants enrolled in the study to widen our scope of coverage.

3. Community Based Organizations
   The Kisumu Site will inform Community Based Organizations (CBOs) within our catchment area about the study. There are a number of CBOs focusing on HIV-related issues within the seven sub-counties in Kisumu. They provide a direct link with the community, and will serve as a liaison to our site, speaking about and referring participants for pre-screening, screening and possibly enrolment.

4. Workplace /Education/ Social events
   The workplace will be a good opportunity to recruit potential study participants. Linkages will be established with the informal sector. The target sites include vendors in the markets, bars, and hot spots for female sex workers. Beaches and the fishing communities within Kisumu County will also be targeted as these areas are regarded high-risk spots.

Study procedures
All major study activities are summarized in Table 3.

Screening- Potential participants will be consented for screening procedures, which will include the following:

- Questions to determine the inclusion and exclusion criteria
- Blood tests (HIV, creatinine, hepatitis B, hemoglobin); up to 21 ml
- Urine pregnancy test

Participants will be invited to return to the clinic in approximately one week to obtain their laboratory results. This time will also allow them to carefully consider their interest in taking PrEP and participating in the study. Those meeting the screening criteria will be offered full informed consent and enrollment. Those not meeting screening criteria will be given further counseling on HIV prevention other than PrEP, if desired. Participants may or may not be informed why they did not meet the screening criteria. During the consent process, participants will be able to indicate whether or not it is appropriate for study staff to conduct off-site visits if they are unable to be reached or if there may be a problem with their Wisepill device.

Table 3. Summary of study procedures												
	S	M0	M1	M3	M6	M9	M12	M15	M18	M21	M24	SSV
Inclusion/exclusions criteria	X	X										
AIM 1												
Data collection												
Cohort/socio-behavioral data		X		X	X	X	X	X	X	X	X	
Wisepill adherence monitoring		on-going										
SMS reminders (if randomized)		on-going (daily or triggered)										
PrEP provision												
PrEP dispensing[1]		X	X	X	X	X	X	X	X	X	X	
Clinical monitoring, incl STIs[2]		X	X	X	X	X	X	X	X	X	X	
Adherence counseling		X	X	X	X	X	X	X	X	X	X	
Laboratory testing[3]												
HIV[4]	X	X	X	X	X	X	X	X	X	X	X	
DBS collection and storage[5]		X	X	X	X	X	X	X	X	X	X	
Pregnancy evaluation[6]	X	X	X	X	X	X	X	X	X	X	X	
Hepatitis B	X											
Creatinine	X				X		X		X		X	
Hemoglobin[7]	X				X		X		X		X	
Pregnancy outcomes[8]												X
AIM 2												
Time and motion studies[9]												
Acceptability questionnaire		X		X			X[10]					
Qualitative interviews (young women)				X			X					X[11]
Qualitative interviews with partners in HIV serodiscordant relationships[12]					X							
AIM 3												
Risk/motivation assessments					on-going (weekly SMS)							
		X		X			X				X	
Process measures			X				X					
Qualitative interviews			X	X			X					
Update of phone number(s)		X	X	X	X	X	X	X	X	X	X	
Exit Interview											X	
AIM 4												
Qualitative interviews			X[13]									
AIM 5												
Hair sample[14]							X	X	X	X	X	
Aim 6												
Social media data												X

S=screening, M=month, SSV= supplemental study visit, STIs=sexually transmitted infections

[1] PrEP will be offered and dispensed (if desired) at each visit. All participants will be encouraged to take PrEP for the first 6 months of the study. Subsequent decisions about continued PrEP use will take place

in individual counseling session with consideration given to risk for HIV acquisition, experiences with taking PrEP and use of alternative HIV prevention options.

[2] STIs will be evaluated based on symptoms.

[3] Blood testing will involve up to 21ml per draw.

[4] We will test for HIV at each study visit and assess any potential seroconversion using serial rapid tests or ELISA. During the third trimester, pregnant participants will be tested with ELISA.

[5] Blood from the venipuncture for HIV testing will be used for making the dried blood spots. For DBS testing, 25 µl of blood will be spotted five times onto protein saver cards (125 µl total). After spotting, the cards will be dried for at least 3 hours or left overnight to air-dry, and then placed in plastic bags and stored in a sample box with desiccant and humidity indicators at 20°C.

[6] Pregnancy assessments will include a urine pregnancy test at screening and enrollment and then as indicated by the WHO pregnancy symptom checklist [48], if requested by the participant, and/or at the discretion of the clinician.

[7] When measured with DBS, levels of tenofovir can be unreliable among individuals who are severely anemic. To confirm the tenofovir levels, we will conduct blood counts at screening and every six months, or as clinically indicated.

[8]Pregnancy outcomes will be assessed up to 6 months after study completion, depending on available resources.

[9] The time and motion studies will be conducted once the sites are running at full capacity (likely several months into the study).

[10] This questionnaire may be given early if a participant does not take PrEP for 12 months.

[11] A subset of qualitative interviews will be performed after 24 months of follow-up if significant discrepancies are seen between Wisepill and DBS adherence.

[12.] A subset of qualitative interviews will be performed at month 6 with partners in serodiscordant relationships.

[13.] These interviews will take place shortly after the screening or M1 visit, depending on when the participant decides not to enroll or to drop out of the study.

[14.] These samples will take place during any routine study visit among participants who collected PrEP at the prior study visit. The time frame listed in the above table indicates that this may happen at any study visit based on the current progress of the study (all participants will be at M12 or later by the time of IRB approval).

Cohort characteristics and socio-behavioral assessment- At enrollment and every 3 months through Month 24, we will obtain the quantitative data as listed in Table 4, which have been shown to impact adherence and risk assessment/decision making. Stigma and self-efficacy will be administered at enrollment, Month 12, and Month 24. Referenced scales (*) have been validated and/or used successfully in sub-Saharan African populations in prior studies. Data will be entered into RedCap (Research Electronic Data Capture) with ongoing quality control checks. RedCap is a secure web-based software program for designing clinical and translational research databases. It is supported by many US academic institutions, including the University of Washington and Massachusetts General Hospital.

NB: The Thika site will use a biometric system (fingerprint scanner) to identify participants throughout the course of the study. Participants will be offered consent form with the option to decline to have their fingerprint taken.

Table 4. Socio-behavioral data (descriptions listed; questionnaire submitted separately)	
Demographics and health	Age, employment, education, marital status, residence type (e.g., with family), reproductive health, distance from clinic, food security, medications, depression* [49]
Taking PrEP and HIV prevention	Disclosure of study participation and PrEP use, belief in PrEP efficacy, modified Necessity and Concern questionnaire [50], time for taking PrEP, SMS preferences (if randomized to SMS reminder arm), help taking PrEP
Alcohol/substance use	Rapid Alcohol Problems Screen-4* [51], use of marijuana and other drugs

Sexual behavior/ intimate partner violence	Number, type of partners (incl. HIV status), use of condoms, transactional sex, abuse
Sexual relationship power	Sexual relationship power sub-scale [52]
Stigma	Perceived HIV stigma scale (modified Berger, adapted for Kenya)* [53, 54]
Adherence	Self-reported ability, rating, frequency of adherence, necessity and concerns as modified from [55]
Self-efficacy/esteem	Rosenberg Self-Esteem Scale* [56, 57]

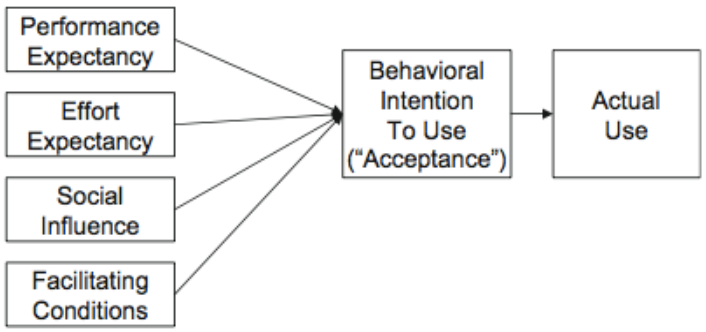
Adherence assessment and impact of SMS reminders (Aim 1)

Wisepill monitoring- We will give all participants a next generation Wisepill device at enrollment and demonstrate its use, together with the participant. Participants will receive PrEP according to the above schedule. Because the device only holds ~1 month of PrEP medication at a time, participants will refill their own Wisepill as needed. We will change batteries at pharmacy visits. Although the battery life should last 6 months, we will change batteries and/or ask participants to charge their devices quarterly to avoid potential data loss. We will track battery voltage to model battery life (i.e., if not changed). At each visit, we will ask participants if any intentional periods of PrEP non-use or Wisepill device non-use occurred and the reason(s) why (e.g., lack of perceived risk, traveling).

Randomization for SMS reminders- Enrolled participants will be randomly assigned in a 1:1 ratio to either SMS reminders or no SMS reminders. The code creating the random allocation order ("the randomization list") will be generated and maintained by the study analyst. A variable size block randomization scheme, stratified by study site, will be implemented to produce the randomization list. The randomization will be implemented by transcribing onto paper within numbered envelopes. Thus, neither participants nor study staff will be blinded to each participant's randomization group assignment. Fidelity of randomization will be confirmed with tracking in RedCap. RedCap will contain a randomization list against which we will compare the actual randomization of participants at the time of enrollment. This process will ensure all participants are randomized as planned.

Provision of SMS reminders- SMS are received without charge in Kenya and cell phones with SMS capabilities are nearly-universally owned in the areas in which we work in Kenya. For the half of the cohort randomized to adherence reminders, the Wisepill server will generate an automated daily SMS containing a reminder of the participant's choice and in her language of choice. Participants will be encouraged to choose a message that will be meaningful to her, but will not put her at risk for any potential social harms if someone sees the message (e.g., a boyfriend seeing the message and suspecting another sexual partner, or unwanted questions about study participation from a family member). For example, a message could refer to a weather report or popular radio program. The content of the message may be changed at each study visit, if desired. Because of the potential for SMS reminder habituation, we will offer participants the option of switching to SMS reminders only triggered by missed doses at each study visit (i.e., 2 hours after the expected dosing time). We will ask participants to keep their cell phones with them and charged. SMS reminders will be suspended if a participant decides not to take PrEP after completing a study visit counseling session; they will be reinitiated if the participant later chooses to start taking PrEP again.

Assessment of the next generation Wisepill device (Aim 2)



Technical functionality- We will determine the number of Wisepill

data transmission events, battery failures, other potential technical problems, and transmission events during two-years of follow-up. Data transmission tracking will include device hardware, cellular network traffic (via our collaborator, mSurvey), and the Wisepill server. In addition, we will measure similar information for the SMS adherence reminders component of Aim 1.

Acceptability and ease of use from the participant perspective- We will use quantitative questionnaires to assess anticipated acceptability of the next generation Wisepill device at baseline, as well as experienced acceptability in all participants at 3 months (short-term) and 12 months (long-term). If women discontinue PrEP before12 months and express no interest in resuming within the remainder of the study period, the long-term acceptability questionnaire may be given at any time after 6 months (participants will be allowed to resume PrEP if they change their minds after completing this questionnaire and are still within the 24-month study period). Additionally, we will conduct serial qualitative interviews in a subset of approximately 50 participants (25 in each site; half randomized to the SMS arm in Aim 1) to gain an in depth understanding of their experience with Wisepill monitoring, SMS adherence reminders, and ease of use of the device from their perspective. They will take place within one week of enrollment and after the participants have had approximately three months and 12 months of experience. Random quota sampling will be used within each category (e.g., approaching every third participant who meets the criteria). After approximately 10 participants have been selected, we will check to make sure that our random sampling is allowing for a range of ages and adherence levels. If this is not the case, we will begin more purposive sampling. Interviews will be digitally recorded and conducted in the participant's preferred language in a private setting. Each interview will last approximately one hour. Additional participants may be approached if needed for theme saturation. We will also conduct separate serial in-depth interviews with up to 30 (15 per site) young women in HIV serodiscordant relationships and their HIV-infected male partners to explore PrEP adherence in the context of serodiscordance among young couples.

The quantitative questions and qualitative interview guide draw from the Unified Theory of Acceptance and Use of Technology (UTAUT) model (see Figure 2 and Table 5) [58]. This model incorporates the standard issues with technology acceptance, as well as potential challenges seen in some settings with Wisepill, such as stigma (social influence) and device size (facilitating conditions).

Costing and ease of use from the provider perspective- Time and motion studies will determine the time necessary to procure, configure, and manage the Wisepill device, including participant interactions. Time and motion studies will be conducted over a two-week period at one or both sites when the study is running at full capacity. We will collect data on the time required to complete each step of the Wisepill monitoring and SMS reminders process. Results from initial time and motion studies will be shared with the teams and strategies for efficiency shared to reduce the time needed for monitoring and intervention. Observing multiple visits will allow estimation of the average time taken for each step; the time taken for research purposes (e.g., data collection) will be noted separately from the estimated time needed for implementation. Multiple staff will be observed and interviewed to capture the range of time and extent of effort required for each step. Interviews may also reflect on the initial stages of technology implementation. Through time and motion studies the number of participants who could be supported by a clinic will be estimated. Together the micro-costing data, time and motion studies, and clinical outcomes will be used to estimate the average cost and effort of real-time adherence monitoring with SMS reminders. Using the estimates of cost and data from Aim 2, we will adapt an existing PrEP mathematical model [59] to estimate the cost-effectiveness of Wisepill, with and without SMS reminders, per incident HIV case averted. These data will be key for decision makers considering implementation of adherence interventions.

Table 5. Questions to be used in assessing Wisepill acceptability	
Model component	**Question description** (questionnaire submitted separately)
Performance expectancy	Perceived usefulness, extrinsic motivations, personal outcome expectations
Effort expectancy	Perceived effort needed to use the device, complexity
Social influence	Perceived norms and stigma
Facilitating conditions/barriers	Presence of storage space, impact of travel, perceived benefits
Behavioral intention to use	Attitude, frequency of anticipated non-use
Actual use	Wisepill opening events while using PrEP

Discrepancies in Wisepill and tenofovir concentrations- Participants with clinically significant differences between Wisepill and DBS adherence (who also provide consent to be contacted after the completion of the study) will be approached within six months of study completion for qualitative interviews to determine potential causes of the discrepancies. Both adherence patterns and drug levels will be shared with participants. Up to 50 such interviews will be conducted.

Prevention-effective adherence (Aim 3)

Risk attitude assessment- At enrollment and months 12 and 24, we will measure each participant's risk attitude with questions concerning their perceived chance of engaging in high risk behaviors and acquiring HIV, as adapted from Weber [36] (e.g., "Rate from 1 [very unlikely] to 5 [very likely] the likelihood of engaging in unprotected sex with someone whose HIV status you do not know".) We will also assess participants risk-seeking attitudes by administering a simple scale containing lottery-based choice tasks-- a standard approach developed by economists [38, 60] and widely used, including by our team in previous studies in Kenya (see the participant-based data collection materials). Participants will be asked to choose between pairs of lotteries that vary in risk and reward; a preference for certain rewards over probabilistic rewards will serve as an indication of risk averse attitudes.

Risk behavior assessments- Following the Month 6 study visit, we will initiate weekly SMS surveys for all participants. The survey will be sent on the participant's preferred date and time and using her preferred language. The initial SMS will consist of a message of the participant's choice that will be meaningful to her, but will not put her at risk for any potential social harms if someone sees the message (as described above). The surveys will be sent through a secure, password-protected, cloud-based data management system at mSurvey that is compliant with all Health Insurance Portability and Accountability Act (HIPAA) data security requirements. These procedures will help safeguard the privacy of our participants. All data will be stored and backed up via Amazon services. Participants will receive approximately $0.50 for each completed survey. The survey questions will ask about sexual behavior, sexual partners, risk perception, and PrEP use in the past week (survey submitted separately). To avoid participants modifying their responses to shorten the survey, those reporting no sexual activity in the past week will be asked "filler questions" (e.g., exercise or work for pay in the past week). The filler questions will not inform primary study aims. SMS survey questions will be sent to all active study participants, regardless of their decision to take PrEP.

Qualitative interviews- During the same serial qualitative interviews described in Aim 2 (approximately 50 women, multiple subsets), we will ask participants about their understanding

of PrEP adherence, including barriers and facilitators, as well as their understanding of HIV risk behavior, risk perceptions, motivation for HIV prevention, and how these factors relate to PrEP use. Specific topics will include 1) pleasure [61], 2) future orientation [62], 3) comparative risk [63], and 4) affect [64].These areas have been associated with risk taking for HIV and other conditions and may impact motivations to take PrEP. Interviews will be done at baseline (within 1 week of PrEP initiation), 3 months and 12 months. Similar topics will be explored with up to 30 young women and their male partners in HIV serodiscordant couples. The one-time interviews will be conducted around month 6. The partners will be interviewed separately.

The qualitative interviews and focus group discussions described in Aim 4 (approximately 60 women and 10-12 focus group discussions), will seek to understand their decision-making around participation in the study, PrEP, and their beliefs about HIV and technology.

Cell phone-related concerns and study contact

We will ask all participants for phone number updates at each study visit. A dedicated line will be established for participants to text or call with any questions about Wisepill, SMS reminders or surveys, or PrEP use, as well as to report any phone number changes. We will call them back so as to minimize any costs incurred by the participant. Participants who lose their phone during the course of the study and do not replace it may be offered use of an inexpensive study phone.

Participant retention and withdrawal

Participants will be tracked through study visits, as well as through their Wisepill device. Individuals missing scheduled appointments will be contacted through study retention teams. They will also be contacted for any non-functional devices, but not because of non-adherence. Participants will have the option of continuing, discontinuing, or reinitiating PrEP at any time for the two years of the study follow-up. We will encourage participants to continue to attend study visits even if they elect not to take PrEP for HIV testing and socio-behavioral questionnaires (months 6 and 12), as well as to facilitate retention.

Safety

Use of PrEP- We will employ clinical monitoring as noted above (Table 3). Creatinine will be tested every 6 months. If the creatinine clearance declines to <60 mL/min, PrEP will be held and a repeat creatinine will be drawn. If renal insufficiency is confirmed, PrEP will be permanently discontinued. Clinical symptoms will be systematically assessed in a structured medical history administered to participants. Clinical side effects of TDF and FTC/TDF that have been reported are primarily gastrointestinal, including nausea, vomiting, and flatulence. Serious adverse events will be documented and reported to all involved ethical review boards per their regulations. Serious adverse events (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 Division of Acquired Immunodeficiency Syndrome (DAIDS) Table for Grading the Severity of Adult and Pediatric AEs [65]. Decisions to hold PrEP due to clinical and/or other laboratory safety reasons, or in the event of overdose, will be at the discretion of the Site Investigator, in consultation with the Principal Investigators.

HIV infection- Participants will be tested at enrollment and every 3 months for HIV as noted above. If found to be positive, the HIV test will be confirmed per Kenya national guidelines.

PrEP will be stopped, counseling will be provided, and participants will be actively linked to HIV care.

Pregnancy- If a woman becomes pregnant during the study, PrEP will continue to be offered, in line with FDA labeling; indeed, the FDA is actively seeking data on TDF/FTC use in HIV-negative women during pregnancy [66] and pregnant women have taken PrEP as part of the Partners Demonstration Project. We will seek additional consent for continued participation and ensure she understands the risks and benefits of continued PrEP use. Monthly visits will be added in between the usual 3-monthly visits for additional side effect monitoring. Pregnancy and infant outcomes will be assessed after study completion pending available resources. Specifically, we will contact all participants who become pregnant 6 months after their due date or as close to that time as possible if the study has already completed. We will ask the participant to attend one additional study visit with her baby (if alive) to determine the baby's vital status, birth weight, and presence/absence of abnormalities as detected through clinical care.

Breastfeeding: According to the Kenyan Ministry of Health guidelines, PrEP may be offered to women who are breastfeeding [67]. In addition, even though PrEP is passed on through breast milk, the exposure to infants is minimal and does not pose substantial risk to infants [68].

Protection against disclosure- Given the sensitive nature of the questions asked by SMS in a potentially vulnerable population, we will conduct process measures at Month 1 and Month 12. Any concerns will be assessed on an individual basis and referrals to counseling will be made as needed. Any harms will be reported to the ethical review boards. If multiple harms are detected, study procedures and SMS content will be reviewed by the community advisory boards associated with the study.

Other factors- Throughout the study, participants will be asked a variety of questions including ones around depression and intimate partner violence (IPV). RedCap has been coded appropriately to flag a participant if they present characteristics or describe instances of one of these factors. Participants will be referred to the appropriate mental health provider or social service agency when necessary.

Data Management

Data will be entered into RedCap (Research Electronic Data Capture) with ongoing quality control checks. RedCap is a secure web-based software program for designing clinical and translational research databases. A data manager at each site will oversee all data collection by study staff and will conduct multiple quality control measures (e.g., assessing for missing data or data entry errors). The data managers will work with the principal investigators at each site to ensure comparable data.

Data analysis

Cohort characteristics and socio-behavioral data- We will use summary statistics to describe the cohort characteristics and socio-behavioral data per Table 3 above. Although the groups are expected to be similar due to randomization, we will look for differences in these characteristics that may affect our conclusions.

Aim 1

Description of enacted adherence and persistence: We will describe adherence as determined by Wisepill: number of missed doses, number of consecutive missed doses, and enacted adherence, defined as the proportion of unadjusted Wisepill openings divided by number of days during periods for which PrEP was available (i.e., picked up from the pharmacy). Enacted adherence will secondarily be produced adjusting for reported PrEP non-use or Wisepill non-use. We will also summarize the persistence of PrEP use, defined as time to the first period at which the participant purposely discontinues (as reported or based on lack of pharmacy pick up) or a 28-day period of no Wisepill openings.

$$\text{enacted adherence} = \frac{\textit{\# of device openings}}{\textit{\# expected openings based on days when PrEP was available}}$$

We will summarize enacted adherence and persistence measures, and use linear regression to quantify the effect of factors influencing adherence, and, separately, persistence, including whether participants receive or do not receive adherence reminders, changes within participants over the time, and socio-behavioral data (Table 3).

Table 5. TFV-DP concentrations in DBS

Doses/week	Median fmol/punch (IQR)
7	1,560 (1,246-2,029)
6	1,332 (1,064-1,732)
5	1,116 (892-1,451)
4	900 (719-1,171)
3	672 (537-874)
2	456 (364-593)
1	228 (162-297)

Additionally, a random sample of DBS from all study visits will be selected for analysis of tenofovir collection. Random samples of the dried blood spots will be determined and sent for processing by Dr. Peter Anderson at the University of Colorado, whose laboratory specializes in this assay. The dried blood spots will be shipped on dry ice through an experienced courier service (e.g., World Courier). While DBS are classified as nonregulated, exempt, we will adhere to CDC DBS shipping guidelines. Correlates between drug concentration and adherence will be drawn from prior models (Table 5). This adherence measure will be summarized for the cohort using descriptive statistics (e.g., median doses per week, number achieving a median of 6+ doses per week). Persistence will be determined as the time to undetectable tenofovir-diphosphate (TFV-DP). NB: We recently received a new award (R21MH1211156; Protocol 2020P002658) to analyze approximately 500 additional DBS from the MPYA cohort. This protocol is currently under review with the MGB IRB.

Assessment of effect of adherence reminders- Using enacted adherence and persistence, we will compare women randomized to SMS adherence reminders to those assigned no SMS reminders, using both intention-to-treat (i.e., as randomized to SMS versus no SMS) and as-used (i.e., enacted adherence limited to months when PrEP is collected). We will conduct similar, but independent analyses with Wisepill and DBS data. With Wisepill data, executed adherence will be calculated for each month, and all months will be compared between those with versus without adherence reminders using a random effects model to adjust for correlation within repeated adherence measures per participant and adjusting for study month. TFV-DP concentrations will be compared between SMS reminders groups using the same modelling strategy. For persistence, we will compare time to discontinuation between groups with versus without adherence reminders using a Cox proportional hazards model.

We will also perform multivariate analyses for both enacted adherence and persistence, measured both by Wisepill and by TFV-DP levels, in order to adjust the effect of adherence reminders for any baseline differences and allow us to estimate the effects of other factors influencing adherence, including socio-behavioral data (Table 3). Similarly, multivariate Cox

regression will be performed to model the effect of SMS reminders and other factors on persistence.

Aim 2

We will use descriptive statistics to understand the quantitative assessment of acceptability. Digital recordings of the qualitative interviews will be transcribed (and translated into English as needed). We will then use an inductive, content analytic approach to analyze the qualitative data. Content analysis refers to systematic process for interpreting the content of textual data through coding and category construction [69]. We will develop a coding scheme through initial review of a randomly selected subset of 33% of interview transcripts. Sections of the transcripts that appear to address concepts of analytic interest (e.g., device design, stigma) will be assigned descriptive labels, or codes. Operational definitions will be developed for the codes to create a codebook, which will be used to code the data [70]. We will use the qualitative data management computer program ATLAS.ti to code the data, which will then be repeatedly sorted and re-reviewed to identify a broader set of concepts (i.e., UTAUT model components, such as social influence). The categories will be constructed from this second, more set of concepts through assignment of descriptive labels, formulation of operational definitions, and selection of illustrative citations from the data. We will review categories and posit semantic links (e.g. causal links, chronological links) among them in the final, interpretive step of the analysis.

Analysis will follow the Joint United Nations Program on HIV/AIDS (UNAIDS) guidelines for costing HIV interventions [71] and will reflect the provider perspective. We will conduct activity-based micro-costing to estimate the incremental costs of the Wisepill and SMS PrEP adherence intervention including start-up, personnel, communication, equipment (Wisepill devices) and overhead costs. Cost data will be collected from the study budget, clinic expense reports, published information on labor costs, and staff interviews. These data will be used to complete intervention cost worksheets. Costs will be categorized as fixed or variable. Variable costs indicate which costs could change (e.g., using free communication instead of standard telephone rates) and influence the estimates from the study.

We will compare enacted adherence as measured by Wisepill to tenofovir levels in DBS. We will determine the frequency of agreement between enacted Wisepill adherence and the corresponding TFV-DP category as described above (including emtricitabine-triphosphate [FTC-TP] for daily dosing). We will also explore continuous analyses with linear regression where the outcome is TFV-DP concentration and predictor is enacted Wisepill adherence (e.g., a 10% increase) for the period preceding the blood draw.

Aim 3

Prevention-effective adherence- We will use weekly reported risk behavior to adjust the Wisepill enacted adherence and persistence of PrEP adherence in Aim 1 as follows:

$$\text{prevention–effective adherence (enacted)} = \frac{\text{\# of device openings recorded}}{\text{\# expected openings based on HIV risk during periods of intended PrEP use}}$$

$$\text{prevention-effective persistence} = \frac{\text{duration of PrEP use (i.e., traditional persistence)}}{\text{duration of HIV risk}}$$

We will summarize prevention-effective adherence and persistence measures. We will also use linear regression to quantify the effect of factors influencing weekly prevention-effective

adherence, and, separately, prevention-effective persistence, including whether participants receive or do not receive adherence reminders, changes within participants over the time followed, and socio-behavioral data (Table 3).

Correlation between risk attitudes and PrEP adherence- Based on the choices made for the series of pairs presented to them, participants will be coded in the data analysis as being risk averse or tolerant. Responses in the risk attitudes scale will also be used to construct a binary measure indicating whether a participant is risk averse or tolerant. We will then compare executed PrEP adherence and persistence, as determined by Wisepill data in Aim 1, for participants who were risk averse and risk tolerant. We will use linear regression to determine the effect of baseline risk attitude and risk perceptions over time on adherence. These models will control for participants' socio-demographic characteristics and also test whether risk attitudes are predictive of adherence when controlling for self-reported sexual behavior. Random effects for participant will be included in the linear models to account for correlation in outcomes within the same person over time.

N.B., For all analysis involving SMS data, we will assess the randomness of the missing data and adjust for any biases accordingly.

Qualitative interviews- We will use an inductive, content analytic approach (as described in Aim 2) to analyze the qualitative data on PrEP adherence, risk behavior, and risk perceptions.

Aim 4

The same inductive, content analytic approach (as described in Aim 2) will be used to analyze this qualitative data.

Aim 5

At a routine study visit, among participants who collected PrEP at the prior study visit, we will ask for 5 strands of hair from the occipital region of the scalp. This will be a one-time procedure per participant.
The hair will be stored in a foil packet at room temperature on site until it can be sent in one batch for processing by Dr. Angela Kashuba at the University of North Carolina, Chapel Hill, USA. Processing requires specialized techniques that are only available in this lab (i.e., infrared matrix-assisted laser desorption electrospray ionization mass spectrometry imaging with 100 μm resolution; see Rosen, Anal Chem. 2016 Jan 19;88[2]:1336-44). Any hair remaining after processing will be destroyed at that time.

Aim 6
Dr. Mohsen Mosleh (of Massachusetts Institute of Technology, MIT) will perform a sentiment analysis to try and assess risk behavior from text message content. All SMS and WhatsApp messages will be deidentified prior to analysis. A data use agreement will be drafted before any data is shared.

Ethical Consideration
The study protocol, site-specific informed consent forms, questionnaires and any subsequent modifications will be reviewed and approved by the IRBs at KEMRI, MGH and the UW. Subsequent to initial review and approval, these IRBs will review the study at least annually.
Study Oversight

Drs. Mugo and Bukusi will be responsible for oversight of the Thika and Kisumu sites, respectively. Drs. Haberer and Baeten will communicate frequently with Drs. Mugo and Bukusi, as well as other study staff, by email and Skype (at least weekly). Drs. Haberer and Baeten will also make study site visits approximately twice annually. All serious adverse events will be reported to the KEMRI, MGH, and UW IRBs according to their requirements (generally 7-10 days).

An independent Data Monitoring Committee (DMC) will be established to review study data every six months. Three areas will be reviewed in detail:

- The primary outcome for this study is the impact of SMS reminders on enacted adherence and persistence of PrEP adherence over a 24-month period. If the DMC finds that participants receiving adherence reminders have significantly worse adherence than those not receiving reminders, we will contact the IRBs associated with this study, as well as the NIMH, for further guidance.
- The DMC will monitor for the safety of PrEP provision individually at every clinic visit and collectively every six months. Particular attention will be paid to any participants choosing to continue PrEP during pregnancy. If serious adverse events are found to be associated with PrEP use, we will contact the IRBs associated with this study, as well as the NIMH, for further guidance.
- The DMC will review the process measures and any reports of social harms related to Wisepill adherence monitoring and/or SMS communication with participants. If >5% of participants report such occurrences, we will contact the IRBs associated with this study, as well as the NIMH, for further guidance.

Informed Consent

Written consent will be obtained for the prospective implementation of all proposed study protocols. Separate informed consent will be obtained to offer enhanced follow-up for HIV uninfected women using PrEP at the time of pregnancy. The consenting process will take place in a private room and the consent form will comprehensively provide the following information:

- Introduction to the consent process, explaining the consent form and compliance with institution policy and country laws
- Emphasis that participation is voluntary
- Nature and purpose of the study
- Explanation of study procedures
- Potential discomforts and risks, as well as plans to protect participants from these risks;
- Potential benefits
- Alternatives to participation in the study
- Confidentiality, including how data will be used and how it will be kept private
- Refusal/withdrawal, including right to withdraw consent and leave the study at any time
- Rights and complaints.

After each major section, research staff obtaining consent will pause and check for understanding -- for example, by asking the potential participant to repeat, in their own words, what "the right to refuse" means. Participants will be offered copies of the informed consent forms. Each study site is responsible for developing study informed consent forms for local use, in accordance with all applicable regulations, based on the samples provided in the Appendix. Each site also is responsible for translating the forms into local languages and verifying the accuracy of the translation by performing an independent back-translation, which will be reviewed and approved by the PIs.

All recruitment, consent, and enrollment procedures, as well as all study procedures, will be conducted in the participant's preferred language (i.e., Swahili, Dholuo, or English).

Risks

Study participants will face the following risks:

1. Risk*:* Taking PrEP may be associated with some health risks. Mild side effects may occur in as many as 1 out of 10 people and include mild kidney function (only detected by laboratory tests), fatigue, upset stomach, vomiting, loose stools, and dizziness. More severe side effects are rare and may occur in less than 1 out of 100 people; these include rash, liver function problems, serious kidney damage and allergic reaction. Small changes in bone strength have been observed, but not associated with any fractures or symptoms. PrEP may interact with some other medications.
   Protection: Participants will be advised to call or come to the study clinic if they have unexplained increased or decreased urination, weight loss, cramps, muscle pain, dizziness, excessive fatigue, nausea, vomiting, or shortness of breath. Study staff will be available 24 hours a day/7 days a week to evaluate potential side effects from taking PrEP. A medical officer from the study team will perform any necessary examinations and determine if PrEP should be stopped and/or if further testing and care is needed. Participants will be ineligible if they have baseline kidney problems or hepatitis B. Creatinine will be tested every 6 months during PrEP use to evaluate kidney function.
2. Risk: Participants may feel anxious, embarrassed, and/or worried during HIV testing.
   Protection: Testing will be normalized as much as possible and participants will receive standard counseling about HIV prevention through PrEP and other means (i.e., condoms, sexual partner reduction, and use of ART in any sexual partners who have HIV infection). Condoms will be available free-of-charge.
3. Risk: HIV acquisition may occur during study follow-up and drug resistance may develop if a participant acquires HIV during a break from PrEP and thereafter resumes PrEP.
   Protection: We will test for HIV infection at every study visit (baseline, month 1, month 3 and every 3 months thereafter up to 24 months total), consistent or greater than current CDC guidelines. Such frequent testing will decrease the potential for drug resistance to develop in the setting of acute HIV infection. If HIV seroconversion does occur, we will provide counseling for potential emotional trauma and assist with linkage to HIV treatment and care programs. We will also assess CD4 count, viral load, and drug resistance. Any seroconverters will be exited from the study and referred to the appropriate care center.
4. Risk: Some participants may experience fatigue from completing study questionnaires and interviews and/or receiving the SMS reminders (if so randomized) and/or the SMS surveys
   Protection: We will keep the questionnaires and interviews as short as possible to minimize the risk for fatigue. We will also allow participants to take breaks when needed. Participants will be advised about the number and frequency of SMS to expect. SMS will be sent at the time and day of the week preferred by the participant, thus minimizing potential for inconvenience. Participants randomized to daily SMS will be able to switch to SMS only for missed doses.
5. Risk: Privacy may be lost through use of the Wisepill device and/or SMS surveys, which may cause discrimination and/or problems in the relationships participants have with their families, sexual partners, or others.
   Protection: We will advise participants on the potential for Wisepill to attract attention and devise strategies for storage. SMS reminders will not mention HIV or medication, unless preferred by the participant. All SMS surveys will require a PIN before any questions are sent. Therefore, only study participants will be able to see them.
6. Risk: Privacy may be lost through security breaches with data collected through the study.

Protection: All hard copy data will be stored in locked cabinets at the research sites. Electronic data includes Wisepill opening events (hosted by Wisepill Technologies), SMS survey data (hosted by mSurvey), and questionnaire data (hosted on RedCap/University of Washington). All electronic data will be stored securely on password-protected databases in compliance with HIPAA standards.

7. Risk: Physical discomfort, bleeding or infection may occur from phlebotomy related to laboratory testing.
   Protection: We will only use trained nurses or phlebotomists in this study
8. Risk: Birth defects could potentially occur due to the use of TDF/FTC during pregnancy. Available human and animal data suggest that TDF/FTC does not increase the risk of major birth defects overall compared to the background rate. If a woman becomes pregnant during the study, PrEP will continue to be offered. However, we will seek additional consent for continued participation and ensure she understands the following risks and benefits of continued PrEP use. Follow-up will increase to monthly throughout the pregnancy for closer clinical monitoring.
   Protection: Women will be assessed for pregnancy at every study visit, so that any pregnancy will be detected early. Any woman found to be pregnant will be counseled on the risks and benefits of continued PrEP use during pregnancy and given the option to continue or discontinue use.
9. Risk: TDF/FTC is passed to nursing infants however these levels are below the proposed paediatric therapeutic doses with current evidence proposing that PrEP can be given to women who are breastfeeding [68].
   Protection: Women will be counselled on the risk and benefits of PrEP use during breastfeeding

Benefits

Participants will receive TDF/FTC PrEP, which is known to help prevent HIV infection, as well as routine testing for HIV, renal function, and hemoglobin levels, pregnancy assessment, and symptomatic screening for sexually transmitted infections. Counseling for HIV prevention will be provided and free condoms will be available. Study staff will also facilitate treatment for any side effects, HIV infection, or any other medical concerns that arise during the study and both study sites are Government of Kenya-approved HIV treatment centers, in addition to their prevention and research activities. Some may benefit from the information learned in the study and/or personal satisfaction from being part of research on HIV.

Care for Persons Identified as HIV-infected

This study will identify persons who are infected with HIV, either as part of the study screening process or during follow-up of enrolled participants. Study staff will provide participants with their HIV test results in the context of post-test counseling. Persons identified as HIV-infected during the study screening process or during follow-up will be actively linked to HIV care services, including primary care and antiretroviral therapy, according to Kenya national guidelines.

Treatment for Injury

Participants will be asked to inform the study 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 study clinic. If treatment is required that is beyond the capacity of the study clinic, the study doctors will refer the participant to appropriate services or organizations that can provide care for the injury. The treatment costs may also be covered by the University of Washington's discretionary Human Subjects Assistance Program (HSAP).

Study Records
Site Investigators will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. The investigator will retain all study records for at least seven years after completion of the study. Study records include administrative documentation and regulatory documentation, as well as documentation related to each participant screened and/or enrolled in the study, including informed consent forms, questionnaires, notations of all contacts with the participant, logs linking participant name to study identification number and other identifying information in study files, and all other source documents. After seven years, these documents may be destroyed.

Confidentiality
Every effort will be made to protect participant privacy and confidentiality to the extent possible. Each study site will establish a standard operating procedure for confidentiality protection; the protections described below will be implemented at all sites.

- All study-related information will be stored securely at the study site. All participant information will be stored in areas with limited access.
- Data collection, administrative forms, laboratory specimens, and other reports will be identified only by a coded number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as cell phone numbers and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems.
- Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

SMS data will be stored securely (password protected and HIPAA compliant) at mSurvey, and Wisepill adherence data will be stored securely at Wisepill Technology. This data will only be linked to a code number, not individual names.
Participants' study information will not be released without their written permission, except as necessary for oversight by:

- The Principal Investigator or designees
- Site IRBs
- Massachusetts General Hospital
- University of Washington
- United States National Institutes of Health (study funder)
- Kenya Medical Research Institute
- National Council of Science, Technology and Innovation (NACOSTI)
- Pharmacy and Poisons Board of the Ministry of Health (PPB)

Investigator roles

Dr. Elizabeth Bukusi and Dr. Nelly Mugo will serve as the site Principal Investigators for this study. Dr. Bukusi will oversee the Kisumu site, whereas Dr. Mugo will oversee the Thika site.

Dr. George Mugendi will manage all direct pharmacy-related issues. Dr. Zachary Kwena will oversee administrative aspects of the study and qualitative interviewing and analysis for the Kisumu site.

Dr. Kenneth Ngure will manage all administrative aspects of the study at the Thika site, as well as oversee qualitative interviewing and analysis.

Dr. Jessica Haberer and Dr. Jared Baeten will serve as the overall multiple-Principal Investigators for the study and will be responsible for study oversight and coordination of project management. Dr. Haberer will also lead adherence measurement and analysis, as well as assessment of HIV risk behaviors and perceptions through the SMS surveys. Dr. Baeten will provide epidemiologic expertise and cross-disciplinary guidance for HIV prevention.

Dr. Ruanne Barnabas will lead the cost and cost-effective analyses within this study.

Dr. Harsha Thirumurthy will support the assessment and analysis of risk perception among participants in this study.

Dr. Ingrid Katz will serve as the Principal Investigator for the proposed supplemental study (Aim 4) seeking to understand why eligible participants may not join the MPYA study and understand community-level influences that may be impacting young women's decisions around PrEP.

Dr. Angela Kashuba will lead the hair analysis.

Dr. Mohsen Mosleh will lead the sentiment analysis for mobile communication data (Aim 6).

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