PI: MATTHEW A. SPINELLI

Clinical Research Protocol

PREP POINT-OF-CARE BRIEF-INTERVENTION FOR ADHERENCE AMONG YOUNG MSM (PREP2-BAY)

Protocol Number:	MH122286
Version Date:	10/07/22
Investigational Product:	Point-of-Care Urine Tenofovir Test
IND Number:	Non-Significant Risk Device (FDA 10/3/2019)
Development Phase:	Pre-submission
Principal Investigator:	Matthew A. Spinelli MD, MAS 995 Potrero Ave, Ward 84 San Francisco, CA 94110
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Approval:

PI Signature (Name and Title)

10/07/22

Date

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the study team with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: MH122286

Protocol Title: PREP POINT-OF-CARE BRIEF-INTERVENTION FOR ADHERENCE AMONG YOUNG MSM (PREP2-BAY)

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Investigator Signature *Date*

Matthew A. Spinelli

Print Name and Title

LIST OF ABBREVIATIONS

Add all other abbreviations referenced in the protocol and delete any not referenced in the protocol.

AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
ICF	informed consent form
IRB	Institutional Review Board
PI	Principal Investigator
PK	Pharmacokinetic
POC	Point-of-care
SAE	serious adverse experience
SOC	Standard-of-care
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	Tenofovir
TFV-DP	Tenofovir-diphosphate
YMSM	young men who have sex with men

PROTOCOL SYNOPSIS

TITLE	PREP POINT-OF-CARE BRIEF-INTERVENTION FOR ADHERENCE AMONG YOUNG MSM (PREP2-BAY)
PI	Matthew Spinelli, MD, MAS
FUNDING ORGANIZATION	U.S. National Institute of Mental Health
NUMBER OF SITES	Study procedures performed remotely (over video chat) at University of California, San Francisco and University of Miami
RATIONALE	Young men who have sex with men (YMSM; ages 18-30 years) have rising HIV incidence in the United States. Pre-exposure prophylaxis (PrEP) is a highly effective medication prevent HIV infection, both at the individual and population level. However, in several clinical trials and demonstration projects among YMSM, a majority of participants had adherence to PrEP sufficiently low to compromise efficacy throughout the study. Unfortunately, pill-counts and self-reported adherence have limitations in this population, and therapeutic drug monitoring using previously available methods requires expensive equipment and specialized staff, meaning it cannot be implemented at the point-of-care (POC). We have developed a novel POC test to measure urine drug-levels to PrEP for the first time, providing the opportunity to target and enhance adherence counseling during a routine clinical visit. Substantial knowledge gaps on the correct counseling approach and framing of the drug-level feedback message must be addressed to use this strategy to improve adherence among YMSM. This study will use a mixed methods approach to test the central hypothesis that an intervention leveraging a POC urine bioassay to detect PrEP adherence can both target and enhance adherence counseling. Brief interventions are a motivational interviewing (MI) counseling approach with wide uptake by primary care providers for substance use prevention and medical therapy adherence. PrEP2-BAY proposes a brief intervention be used as the framework for POC drug-level feedback among YMSM using PrEP. This study will test the acceptability and preliminary impact on long-term adherence, measured through hair tenofovir levels, of the brief intervention in a pilot randomized controlled trial among YMSM. This proposed research plan has the goal of optimizing PrEP's impact through a novel adherence support intervention. The findings of this proposal will lead to a R01 application to test a POC bioassay-enhanced adherence brief intervention among YMSM in a multi-city trial, with the goal of reducing the burden of HIV among MSM.
STUDY DESIGN	This is a randomized, unblinded, open-label pilot study

PRIMARY OBJECTIVE	To test the acceptability to participants and impact on a longer-term metric of adherence among participants (assessed via tenofovir levels in hair) of implementing POC urine tenofovir testing and providing adherence feedback and motivational interview-based counseling among YMSM in the U.S.
NUMBER OF SUBJECTS	60 participants, 40 in the intervention arm and 20 in the standard-of-care arm
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Age 18-30 years. 2. Primary sexual partners are male sex at birth 3. Able to understand, read, and speak English. 4. Currently taking TDF/FTC-based, daily PrEP and planning to continue for at least 3 months 5. Willing to provide a hair sample Exclusion Criteria: 1. Any health condition that may interfere with participation or the ability to provide informed consent, including any debilitating or life-threatening conditions 2. Currently enrolled in another HIV intervention study. 3. Known to be HIV-infected.
POC TESTING	Urine tenofovir testing by lateral flow assay performed at each of 2 counseling sessions approximately 2-3 months apart
CONTROL	Participants will continue to receive standard of care at their PrEP clinic without the PrEP2-BAY adherence counseling intervention
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Participants will be enrolled in the study for a maximum of 3 months, including the enrollment period and 3 months of study follow-up.
PRIMARY ENDPOINT	• *Acceptability:* Number of participants indicating satisfied or very satisfied with the intervention • *Description:* Number of participants reporting to be "satisfied" or "very satisfied" about their overall experience on a five-point Likert scale. • *Time Frame:* 3 months
SECONDARY ENDPOINTS	• Change in tenofovir levels in hair from baseline and after 3 months of follow-up
PLANNED INTERIM ANALYSES	When approximately 50% of patients have completed all study procedures, an interim analysis of all data will be conducted by an

	independent DSMB. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	Acceptability will be the primary outcome for this pilot randomized controlled trial, and will be assessed via tabulation of survey results with graded answers in the intervention arm. Frequency distributions of the Likert scale will be summarized. Advantages and disadvantages of the bioassay enhanced brief adherence intervention will be tabulated, including manually reviewing and assigning open-ended responses under the "other" option to appropriate pre-specified categories. We will use a threshold of ≥75% reporting that they were at least somewhat satisfied with the full PrEP2-BAY intervention. After analysis of the quantitative results, we will explore mechanisms of acceptability using a sequential explanatory mixed methods approach. Qualitative interviews from the participants and providers will be performed, a debrief report will be prepared, and audio recordings will be professionally transcribed. Coding and analysis will be performed in the Dedoose cloud-based analysis platform to facilitate collaboration and comparison of coding transcripts. At least 10% of transcripts will be double-coded and compared among the analytic team and inter-coder agreement will be calculated. Inconsistent results will be reviewed by coders until consensus on codes and themes is reached. Preliminary impact on adherence as assessed by hair tenofovir levels (long-term adherence): The first adherence analysis will include use of a mixed effects logistic regression model to estimate the effect of the intervention vs. SoC arm on optimal vs. sub-optimal adherence (<700 fmol/punch) equivalent to at least 4-times weekly average dosing over the prior three months. We will include a random intercept term to account for within-person correlation over two timepoints; and time points will be included as a categorical variable to account for systematic changes over time. We will also analyze continuous tenofovir-diphosphate levels between intervention and SoC arms using a censored-mixed effects linear regression with logarithmically transformed levels of tenofovir in hair.
Rationale for Number of Subjects	We will assess sample size based on the primary endpoint of acceptability, with a threshold of ≥75% reporting that they were at least somewhat satisfied with the full PrEP2-BAY counseling intervention. We will base our estimate of acceptability on a similar intervention performed among Los Angeles MSM (PATH-PrEP),[1] which was ~>90% acceptable. Using an estimate of PrEP[2]-BAY being somewhat acceptable for 90% of the 40 individuals in the intervention

	arm, we would have 82% power to detect acceptability of 75% or less with a one-sided alpha of 0.015.

1 BACKGROUND

Adherence challenges in YMSM threaten to compromise PrEP's effectiveness. Men who have sex with men (MSM) are the only risk group in the U.S. who have not experienced decreased HIV incidence, with increasing incidence specifically demonstrated among young MSM (YMSM).[2-5] PrEP with adequate adherence is highly effective, both at the individual and population level.[6-9] A recent analysis demonstrates that, among sexually active US MSM, the proportion eligible for PrEP has jumped from 24.7% in 2015 to 45% today with an update in practice guidelines.[10] Indeed, rising numbers of U.S. MSM have initiated PrEP, with up to 50% of MSM having tried PrEP in the prior year in some districts, including San Francisco.[11,12] PrEP expansion is a critical component of the newly-launched End the HIV Epidemic campaign in the U.S.[13] However, poor adherence can compromise PrEP's effectiveness in the populations at greatest risk. Data from two U.S. PrEP demonstration projects has shown that up to 66-78% of YMSM exhibit low PrEP adherence.[14,15] Furthermore, a drop-off in adherence may herald future PrEP discontinuation, meaning that new non-adherence may be a critical period for intervention in individuals who remain at risk.[16] Although some stop PrEP due to decreasing HIV risk, many who stop PrEP remain at risk of HIV:[17] in a Montreal clinic, the HIV incidence after stopping PrEP was as high as the placebo arm of the iPrEx trial.[18]

Objective adherence monitoring effectively identifies adherence challenges. Pharmacologic metrics of adherence, where drug levels are measured in a biomatrix such as dried blood spots, plasma or hair, predict the efficacy of PrEP better than other measures such as self-reported adherence.[7,19-24] The low correlation between self-report and pharmacologic metrics was seen not just in randomized trials, but also in open label studies after the efficacy of PrEP was known.[25] Among YMSM in particular, the U.S. demonstration projects for young and adolescent MSM (Adolescent Trials Network (ATN) studies) demonstrated that self-reported adherence and electronic pill-cap monitoring (via Wisepill) both had low correlation and accuracy when compared to pharmacologic measures of adherence (drug levels in hair and dried blood spots, DBS),[25] echoing findings in other populations.[6,7,22,23,26] As a result, pharmacologic metrics of adherence are now often included in PrEP roll-out projects and demonstration studies to aid in outcome interpretation.[6,22,27,28]

Point-of-care (POC) urine adherence screening is now feasible and scalable. Previously available methods to measure drug levels for pharmacologic monitoring, no matter which biomatrix tested, required expensive spectrometry-based equipment, usually liquid chromatography/tandem mass spectrometry (LC-MS/MS) machines. Moreover, LC-MS/MS-based methods require long turn-around times and personnel with specialized training. A point-of-care (POC) method to measure drug levels in urine using a low-cost (<$2), easy-to-perform, rapid turnaround (<2 minutes) antibody-based assay has recently been developed for tenofovir disoproxil fumarate/emtricitabine (TDF/FTC)-based PrEP.[29-31] Urine collection is noninvasive and preferred among youth over blood sampling.[32,33] Furthermore, POC adherence monitoring could be performed on urine specimens already collected for gonorrhea and chlamydia infection STI screening as part of routine PrEP care for MSM,[11] requiring few changes in procedures and minimal time to implement in clinical settings.

Monitoring and feedback on adherence metrics or clinical outcomes can be used to enhance adherence counseling across multiple disease states. Patients adhere to life-saving cardiovascular and diabetes medications approximately 50% of the time.[34] Monitoring and feedback of disease outcomes is used to motivate adherence across prevention and treatment of a variety of disease states, such as prediabetes/ diabetes, prehypertension/hypertension, obesity, and heart failure (hemoglobin A1c and glucose; blood pressure recordings; weight; remote pulmonary artery pressure monitoring respectively).[35-41] Furthermore, objective adherence monitoring is now performed for several conditions;[42-47] examples include urine drug-level testing for anti-hypertensive medications in resistant hypertension, leading to subsequent improvements in medication adherence and blood pressure,[44,48] and remote monitoring of insulin delivery and carbohydrate entry with insulin infusion pumps among adolescents with type 1 diabetes, leading to improved adherence and glycemic control.[49-51] Finally, studies have utilized objective adherence monitoring, including drug-level measurement, to enhance motivational interviewing-based adherence counseling to improve adherence in severe mental illness, substance use, asthma, obstructive sleep apnea, and HIV treatment.[52-58]

Real-time adherence feedback, contextualized through counseling, can be used to interpret and motivate adherence to PrEP. In the iPrEx-Open Label Extension (OLE) study conducted among MSM and transwomen, plasma TFV levels were analyzed and feedback was provided at a later visit.[59] Many with low adherence noted that feedback encouraged them to improve their adherence, while those with high adherence felt that the result motivated them to maintain their adherence.[59] However, participants reported that adherence feedback would have less impact on their behavior without contextualization through counseling.[59] A demonstration project in Los Angeles MSM therefore included MI-based counseling with plasma TFV-level feedback. The study demonstrated high acceptability, with a trend towards improved adherence among those who received their drug-levels.[1] MSM found drug-level feedback with MI-based counseling highly acceptable, particularly when contextualized as "level of HIV protection," with participants competing to achieve the highest drug level result.[1,60] Finally in HPTN 082, a study of drug-level feedback using lab-based TFV-diphosphate monitoring in DBS among young African women on PrEP, long delays in receiving results limited acceptability, with the investigators recommending use of POC drug level testing in future studies.[61,62] Based on the evidence available, (1) drug-level feedback should be supported by counseling to contextualize results and motivate improved adherence; and (2) drug-level feedback should be provided as close as possible to the visit before recall of recent adherence and motivation waned. [59,60,63] However, POC objective adherence metrics have not been available until now.[29,30]

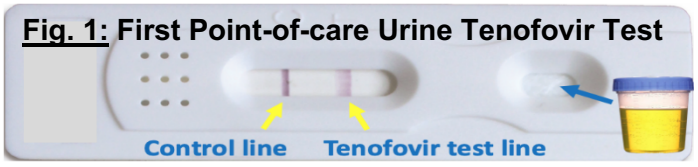
A POC bioassay-enhanced PrEP adherence brief intervention is promising and feasible for busy clinical settings. Motivational interviewing (MI)-based techniques to improve medication adherence are effective and have been embraced by primary care and HIV providers for prevention and treatment of chronic conditions.[64,65] Brief interventions are structured MI-based strategies most widely used for substance use interventions,[66] but have since been adapted to interventions to improve medication adherence. [64,66-68] To our knowledge, brief interventions have not yet been adapted to PrEP use. These brief interventions have 3 basic steps (1) screen for adherence challenges and provide adherence feedback, (2) enhance motivation, and (3) strategize and jointly set goals to improve

adherence.[66] Due to their efficacy, simplicity to learn and teach, and ability to be performed in short clinical encounters, brief interventions have received widespread uptake among primary care providers.[64,69] Brief interventions have been adapted for use with adherence monitoring (step 1 above) using the metrics of self-reported adherence and electronic pill-cap monitoring systems.[64,70,71] However, given greater accuracy of therapeutic drug monitoring (TDM)[25] to monitor PrEP adherence and the predictive ability of TDM to identify individuals at risk of HIV due to low adherence,[6,72] a brief intervention triggered and informed by a POC adherence metric could both improve adherence and prevent HIV infections.

Preliminary Data: Below, I present preliminary data on (1) adherence in YMSM at SFCC; (2) validation of the urine POC immunoassay; (3) barriers to adherence reported by SFDPH PrEP users and medical providers; and (4) a conceptual model of PrEP adherence and proposed mechanisms of behavior change via PrEP^2-BAY.

YMSM have adherence challenges and a drop-off in adherence heralds future PrEP discontinuation. In an analysis of data from the U.S. PrEP Demonstration Project,[28] conducted between October 2012 and February 2015, for which SFCC was the largest site, we examined short-term adherence to PrEP using emtricitabine-triphosphate (FTC-TP) levels in dried blood spots (DBS). FTC-TP assesses adherence in the prior week similar to urine tenofovir (TFV) measurement.[73,74] We found that 25% of participants had undetectable FTC-TP levels over the study duration, and a drop-off in short-term adherence heralded future PrEP discontinuation (adjusted hazard ratio: 6.3; 95% Confidence Interval (CI): 3.8-10.2).[16] FTC-TP levels predicted future discontinuation more strongly than long-term adherence metrics (e.g. TFV-diphosphate levels in DBS).[16] Younger (age<30) vs. older MSM had 2.5-fold higher odds of low FTC-TP (95% CI: 1.7-3.9).

The POC urine immunoassay is sensitive, specific, and highly correlated with gold-standard metrics; low adherence via the assay identified MSM at risk of future HIV seroconversion. Samples from a directly observed therapy (DOT) study (n=30) ,where TDF/FTC was given to HIV-uninfected volunteers at 2, 4 and 7 doses per week, were used to compare urine TFV levels by the novel immunoassay with levels derived from the analytic gold standard, LC-MS/MS (R01 AI143340 PI: Gandhi). The novel immunoassay was sensitive (94%), specific (99%), and the correlation was high (0.92, p<0.001).[29] A cut-off of 1,500 ng/ml accurately classified 98% of patients who took a dose within the last 24 hours as adherent. The immunoassay has now been developed, validated against LC-MS/MS concentrations with high sensitivity and specificity, and packaged into a POC test with this cut-off (**Fig. 1**).[31] Finally, in a secondary data analysis of a large PrEP demonstration project, the iPrEx-OLE study, we found that low vs. high urine TFV was associated with 14-fold higher odds of future HIV seroconversion (95% CI: 1.3-1197).[72]



Barriers to PrEP adherence in YMSM could be amenable to counseling; drug-level feedback can further enhance adherence counseling. To assess barriers to non-adherence that could potentially be amenable to counseling, we analyzed preliminary data from the PrEP Persistence Study (R01 MH109320 PI Buchbinder) using the situated-Information-Motivation-Behavioral Skills model (sIMB).[75,76] The PrEP Persistence study performed in-depth interviews among 28 PrEP users (50% age<30) and 18 PrEP providers to assess barriers and facilitators of PrEP persistence (continued PrEP use over time).[77] YMSM, in particular, reported that (1) additional *information* about addressing missed doses and adherence necessary for protection would be helpful; (2) they experienced difficulty finding *motivation* for daily pill-taking in the context of other obligations and stressors; and (3) they were "taking a daily medication for the first time," and thereby, could have used additional support in developing a pill-taking routine. In a presentation of preliminary data regarding the POC adherence test to the SFDPH Bridge HIV community advisory group (CAG), members felt that drug-level feedback would enrich adherence counseling if delivered supportively. One CAG member stated, "It shows my doctor values my protection [from HIV] so much that they are double-checking that the medication is in my body" **(Fig. 2).**

Fig. 2: Themes and illustrative quotes from preliminary data

Developing motivation for adherence is a challenge

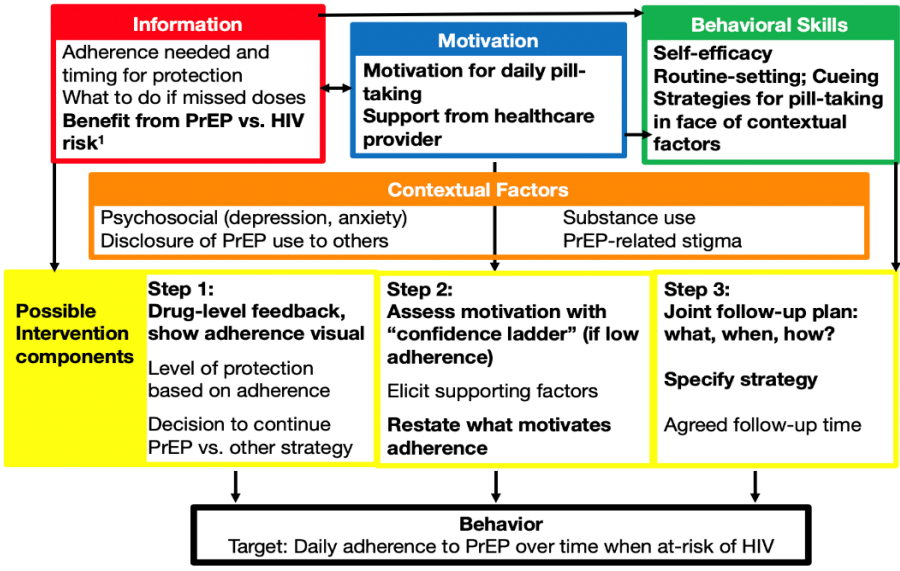
"Remembering to take the pill, on top of work, school, you know, it sometimes feels like a lot and I'm trying to stay…motivated" (age 19)

Behavioral skills support PrEP adherence

"I got into a routine, so I knew I was consciously doing it. I would put one in my coin pocket so that I had one on me…like a backup plan" (age 27)

Drug-level feedback, if real-time, is motivating

Fig. 3: Adapted situated Information Motivation Behavioral Skills (sIMB) Model for PrEP Adherence and how PrEP^2-BAY could address these factors



1.Bold indicates proposed aspects of the model that will require additional testing in Aims 1 & 2.

We have developed a preliminary conceptual model of PrEP adherence among YMSM. Guided by factors in our preliminary data and literature review, our conceptual model **(Fig. 3)** is based on the situated Information-Motivation-Behavioral Skills model[78] (sIMB; previously applied to HIV therapy[75,79] and more recently to PrEP adherence among MSM and YMSM[80-82]). We posit that the PrEP^2-BAY intervention (presented in the yellow box) can foster pill-taking by enhancing adherence information (via drug-level feedback and discussion of timing of HIV protection based on adherence[1,59]); motivation (through MI components including: (1) assessing readiness for behavioral change; (2) discussing sources of support and restating motivation to improve[83-85]); and behavioral skills (setting a

joint follow-up plan, specifying a reminder, cueing, or strategy, and agreeing on a follow-up time with the provider by phone or in-person[65,81,86]).

In summary, preliminary data reveal the need for additional PrEP adherence support among YMSM. In addition to receiving support for psychosocial challenges, YMSM report that interventions which enhance motivation to take PrEP and encourage the development of pill-taking strategies, which is the focus of PrEP^2-BAY, are likely to be successful. Prior studies of drug-level feedback to support adherence reveal a need to (1) contextualize results and motivate improvement with counseling and (2) provide information on drug levels in real-time.

2 STUDY RATIONALE

There are three important aspects that support the implementation of this pilot randomized controlled trial: (1) we will assess implementation of the first POC metric for assessing PrEP adherence objectively among MSM for the first time; (2) we will develop the first brief intervention for PrEP adherence; and (3) we will develop adherence support tailored specifically for YMSM, a population with rising HIV incidence in the U.S.

1. We will use the first POC objective adherence assessment to support PrEP adherence among YMSM. Although pharmacologic metrics of adherence have been previously used to enhance and target adherence counseling, no clinically-validated POC metric for PrEP adherence has existed until now.[29-31] This novel easy-to-perform POC urine assay will permit drug-level adherence feedback to be delivered in the context of routine PrEP clinical visits by the patient's clinician, before memory and motivation to improve on recent adherence patterns has waned. This approach has the potential to be adapted to other PrEP strategies, such as tenofovir alafenamide (TAF),[87,88] as well as to HIV treatment and the management of other chronic diseases.

2. We will adapt an adherence screening and brief intervention to PrEP. This study will adapt an MI-based brief intervention widely used in primary care settings for other disease states for use in PrEP. Brief interventions have been effective in other contexts to support medication adherence[64] and have high uptake among primary care providers.[66,89] Given that brief interventions are simple to learn and quick to perform, they have the potential for scalability and adoption across a variety of primary care and sexual health clinic settings. However, to our knowledge, no brief intervention has yet been developed for PrEP adherence.

3. We will develop an adherence tool specifically tailored for YMSM. YMSM are a population with rising HIV incidence.[2-4] YMSM have unique medical and sexual health needs in the context of negotiating independence from caregivers, exploring sexual identity, and if interested in PrEP, often taking a medication for the first time.[90] We will develop a counselling tool specifically developed for YMSM's sexual health needs and goals and enroll YMSM ages 18 and older to fully explore the tool among adolescents.

3 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective is to assess the acceptability of the PrEP2-BAY intervention over a three-month period, implemented over two counseling sessions in concert with PrEP adherence feedback among YMSM using PrEP.

3.2 Secondary Objectives

The secondary objective is to assess the impact of the PrEP2-BAY intervention on long-term PrEP adherence (using tenofovir levels in hair) over a three-month period.

4 STUDY DESIGN

4.1 Study Overview

We will conduct a 3-month pilot study of the PrEP2-BAY intervention to assess its accessibility and the preliminary impact on adherence. Participants will be randomized 2:1 to the additional PrEP2-BAY adherence intervention vs. continued standard of care at their PrEP clinic.[28] We will assess the acceptability of the intervention through surveys and interviews. Finally, we will assess preliminary impact on long-term adherence through measurement of tenofovir levels in hair compared from baseline to month 3 across study arms.

5 CRITERIA FOR EVALUATION

5.1 Primary Endpoint

Acceptability will be the primary outcome for this pilot randomized controlled trial, and will be assessed via tabulation of survey results with graded answers in the intervention arm. We will use a threshold of ≥75% reporting that they were at least somewhat satisfied with the full PrEP2-BAY intervention. After analysis of the quantitative results, we will explore mechanisms of acceptability using a sequential explanatory mixed methods approach.

5.2 Secondary Endpoint

Preliminary impact on adherence as assessed by tenofovir hair levels (long-term adherence): Change in tenofovir levels in hair from baseline and after 3 months of follow-up will compared between the intervention and standard of care arm.

6 SUBJECT SELECTION

6.1 Study Population

We will recruit 60 YMSM (ages 18-30), who are male sex at birth, through advertisements on social networks who are currently using PrEP who are willing to give urine and hair biospecimens and to enroll in the PrEP^2-BAY trial. We will obtain written informed consent from participants prior to enrollment in the study.

6.2 Inclusion Criteria

1. Age 18-30 years.
2. Primary sexual partners are male sex at birth
3. Able to understand, read, and speak English.
4. Currently taking TDF/FTC-based, daily PrEP and planning to continue for at least 3 months
5. Willing to provide a self-collected hair sample

6.3 Exclusion Criteria

1. Any health condition that may interfere with participation or the ability to provide informed consent, including any debilitating or life-threatening conditions
2. Currently enrolled in another HIV intervention study.
3. Known to be HIV-infected

7 CONCURRENT MEDICATIONS

The participant may continue to use concomitant medications as recommended by the primary PrEP provider. The study will not provide PrEP medication and will not review PrEP safety labs. The study will provide additional PrEP adherence counseling only in the intervention arm, and the standard of care arm will receive no changes to the current PrEP care that they are receiving outside of the study. Concomitant medications will not be collected as they are not expected to impact interpretation of study results.

8 RANDOMIZATION

8.1 Method of Assigning Subjects to Treatment Groups

Up to 60 eligible participants will be randomly assigned to the PrEP2-BAY adherence counseling intervention or to continue standard of care with study assessments only in a 2:1 ratio using a Stata-based computer-generated randomization scheme developed by the study statistician, which will be integrated into the Redcap study tracking forms.

8.2 Blinding

Due to the intervention involving an adherence counseling intervention, all procedures will be open-label and no blinding will occur.

9 STUDY PROCEDURES AND GUIDELINES

9.1 Recruitment and Consent:

This study involves two video (Zoom)/phone research visits for each of the 60 participants. Potential participants who are interested in participating in the study will contact the recruitment website/email address provided on recruitment notices on social networks. First, the study coordinator(s) will evaluate participants for eligibility for the study as per the inclusion criteria above. All participants will be informed of the purpose of the study, risks and discomforts involved, potential benefits, etc. Participants will be given as much time as necessary to consider study participation and are offered the opportunity to review the consent form on their own to provide adequate time to consider participation. The study team will engage the potential participant in a dialogue, using open-ended questions about the nature of the study or the experimental treatment, the risks and benefits of participating, and the voluntary nature of participation. Potential participants will be asked or shown a series of questions to assess their understanding of the study purpose, procedures, risks and benefits, as well as the voluntary nature of participation. Informed consent will occur remotely using the phone/zoom, and the signature via Docusign.

Randomization
Randomization will occur in the screening/enrollment visit after the informed consent procedures are performed. Eligible participants will be randomly assigned to the PrEP2-BAY adherence counseling intervention or to continue standard of care with study assessments only in a 2:1 ratio using a Stata-based computer-generated randomization scheme.

9.2 Hair Sample Collection

Prior to the Month 0 visit, hair collection instructions will be sent to the participant. Instructions will be provided and will be reviewed with the participant at the Month 0 visit. All participants will self-collect (at home) hair samples using a pair of scissors at study enrollment and at three months and will place them in a pre-addressed and prepaid envelope to be sent back to the UCSF HAL. Approximately 50 strands of hair will be collected (less than is lost from the scalp in a day). Home collected hair specimens will be used for measurement of tenofovir, a marker of long-term adherence to PrEP. Participants will send the hair sample via the mail to the UCSF Hair Analytic Lab for analysis. No other analyses will be performed on this sample and it will be destroyed after analysis.

	Screening/ Enrollment	Month 0	Month 3
Assess eligibility	√		
Informed consent	√		
Randomization	√		

Hair TFV Levels		√	√
POC Urine Testing (intervention arm only)		√	√
PrEP2-BAY Counseling Intervention (intervention arm only)		√	√
Online questionnaire		√	√

9.3 Urine Sample Collection and Analysis (Intervention Arm Only)

Prior to the Month 0 visit, urine test kits will be sent to all participants in the intervention arm. Urine samples will be collected by the participant before or during the video visit only for participants in the intervention arm. Urine is collected with a volume of at least 5mL into a urine collection cup provided to the participant. The urine may be collected at the beginning of the urine stream (no need for clean catch). The participant will be provided instructions on how to complete the urine test, and may discuss any questions with the research coordinator at the time of enrollment/first study visit

The participant will be provided a $50 cash or gift card reimbursement for completion of all study procedures at each visit, including the survey and urine collection. Reimbursement may be provided via an e-gift card or check.

Device for Tenofovir Testing

We obtained pre-trial consultation advice from the Food and Drug Administration's (FDA's) Center for Devices and Radiological Health (CDRH) regarding the our use of the novel point of care urine tenofovir assay in PrEP2-BAY and verified that the urine tenofovir assay is not Investigational Device Exempt (IDE) because we are returning test results to participants in the intervention arm of the trial. Per FDA regulations (21516 CFR 812), the alternative determinations applicable to our studies are either Nonsignificant Risk (NSR) or Significant Risk (SR). Under FDA 21 CFR 812.3(m), a Significant Risk (SR) device is defined as an investigational device that "Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject; Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or otherwise presents a potential for serious risk to the health, safety, or welfare of a subject." The urine assay does not meet these criteria as it is noninvasive and merely tests levels of tenofovir in urine samples. Although test results will be shared with patients, which excludes it from the exempt category, no clinical decisions will be made based on the results. While the assay will be used to measure medication adherence, the collection of adherence information does not present a potential for serious risk to the health, safety, or welfare of the subject. Therefore the urine assay meets the criteria under the IDE.

Nonsignificant Risk Medical Device study with additional details provided here:

The non-invasive urine assay will be used to detect the absence or presence of tenofovir (the metabolite of TDF) in urine to improve adherence counseling. TDF is used in HIV treatment regimens worldwide and is also the only agent (in combination with emtricitabine) approved for pre-exposure prophylaxis (PrEP) worldwide. The threshold of the assay was designed to distinguish between people who have taken TDF within the prior four days ("adherent") versus those who have not ("non-adherent") taken TDF within the prior four days. Participants who are considered "adherent" by the assay in the intervention arm of PUMA will be informed of the result and continue to receive standard adherence counseling. Participants who are considered "non-adherent" by the assay will receive enhanced adherence counseling with positive messaging (detailed below).

The antibody that was developed against tenofovir for this novel assay is highly selective. As above, the assay has been demonstrated to have very high sensitivity and specificity in our recently concluded clinical validation studies against both the gold standard of measuring drug levels, LC-MS/MS, and the laboratory-based method of performing immunoassays (enzyme-linked immunosorbent assay or ELISA). Therefore, this test has a very low rate of false positivity and we have designed it to have a very low false negative rate. In the unlikely situation of false positive results (where the results indicate "adherent" when the participant is not taking their medication), participants will continue to receive standard adherence counseling. In the very unlikely event of false negative results (where the results indicate "non-adherent" when the participant is taking their medication) the participant will receive enhanced adherence counseling (which does not meet the definition of "significant risk") in the intervention arm of PUMA. Therefore, participant access to standard adherence counseling will not be affected by a false positive result. We do not anticipate any adverse consequences for participants who receive enhanced adherence counseling due to being wrongly classified as non-adherent (a very rare event). The feedback and adherence counseling will be delivered in a supportive non-judgmental manner.

The FDA confirmed with our study team on October 3, 2019 that they approve the NSR designation of the urine device (Email dated October 3, 2019 from Kellie B. Kelm PhD, Acting Director, Division of Chemistry and Toxicology Devices | OHT7: Office of In Vitro Diagnostics and Radiological Health, Office of Product Evaluation and Quality, CDRH | Food and Drug Administration states "Since the therapies that will be given are approved, given at approved doses and the adherent patients get standard adherence counseling and the non-adherent patients get enhanced adherence counseling with positive messaging, the impact of a false negative and false positive are minimal. We would agree these studies using an investigational device appear to be non-significant risk". This designation of NSR for the urine assay by the FDA is attached. Finally, the study staff at will follow the abbreviated requirements at 21 CFR 812.2(b), which require devices to be clearly labeled as investigational, under study, and marked clearly to specify that no clinical decisions should be based on the outcome of the results. All research participants in PrEP2-BAY will signed written informed consent forms prior to participation and will cite the urine test as investigational.

9.4 Adherence Counseling Session (Intervention Arm Only)

Participants in the PrEP2-BAY intervention arm will complete two individually delivered sessions via zoom designed to enhance intrinsic motivation and self-efficacy for maintaining adherence to PrEP and addressing the intersection of substance use and HIV risk. Session 1 focuses on supporting efforts of participants to continue taking PrEP adequately to achieve protection from HIV infection. Session 2 focuses on addressing the intersection of substance use and HIV risk. Counseling sessions will also reflect on results of the urine test collected and analyzed immediately prior to the session by the participant. The counselling intervention manual is also attached.

9.5 Survey Collection

The quantitative survey will be performed and collected using Redcap software either on the participants phone or home computer. The participant identification number will be inputted into the survey to allow linking of the survey to the participant's urine sample. The survey will take 20-30 minutes to complete and contains approximately 100 questions. The survey will be completed by the participant after each research visit.

9.6 In-depth Interviews

In-depth interviews will be conducted among 20 YMSM to assess acceptability, as well as to explore mechanisms by which the intervention motivated changes in adherence. We will use purposive sampling among participants in the intervention arm, with a goal to include 15 individuals who reported adherence challenges and 5 who did not report adherence challenges, as well as achieve a racially/ethnically and geographically diverse sample of respondents. Participants will receive an additional $50 reimbursement for completing an interview.

9.7 Early Termination of Study Participation

Participants may voluntarily withdraw from the study for any reason at any time. The site investigators, with the approval of the Protocol Team, withdraw participants before their scheduled termination visit to protect their safety or staff safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities (including the OHRP and US FDA), or IRB terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records.

9.8 Risks to Participants

There is potential for loss of confidentiality in all research, but risk to participants will be minimized by training all staff in the ethical conduct of research. Data for the participants in this study will be obtained from the medical record, or from behavioral questionnaires administered (via tablet or personal electronic device).

If data related to illicit drug use were disclosed due to a loss of confidentiality, there could be risk of criminal justice involvement.

There is no substantial risk for urine collection or performance of the urine point of care test.

Participants may feel slight pulling at the scalp when using scissors to collect a hair sample.

Participants will be asked questions about their sexual behavior that may make them feel uneasy. Participants do not have to answer any question that they do not want to and can stop answering the questions at any time. Participants may also become embarrassed, worried, or anxious when being counseled about PrEP.

Strict protection of the data will be maintained through using password protected databases There may be risks of discrimination or other personal problems from being in this study. The most common risks we know about are family or friends worrying, getting upset or angry, or assuming that you are HIV-infected and treating you unfairly as a result. The study staff will take the same steps to protect participant privacy. The participant may be embarrassed or feel uncomfortable with some of the questions that are asked during the study. The participant does not have to answer any questions that make them uncomfortable.

9.10 Benefits to the Subject or Future Benefits

The participant may receive no immediate benefits from the research study. It is possible that the participant may improve their PrEP adherence behavior, which could lead to decreased HIV risk. The participant may also feel satisfaction at having contributed to knowledge within a health field.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

10 Data management and analysis

10.1. Data management

Questionnaire data will be collected online using Redcap and stored in password-protected databases. All study staff will be trained in Good Clinical Practice (GCP) and will have received additional training about maintaining confidentiality.

All assessments (questionnaires, CRFs) will be identified by only a coded number to maintain participant confidentiality. All study staff will be trained in Good Clinical Practice (GCP), Human Subjects Protection (HSP) and will have received additional training about maintaining confidentiality. Only study staff will have access to individually identifiable study data.

Audio-recorded qualitative interviews will be recorded onto digital media using a portable recorder that records directly into computer readable format and can be transferred from the recorder and stored in an encrypted volume that is then stored on a secure computer or burned on a DVD which will be stored in a locked cabinet. The data will be transferred via USB cable to a password-protected, encrypted volume created on a laptop computer. Only study personnel will have access to the password. A copy of the encrypted volume would be stored on secured servers at one of the research institutions for study team members at different research sites to access. The encrypted volume will be opened (mounted) only when it is being used for analysis purposes. At all other times, the encrypted volumes containing the data will remain closed (dismounted) and thereby encrypted. Because the data are stored in an encrypted format, the risk of unauthorized access is very low.

10.2 Statistical Analysis

Acceptability, the primary outcome, will be assessed through tabulation of survey results and in-depth interviews. We will use a threshold of ≥75% reporting that the full PrEP^2-BAY intervention was at least somewhat acceptable on a 5-point Likert scale, and then explore potential mechanisms through in-depth interviews using a sequential explanatory mixed methods approach.[91] For the interviews, we will analyze transcripts using the codebook and theoretical model developed in Aim 2, applying it to a subset of transcripts. We will seek 90% agreement among coders prior to applying codes to the entire set of interviews. We will use code reports to organize findings into emergent themes and discuss these as a group and with the HIV prevention community advisory group.

Preliminary impact (adherence) will be assessed via a long-term adherence metric, namely DBS TFV-DP levels. We will use mixed effects logistic regression for high adherence (at least 4 times weekly dosing; TFV-DP≥700 fmol/punch) comparing the interaction of adherence by intervention arm with time. Random intercepts will accommodate paired adherence levels. As an additional adherence outcome, we will examine continuous DBS TFV-DP levels using censored mixed-effects linear regression in a similar fashion.

10.3 Qualitative Data analysis

Recordings of the in-depth interviews (IDIs) will be analyzed using software for qualitative analysis. Interviewers will complete a debrief report promptly following each interview to capture results relevant to the study objectives. Debrief reports will also include an assessment of whether the interview merits additional in-depth analysis. Debriefing reports have been shown to be of sufficiently high quality to use as a primary source.[92] Debrief reports and selected transcripts will be reviewed for emergent themes and results relevant to the study objectives. Team members will create summary reports based on this analysis for use in providing feedback and suggestions in achieving study goals, and to contribute to manuscript development. Debrief reports will be reviewed promptly in order to provide feedback and suggestions for subsequent interviews..

11. Safety Monitoring and Clinical Data Review

11.1. Safety Monitoring and Clinical Data Review

A multi-tiered safety review process will be followed for the duration of this study. Close cooperation between the PI, investigators, study coordinator, statistician, and other study team members will be necessary to monitor participant safety and to respond to occurrences of toxicity in a timely manner. The research team will have regularly scheduled meetings during the period of study implementation, and additional ad hoc calls will be convened if required.

11.2 Reporting Requirements for this Study

This study will follow safety reporting requirements as outlined by the UCSF IRB. All adverse events that are definitely, probably, or possibly related, AND serious or unexpected, will be reported to the IRB within 5 working days of PI awareness. All AEs meeting these criteria will be reported to the study PI within 48 hours of site awareness, to allow ample time for IRB notification. The NIH Project Officer will be provided copies of these reports at the time of IRB reporting and informed of any actions taken by the IRB as a result of such events.

Serious adverse events are any AEs that result in any of the following outcomes:

- Death,
- Life-threatening adverse experience,
- Inpatient hospitalization or prolongation of existing hospitalization,
- Persistent or significant disability/incapacity,
- Congenital anomaly/birth defect, or cancer, or
- Any other experience that suggests a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above

Unexpected AEs are those that exceed the nature, severity or frequency described in the current IRB Application including the protocol, consent form and investigator brochure (when applicable). An unexpected AE also includes any AE that meets any of the following criteria:

- Results in subject withdrawal from study participation,
- Due to an overdose of study medication, or
- Due to a deviation from the IRB approved study protocol

In addition, all SAEs will be reported to the study team within 72 hours of recognition by study staff.

11.3 Data Safety Monitoring Board (DSMB)

We will form a dedicated DSMB for PrEP2-BAY. Membership will include a researcher with experience in conducting trials to address PrEP uptake and persistence; a clinician with expertise in HIV treatment and prevention, including PrEP adherence measures; a biostatistician with expertise in PrEP intervention trials; and a community member.

The purpose of the DSMB will be:

- To ensure the safety of trial participants
- To preserve validity and integrity of research data
- To facilitate the availability of timely as well as reliable findings to the broader clinical community

The DSMB will meet by teleconference every 6 months, and more frequently as needed. No DSMB members will be permitted to have any financial interest related to the outcome of the trial. Individuals on the DSMB will be required to disclose in writing to the NIH project officer of any potential conflicts of interest, actual or implied.

The DSMB will review the PrEP2-BAY protocol prior to launch of the trial, and monitor follow-up to identify unexpected events that change the known risks to participation. The DSMB may make recommendations to continue, modify, or terminate the trial based on their findings. Recommendations will be made in writing to the PI and the NIMH Program Officer.

The DSMB report will contain a brief description of the trial, baseline socio-demographic characteristics of participants (total and by group), status of recruitment, retention, and disposition of study participants (total and by group), description of any quality assurance or regulatory issues, a report of AEs and SAEs (including social harms) (total and by study group), and the status of outcome data. Protocol compliance will be evaluated by reviewing: the expected recruitment rate, study drop-outs and reasons for leaving the study, data quality assurance reports, overall data flow procedures, questionnaires completed and CRFs entered; protocol deviations; protocol violations; missing data; staff omissions; subject refusal to provide data. The outcome data report will include outcome data analyzed by group, with calculation of p-values at the direction of the DSMB, and include all primary and secondary outcome variables.

11.4 Social Impact Reporting

Although the study site will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that a negative social impact may result (e.g. participants could be perceived as being HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. In the event that a participant reports a negative social impact, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. Staff will provide such care and counseling in accordance with standardized guidance.

12. Laboratory Specimens and Biohazard Containment

Hair specimens will be collected at screening and at the month 3. Specimens will be collected via home mailer and shipped to the UCSF Hair Analytical Laboratory. There is no risk of bloodborne pathogen transmission via hair samples.

13. Administrative Procedures

13.1. Training

Recruiters and staff who collect data will complete CITI GCP and HSP training, as well as protocol specific training. Trained qualitative interviewers will conduct the in-depth interviews and code the responses.

13.2. Confidentiality

All staff are required to sign an oath of confidentiality and receive annual training on maintaining confidentiality, privacy, and handling questions about study participants from friends, employees, and insurance companies. Study staff will discuss any privacy concerns the participant may have regarding the need to contact them, via phone or e-mail, and contact methods will be tailored accordingly. A participant’s involvement in this study will not be divulged without the subject’s written permission, except as necessary for monitoring by the sponsor and/or its contractors; other government and regulatory authorities, and/or the local IRBs.

Information collected from subjects will be handled in the most confidential manner possible. All data will be coded by a subject number. Personal identifier records will be kept in a password protected computer files and double-locked cabinet at the study site, and any forms with identifying information will be stored separately from other study data. Digital audio recordings will be encrypted and stored on password protected computers until destroyed. Transcripts of the recordings will be transcribed in such a way as to not have any identifying information present. Interviews will take place by

videoconferencing (zoom). Questionnaires and surveys will not include any personal identifiers.

13.3. Informed Consent

The informed consent process will conform to local IRB consent standards. Informed consent will be obtained electronically via DocuSign, before any study procedures are initiated. Potential participants will receive a copy of the informed consent form and the Experimental Subject's Bill of Rights, and a study staff member will offer to review the form with the participant, and answer any questions the participant may have.

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