Connecting Youth and Young Adults to Optimize PrEP Adherence and Care: Testing the Efficacy of the PrEP iT! Intervention

Short Title: PrEP it Together

Funding provided by:
National Institute of Mental Health (NIMH)
of the U.S. National Institutes of Health (NIH); R34MH116878

Regulatory/Ethics Review:
San Diego State University Human Research Protection Program (HRPP): **# HS-2019-0291**

HHRI HIV Research Program Protocol # PCC-012

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Protocol Date: 14-SEPT-2020
Revision Date(s):
Version Number: ***v1.0***
Approval Date: TBD

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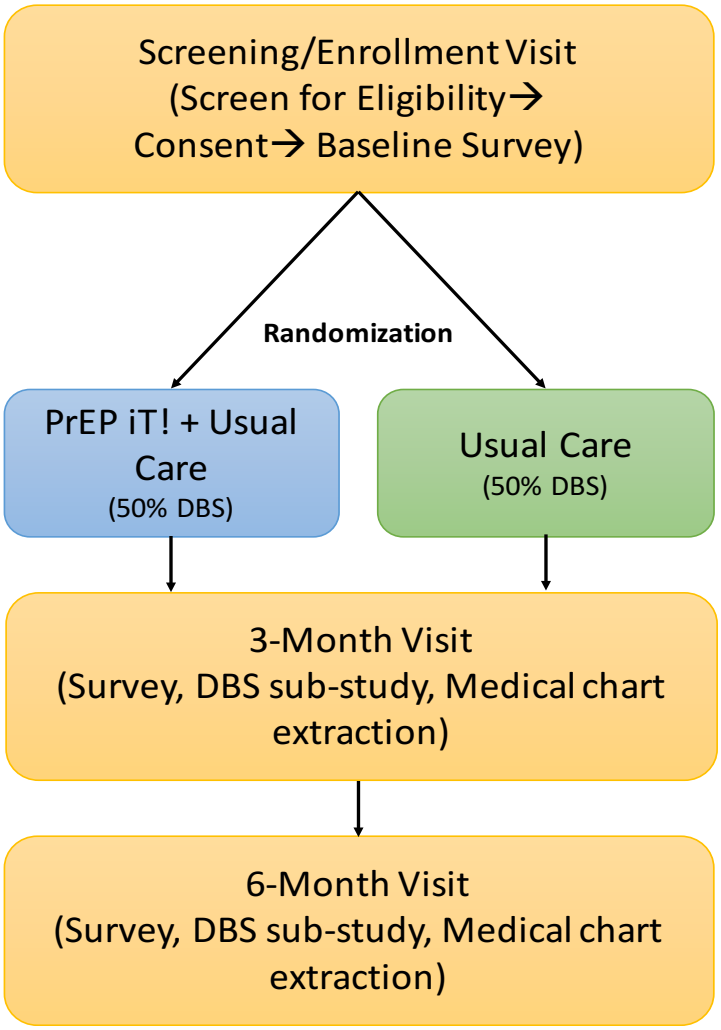
i. LIST OF ABBREVIATIONS

AE:	Adverse Event
ARV:	Antiretroviral
ART:	Antiretroviral Therapy
CAB:	Community Advisory Board
CDC:	Centers for Disease Control
CFR:	Code of Federal Regulations
CRF:	Case Report Form
CLIA:	Clinical Laboratory Improvement Amendments
CONSORT:	Consolidated Standards of Reporting Trials
CQMP:	Clinical Quality Management Plan
DAIDS:	Division of AIDS
FDA:	U.S. Food and Drug Administration
FTC:	emtricitabine
FTC-TDF:	emtricitabine-tenofovir disoproxil fumarate (or 'Truvada')
FTC-TAF:	emtricitabine-tenofovir alafenamide (or 'Descovy')
FWA:	Federalwide Assurance
GCP:	Good Clinical Practices
HH:	Hennepin Healthcare
HHRI:	Hennepin Healthcare Research Institute
HHS:	U.S. Department of Health and Human Services
HIV:	Human Immunodeficiency Virus
HSRC:	Human Subject Research Committee
IC:	Informed Consent
ICF:	Informed Consent Form
ICH:	International Conference on Harmonization
IoR:	Investigator of Record
IRB:	Institutional Review Board
ISO:	International Organization for Standardization
LoA:	Letter of Amendment
MOP:	Manual of Operating Procedures
MSM:	Men who have sex with men
NIAID:	National Institute of Allergy and Infectious Diseases
NIH:	National Institutes of Health
NIMH:	National Institute of Mental Health
OHRP:	U.S. Office for Human Research Protections
PI:	Principal Investigator
PK:	Pharmacokinetic
PrEP:	Pre-exposure prophylaxis
PrEP iT!:	the 'PrEP it together' mobile intervention
SAE:	Serious Adverse Event
SDSU:	San Diego State University
SOP:	Standard Operating Procedure
STI:	Sexually Transmitted Infection
SUSAR:	Suspected, Unexpected Serious Adverse Reaction
TDF:	Tenofovir disoproxil fumarate
TAF:	Tenofovir alafenamide
WHO:	World Health Organization
YMSM:	Young men who have sex with men

ii. PROTOCOL SUMMARY

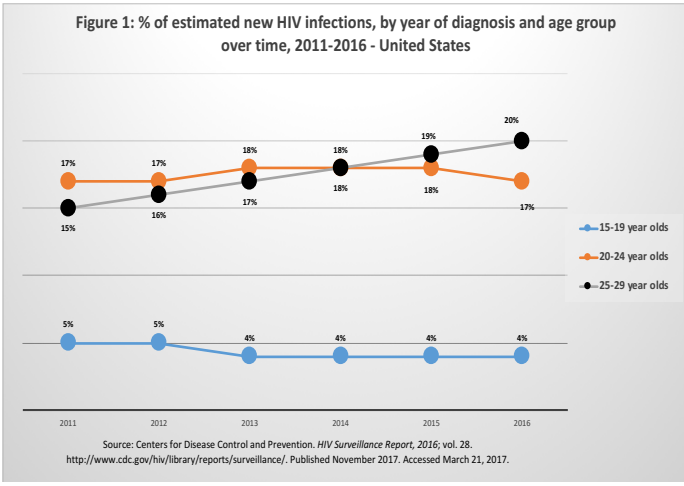
Category	Description
Full Title	Connecting Youth and Young Adults to Optimize PrEP Adherence and Care: Testing the Efficacy of the PrEP iT! Intervention
Short Title	Prep it Together
Clinical Trial Phase	Phase 2
IND Sponsor	N/A
Conducted By	San Diego State University Hennepin Healthcare Research Institute
Lead Investigators	Keith Horvath (PhD), Jason Baker (MD, MS)
Sample Size	85 participants (5 Usability, 80 trial)
Study Population	Younger men who have sex with men (MSM), ages 18-29 years
Accrual Period	Anticipated enrollment 1 year
Study Design	Randomized Clinical Trial
Study Duration	6 months
Intervention	PrEP mobile intervention vs. Usual Care
Primary Objective	Feasibility (via recruitment and study retention) and acceptability (via System Usability Scale) of the PrEP iT! intervention
Key Secondary Objectives	Adherence, as self-reported in the mobile intervention Adherence, objective as measured via TFV blood levels Linkage and follow-up with PreP medical care Stigma-related concerns

iii. GENERAL STUDY DESIGN SCHEMATIC:



1. INTRODUCTION

1.1. Background and Rationale



Over one million people live with HIV in the US, with 40,324 estimated number of new infections in the US and its six dependent areas in 2016.[1] Young men who have sex with men (YMSM), especially those who are Black and Hispanic/Latino, are disproportionately impacted by HIV. In 2016, persons 15-29 years old accounted for 41% of new HIV infections in the US (**Figure 1**), of which 82% are attributed to male-to-male (including MSM/IDU) sexual contact.[1] Among this group of adolescent and young adults, 25-29 years olds have the highest rates of HIV infection among any age group, having risen from 30.0 to 34.7 per 100,000 between 2011-2016.[1] When restricted to new HIV infections among MSM (including MSM/IDU) in 2016, 40% were among Hispanic/Latino and black MSM ages 20-29 years.[1] The US National HIV/AIDS Strategy emphasizes the need for HIV prevention specifically among MSM, and to implement behavioral approaches that "take into account the complex interplay of individual behavior, social structure, and biomedical factors on continuum of care outcomes."[2] Similar recommendations were made by the National HIV/AIDS Policy and the CDC.[2-4] The *PrEP iT!* intervention studied here attempts to address these recommendations.

PrEP is highly effective at preventing the acquisition of HIV infection. In 2012, daily oral emtricitabine-tenofovir disoproxil fumarate (FTC-TDF), or 'Truvada', was approved by US FDA for PrEP, based on randomized controlled trial (RCT) data demonstrating efficacy for HIV prevention (**Table 1**).[5-10] These findings prompted recommendations by the IAS-USA and CDC for PrEP provision.[3, 4] Since that time, the combination of FTC plus tenofovir alafenamide (TAF), or 'Descovy', was found to be non-inferior to FTC-TDF[13] has been approved by the US FDA for PrEP. Additional strategies beyond daily PrEP are being studied. For example, the use of PrEP before and immediately after a sexual exposure (or 'on-demand' PrEP) was shown to reduce risk for HIV infeciton by 86%.[11]

Table 1: Summary of PrEP Trials and Prevention Rates

STUDY	Population	Risk Reduction in HIV Infection	Study Drug
iPrEx[5]	MSM	**44%**	PO Truvada
TDF2[6]	Heterosexual	**62%**	PO Truvada
Partners PREP[7]	Sero-discordant couples	**67%** **75%**	PO tenofovir PO Truvada
FemPREP[8]	Women	**No efficacy**	PO Truvada
VOICE[9]	Women	**No efficacy**	PO TFV or Truvada
Bangkok[10]	IVDU	**49%**	PO daily tenofovir
iPERGAY[11]	MSM	**97%**	'on demand' Truvada
PROUD[12]	MSM	**86%**	PO Truvada
DISCOVER[13]	MSM	**Non-inferior**	PO Truvada vs Descovy

The effectiveness of PrEP for HIV prevention requires adherence and retention along the PrEP Continuum of Care.[14] In the iPrEx study, new HIV infections were reduced by >90% among participants with detectable drug in blood, compared to a 44% reduction overall in intention to treat analyses. Refinement through pharmacologic analyses show a risk reduction of 76% for two doses per week and 96% for four doses per week.[15] Furthermore, in two studies where PrEP was not efficacious (Table 1),[8, 9] adherence and drug levels were much lower. Ultimately, as options for PrEP regimens and dosing strategies evolve and choices increase, it will nevertheless remain critical that patients continue to adhere to PrEP during periods of high risk in a specified manner that has been proven to be efficacious.

Young MSM on PrEP face traditional and stigma-related adherence barriers, which have slowed PrEP scale-up for YMSM and may limit the public health impact. Data from 2 PrEP trials with YMSM by Hosek and colleagues[16, 17] inform this study. In ATN 110,[17] 200 18-22 year olds were provided PrEP and followed for 48 weeks, with monthly visits through week 12, followed by quarterly visits thereafter. Protective drug levels ($\geq$4 doses per week) decreased from 56% at week 4 to 34% at week 48, with a noticeable drop-off when quarterly visits were implemented. The ATN 113[16] trial showed that among 76 15-17 year olds, protective adherence decreased from 60% at week 4 to only 28% by week 48. Similar to ATN 110, the drop in protective TFV levels was apparent after youth transitioned from monthly to quarterly visits. Youth in both studies reported typical adherence barriers (e.g., pill size, too busy, forgetting, change in routine). Additionally, they reported PrEP-related stigma concerns, such as worrying that others will think they are HIV+ or find out that they are having sex with men. This study protocol will evaluate the PrEP-iT mobile intervention as a youth-specific strategy to improve PrEP adherence and retention in PrEP care.

Summary of the scientific premise:

- YMSM are at the highest risk for HIV acquisition in the US, and are the focus of this study.
- PrEP is a highly effective prevention strategy, but requires adherence and retention to care.
- YMSM require frequent, developmentally-appropriate supports that address traditional and stigma-related barriers to achieve full PrEP adherence and retention in care

1.2. Objectives and Hypotheses

The long-term goal of this research is to create an effective and sustainable program to support PrEP adherence and retention in PrEP care among YMSM. The intervention in this study is a mobile device peer support platform tailored to YMSM, called "*PrEP it Together" (or PrEP iT!)*. Grounded in the principles of the Technology Adoption Model[18] and the Information (**I**), Motivation (**M**), and Behavioral Skills (**B**) model,[19, 20] the primary components of *PrEP iT!* are: PrEP adherence, appointment and sexual activity self-monitoring; tailored PrEP information; text messages for PrEP adherence and healthcare appointments; and an "ask the expert" feature. The objective of this study protocol is then to evaluate the PrEP iT! intervention experimentally, to characterize the potential utility and efficacy as a strategy for improving PrEP adherence and retention in care among YMSM at risk for HIV infection.

Primary Aim: Conduct a pilot randomized controlled trial to assess the feasibility, acceptability and preliminary impact of the *PrEP iT!* mobile intervention for YMSM

Hypotheses: The PrEP iT! intervention will be a feasible strategy to implement and highly acceptable among YMSM using PrEP. The intervention will also improve adherence to PrEP dosing, timely engagement in routine PrEP medical care, and reduce stigma-related barriers.

2. METHODOLOGY

2.1. Trial Design

We propose to evaluate the feasibility, acceptability and preliminary impact of *PrEP iT!* using a randomized controlled trial (RCT) study design. Young men who have sex with men (YMSM) recently (re)initiating PrEP will be randomized to receive either *PrEP iT!* plus usual care or usual care alone, and followed for 6 months. Assessments and study data collection will occur at entry ('baseline'), and then again at 3-and 6-months in-person or online via an online HIPPA-complaint teleconferencing platform such as Zoom. A total sample size of n=80 participants will be enrolled in this pilot study phase.

The purpose of this pilot study phase is to inform the development of a subsequent clinical trial to more definitely establish the potential benefit of the *PrEP iT!* mobile intervention. A RCT study design was chosen to most closely mimic the procedures and process of the larger efficacy trial by identifying unforeseen challenges.

2.2. Study Population

The target population will include YMSM (age 18-29) who have started PrEP for HIV prevention. Participants will either be initiating PrEP for the first time, or re-initiating PrEP after having not taken PrEP for ≥3 months, or self reported imperfect PrEP adherence. This study will focus on cis-gender (i.e., are assigned male at birth and currently identify as male) MSM. Transgender women are also a priority risk group for HIV prevention initiatives, but stigma and barriers to PrEP adherence likely differ from cis-gender MSM. In addition, the sample size of this pilot study precluded the ability to conduct meaningful subgroup analyses on transgender participants. Additional detailed eligibility criteria are listed below.

2.3. Eligibility Criteria

Inclusion criteria:

1) Prescribed PrEP by a healthcare provider;
2) Self-reported 18-29 years of age;
3) Assigned male at birth;
4) Current male gender identification;
5) Gay, bisexual or other non-heterosexual identity or has had sex with a man in the past year;
6) HIV negative (HIV negative test in the past 3 months)

7) Either started or restarted PrEP in the past 30 days or started PrEP more than 30 days ago and self-reports not always taking PrEP in the past 30 days;
8) English-speaking (as the intervention will be built in English);
9) Able to meet with project staff at baseline and follow-up visits;
10) Regular access to SMS or the internet, either through a mobile device, tablet computer, and/or desktop or laptop computer.

Additional exclusion criteria:

- Not prescribed PrEP by a healthcare provider;
- HIV positive (by a reactive HIV antibody or detectable HIV RNA level);

2.4. Recruitment

Participants will be recruited from clinical settings where PrEP care is delivered as well as via social media advertisement that targets potential PrEP users within the MSM community. In Minneapolis, specific settings that will be a focus of recruitment efforts include the Hennepin County Public Health clinic ('Red Door' clinic), the Hennepin Healthcare HIV clinic ('Positive Care Center') as well as HIV prevention organizations within the Twin Cities (e.g., Youth AIDS Project). Recruitment and enrollment of study participants will be concurrent with their PrEP clinical visits when possible, or online via a HIPPA-compliant teleconferencing platform such as Zoom. Whether recruited within these facilities or via social media advertisements, HHRI research staff will interview candidate participants to assess for potential eligibility. Following this, interested participants will undergo informed consent procedures, both verbal and written, followed by screening visit to verity eligibility. Additional detail outlining participant recruitment, including digital and paper recruitment materials, is provided in the study MOP.

2.5. Study Intervention (PrEP-iT! mobile intervention)

- PrEP Adherence, PrEP Appointment, and Sexual Activity Self-Monitoring: Participants will be able to report their daily adherence to PrEP and their healthcare attendance through a simple interface in the app homepage. Participants will regularly receive messages that reflect their level of PrEP adherence. For example, if they have taken PrEP 5 days in a row, they would get a message stating "Great job [username], you've taken PrEP 5 days in a row!". If, for example, they missed their PrEP doses for 2 days, a message would appear stating, "Looks like you haven't taken PrEP in a few days – tell us reasons why?" The participant would then see a list of the most common reasons he may be missing doses, including:
  - I forgot
  - I didn't have it on me when I usually take it
  - I ran out of PrEP
  - Having trouble paying for it
  - I'm not having sex
  - I was traveling and didn't bring it
  - I was drinking or using a drug and forgot to take it
  - I'm in a monogamous relationship
  - I don't like the way it makes me feel

The participant would then be provided a list of resources in the app that addressed that barrier.

Participants will be able to input their next PrEP healthcare appointment and have the option of placing that appointment on their calendar. They are given the option to customize how that appointment will appear on their calendar to protect their confidentiality. Finally, participants will be given the option to self-monitor their sexual activity. If they choose to, then this interface will appear below the PrEP adherence interface (if they do not activate this option, then they will not see it). The sexual activity self-monitoring will use the same simple interface as the adherence self-monitoring.

- *PrEP iT!* Tips: We will develop *PrEP iT!* "tips" to provide YMSM with information, motivation, and behavioral skills related to PrEP knowledge, attitudes, and stigma profile; PrEP healthcare engagement; and sexual risk. As we have done in prior studies, research staff created approximately 150 "tips," which are pieces of content in the form of text, videos, GIFs, and links. Participants can browse these tips through a simple interface or through a key word search.
- Text Messages for PrEP Adherence and Healthcare Appointments: Text messages will be sent as reminders to log into the site when a participant hasn't done so in the prior week. Text messages are generic to minimize any potential disclosure. If the participant chooses, they may also receive a generic SMS reminders to attend their upcoming appointment.
- Ask the Expert: Participants will be able to send an anonymous question within the *PrEP iT!* app (that will send an email to research staff with no identifying information about the user) about PrEP, PrEP care, sexual health, or other health topics relevant to their wellbeing. Research staff will triage the question to the investigator with expertise in that area who will respond within 48 hours by posting the anonymous question and the expert answer to the community wall so that all users to may view it. This feature is similar to the "Ask the Expert" feature commonly used on health websites.
- Levelling Up: Gamification components will be used to motivate participants to engage with *PrEP iT!* Users will move to higher levels as they interact with PrEP iT! With each new level, users will be able to unlock new features (e.g., color themes) to motivate them to engage with *PrEP iT!* Users will be able to see what level they are currently at and how many points they need to reach the next level in the profile area.

Possible risks associated with the PrEP iT! mobile intervention, or study participation more broadly, are outlined with the study ICF (appendix A).

2.6. Outcomes

Primary Outcome

- Feasibility
- Acceptability

Secondary Outcomes

- Utilization of individual features of mobile intervention
- Adherence, self-report to PrEP
- Adherence, objective via tenofovir diphosphate (TFV-DP) levels in dried blood spots (in 50% of participants)
- Clinical visits for PrEP care

- Stigma-related barriers
- HIV seroconversion

2.7. Study Visit Procedures

Study candidates, whether referred by PrEP clinic staff or self-referred from recruitment materials, will be assessed for potential eligibility through a self-directed online screening survey, or through research staff who can assess eligibility by telephone or by assisted participants with completing the online survey. All interested candidates will then undergo a study visit, during which their eligibility will be confirmed followed by informed consent. After consent procedures, participants will complete a computer-assisted baseline survey and complete enrollment visit procedures.

After enrollment, participants are randomized 1:1 to either the intervention (PrEP iT! + usual care) or control (usual care) arm. All participants will be provided usual PrEP educational information encouraged to attend their regular healthcare visits. Participants randomized to the intervention arm will be guided through setting up their user account and user profile, provided with basic training on how to navigate and use intervention components, and given the opportunity to ask questions.

Both control and intervention participants will be offered an optional blood draw at their enrollment and 6 visits. Blood samples and the information collected may be used by the study sponsor, its research partners or companies for additional testing of Tenofovir and metabolites. At the end of this study, these samples may be held in storage by Hennepin Healthcare Research Institute for up to 20 years. After 20 years, the samples will be destroyed. Participants can request that their samples be destroyed at any time by writing to investigators.

YMSM will undergo a follow-up assessment at both 3- and 6-month visits. The follow-up visits include ascertainment of clinical information that was conducted as part of usual PrEP care (e.g., repeat testing for HIV and other STIs), completion of a computerized survey assessment, and collection of a dried blood spot specimen for the TFV-DP analyses. If visit is in person, a finger prick will be done to collect several drops of blood. If visit is online, a self-collection kit will be mailed to participants home where they collect blood by pricking their finger, and then mailing the blood sample to a lab in a pre-paid mailer. See Clinical Management below for procedures for procuring care for diagnoses or disease events that are identified during study conduct.

A complete list of study visit procedures, data collection, and evaluations performed at Screening, Enrollment and/or Follow-up study visits is listed below in **Table 2**.

Table 2: Study Visit Procedures and Evaluations

Measure	Screening Assessment	Enrollment Visit	3 Month Visit	6 Month Visit
RCT online screener	**X**			
Informed Consent		**X**		
Verification of eligibility		**X**		
Randomization		**X**		

Participant and clinical data				
Demographic information	**X**			
HIV status	**X**	**X**	**X**	**X**
PrEP medications and strategy		**X**	**X**	**X**
Medical history		**X**	**X**	**X**
Clinical labs		**X**	**X**	**X**
Disease or clinical events		**X**	**X**	**X**
Surveys Items/Scales				
Demographics and Baseline Characteristics		**X**		
Technology Use Questions		**X**	**X**	**X**
eHealth Literacy		**X**	**X**	**X**
HIV Negative Cascade		**X**	**X**	**X**
U=U Questions		**X**	**X**	**X**
Substance Use		**X**	**X**	**X**
Sexual Risk Behavior		**X**	**X**	**X**
Mental Health		**X**	**X**	**X**
Social Support		**X**	**X**	**X**
Technology Use Questions			**X**	**X**
Intervention Acceptability			**X**	**X**
Exit Interview				**X**
Specimen collection				
Dried Blood Spot Collection		**X**	**X**	**X**
Blood for Storage		**X**		**X**

2.8. Participant Retention

Every attempt will be made to complete follow-up study procedures and data collection for all randomized participants. Our retention process will leverage the use of multiple contact methods - including telephone calls, text messages, e-mail reminders, and social media – and ask permission for the use of each.

3. DATA COLLECTION AND CLINICAL MANAGEMENT

3.1. Case Report Forms

All participant and clinical data collected will be entered into Qualtrics and/or web-based case report forms (CRFs) using REDCap (Research Electronic Data Capture) open software. REDCap provides a secure, web-based, flexible system to enter data within CRFs including real time validation rules that also facilitates audit trails and reporting. This data management system is fully compliant with all GCP and U.S. DHHS OHRP, NIH, FDA, ICH, and HIPAA regulations. The REDCap study database will be stored on secure servers at the Hennepin Healthcare Research Institute. Qualtrics data will be securely stored on servers at San Diego State University.

Each participant will be assigned a participant identification (PID) number, which will be used as the sole identifier within CRFs and the study database. No data will be collected or stored on any individual participant devices. A key linking the PID to identifying information on the participant will be stored within the primary study materials, and kept in a secure location (i.e., locked storage behind a locked door) within HHRI. Paper source documentation will also be collected as needed to assist with visit conduct, and verify eligibility and clinical data as part

of study procedures. All paper source documentation and study visit CRF information will be stored within the participant study binder, and kept in a secure location.

The original paper study data records will be archived for 7 years following completion of the study. Plasma from the optional blood draw will be stored for 20 years.

3.2. Clinical Data Collection

Data related to participant clinical characteristics, including eligibility criteria and follow-up visit evaluations, will be obtained via history and verified via the electronic medical record (EMR). Permission to access clinical and protected health information (PHI) is included within the ICF (Appendix A). For participants receiving PrEP care at Hennepin County Public Health clinical and Hennepin Healthcare, the same EMR system is used for all clinics that can be accessed by HHRI research staff. For participants receiving PrEP care at other outside community clinics, a release of information will be obtained to access clinical source documentation. In addition, direct access of health records by participants (e.g., via MyChart or other patient access software) may be used to verify clinical health data that is entered into study database CRFs.

3.3. Survey Data Collection

All computer-assisted surveys will utilize Qualtrics, a HIPPA-compliant platform. Survey data collection may occur on a desktop/laptop or tablet computer, and will be housed on the San Diego State University server.

3.4. Data Collection via the PrEP iT! Web Application

The research team has developed a sophisticated back-end content management system (for content creation and editing), as well as a real-time intervention use data capture and reporting system, to assess how PrEP iT! is accessed and what components are used most often to inform future optimization.

Data reports will include the following:

TBD information about each report and the variables that will be assessed in each report.

Data will be housed on physical servers residing in a secure facility that is audited to SOC3 SSAE-16 standards. Data security protections include:

Server

The website databases and application will reside in a single tenant “private cloud” under the exclusive control of our partner, Radiant Digital. The website databases and application will be logically segmented in virtual private servers, ensuring that data may not be accessed by applications outside the context of the project.

Data Privacy

To promote confidentiality of participant data, each participant will be assigned a study PIN login to the program during the evaluation. Users will access the system via this study PIN and an associated user-selected password. All communication between the app and server-side systems will be conducted using secure methods (e.g., SSL). All server-side systems will

utilize a database-level encryption scheme to store data. No data will be collected or stored on any individual participant devices.

Data Classification
The system will collect a single identifier-the user's phone number-for the purpose of sending out SMS texts as part of the intervention. Thus, we anticipate that the program will be classified as collecting PII (Personally Identifiable Information).

3.5. Dried Blood Spots (DBS) for Tenofovir Diphosphate (TFV-DP) Levels.
Tenofovir (TFV) is a primary component of the PrEP medication, and TVF drug levels will be assessed in a random subset of participants (≥50%) to evaluate objective adherence. TFV is phosphorylated in cells to TFV-diphosphate (TFV-DP), which is both pharmacologically active (in relevant cells) and demonstrates a longer intracellular half-life compared with the parent drug in plasma. The presence of TFV-DP in red blood cells (RBCs) can be measured within a dried blood spot (DBS) analysis. TFV-DP levels in DBS will be measured by Dr. Peter Anderson's Laboratory using established standardized protocols.[21] Through this methodology, estimates can be made of the number of TDF doses taken over a 7-day period.

Blood collection for DBS sample acquisition can be done via venipuncture or fingerstick. Blood drawn by venipuncture should utilize an EDTA collection tube, and processed within 60 minutes of collection by applying the blood directly onto the designated circle on the collection card. Blood from finger stick should be spotted on the card immediately by touching the blood drop to the card without pressing the finger to the card. After blood is applied, the cards are air dried for several hours (overnight is acceptable) and then stored in low gas-permeability bags. DBS card specimens are then stored under frozen conductions (20°C, or -80°C) until analysis. Specimens will be labeled with PID, study, date, and visit type, but will not include any individual identifying information. Please see the study MOP for additional step by step details on blood collection, processing to DBS cards, storage and shipping instructions.

3.6. Blood Collection for Plasma and Serum Storage
Participant blood samples will be collected by venipuncture into an EDTA and Serum Separator collection tube. For efficiency, all plasma and serum specimens will be processed in the same manner. After blood draw procedures, specimens will be centrifuged within 60 minutes of collection, with plasma or serum aliquoted into 2.0mL cryovials for storage at -80˚C. Specimens will be labeled with PID, study, date, and visit type, but will not include any individual identifying information. Please see the study MOP for additional step by step details on blood specimen processing, storage and shipping instructions.

3.7. Clinical Management of Adverse Events or Other Disease Events
Clinical events and side effects related to PrEP will typically be managed in the context of clinical care that participants are receiving, and will not involve study staff. However, if symptoms or events are identified during the context of study visits, research staff will refer participants for clinical care at HH clinical facilities or their primary provider. HHRI research visits occur in the same clinic that HH HIV and PrEP services are delivered, and across the street from the Hennepin County Public Health Clinic. Similarly, for any event unrelated to PrEP care research staff will also refer participants for clinical evaluation. If urgent or emergent care is required, participants will be referred to the HH urgent care or emergency department, which are located in the same facility that HHRI research visits are conducted.

In the event that HIV acquisition were to occur during the study, research staff would support immediate referral to an HIV clinic with rapid access to care and treatment (e.g., this would typically be available on the same day at the HH HIV clinic). Participants will be undergoing routine HIV testing at regular intervals as part of usual PrEP care. If participants have missed routine PrEP care visits, HIV testing will be offered in the context of any research visit upon request. The clinical context where HIV testing is performed will typically facilitate access to HIV treatment and care, but research study staff will facilitate this referral and linkage to HIV care if it has not occurred when participants are seen in research visits. Should any participant test positive for HIV in another community setting during the study, the study team will also assist with any resource information or direct referral to an HIV clinic.

3.8. Study Withdrawal

Participants may withdraw from study participation at any time. If participants elect to withdraw from the study, they will be asked if the study information and specimens collected up to that point can be used in analyses. In addition, participants will be asked if information related to their ongoing PrEP care (e.g., if they are continuing to engage in and receive care) may continue to be collected through the medical record for the duration of their previously anticipated study participation. Every attempt will be made to minimize missing data.

3.9. Study Data Storage and Retention

The original paper study data records will be archived for 7 years following completion of the study. Plasma from the optional blood draw will be stored for 20 years.

4. SAFETY AND ADVERSE EVENTS

4.1. Adverse Event Definitions

Adverse Event (AE): Any untoward medical occurrence in a clinical research participant administered an investigational product and which may or may not have a causal relationship with study participation. If a preexisting condition worsens post-enrollment (frequency and/or severity grade increases), it should be reported as an adverse event.

Serious Adverse Event (SAE): An AE that results in any of the following:

i. Death,
ii. A life-threatening condition,
iii. A congenital anomaly/birth defect,
iv. Inpatient hospitalization or prolongation of existing hospitalization,
v. Persistent or significant disability/incapacity,
vi. An important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require intervention to prevent one of the outcomes listed above.

Grading Adverse Events: There are five severity grades that can be assigned to adverse events, which are defined as follows:

i. Grade 1 = Mild
ii. Grade 2 = Moderate
iii. Grade 3 = Severe

iv. Grade 4 = Potentially life-threatening
v. Grade 5 = Death

4.2. Adverse Event Data Collection and Documentation

Data Collection: In addition to a medical history, clinical laboratory data will also be collection at enrollment. Following enrollment, information will then be collected on any new adverse event that occurs within 30 days following study visit procedures.

Documentation: Information on adverse events will be recorded on study visit CRFs (through the online REDCap interface). An assessment will be made by study investigators with respect to the severity grade and relationship of the AE to study participation (see 4.2 below).

Additional information ascertained for each adverse event includes: a) date of onset, b) relationship to study participation (see section 4.3 below), c) any action taken on study procedures, d) the outcome of the adverse event (e.g., resolved or ongoing), and e) whether the adverse event qualifies as a serious adverse event (including the SAE criteria fulfilled).

A narrative is required and is to be included in source documentation for all serious adverse events, as well as any other untoward events involving risks to participants that is unanticipated or unexpected and are reasonably believed to be related to research participation. The circumstances surrounding these events should be reported using the serious adverse event CRF, and reviewed with the principle investigator as soon as the event is known.

NOTE*: information on adverse event do NOT need to be reported if ≤ grade 2.*

4.3. Relationship to Study Participation

For all adverse events that occur within 30 days of study visit procedures, study investigator(s) will assess the potential relationship of the event to the study and designate one of the following:

i. Definitely or Probably Related: the adverse event is reasonably related in time, and the adverse event is more likely, or definitely, explained by study participation than other causes.
ii. Possibly Related. The adverse event is reasonably related in time, and the adverse event could be explained by the study or equally well by causes other than study participation.
iii. Not Related. The adverse event is clearly explained by an alternative explanation not related to study participation.

4.4. Review and Reporting of Adverse Events

NOTE: All adverse events that are collected and documented, whether or not they are serious or related to study participation, are reviewed weekly by the study investigator(s) for determination of grade, severity, relationship to study participation, and need to refer for additional medical evaluation.

The SDSU IRB will receive safety reports for all adverse events that are: **serious and unexpected**. Time frame for reporting will be:

i. Reports for serious adverse events that are definitely, probably, or possibly related to study participation will be sent within **2 working days** of knowledge of the event.
ii. Serious adverse events not related to study participation will be reported as part of usual study reports at pre-specified intervals (e.g., bi-annually, annually).

Aggregate annual reports will also be created and submitted to the IRB, which will include information on unexpected adverse events or any unanticipated problem that poses risks to participants, and is believed to be related to research participation.

5. STATISTICAL METHODS

5.1. Sample Size Considerations

The sample size for this proof-of-concept study (n=40 per group; n=80 total) is consistent with recommendations of sample sizes for pilot studies of this nature.[22] Power calculations are presented for the two adherence outcomes: TFV-DP levels and the adherence score. For the TFV-DP levels (n=20 in each arm), prior research suggests that approximately 40% will have levels TFV-DP levels >700 fmol/punch at 3 months. Assuming a type I error of 5% and using a chi-square test statistic, we have 80% power to detect a relative risk of 2.0 or larger (i.e., that the intervention group is 2.0 times as likely to have high levels of TFV-DP as the control group). Adherence may decrease by 6 months, increasing our detectable effect. If we assume 30% adherence at 6 months, we have 80% power to detect a relative risk of 2.4 or higher. For the adherence score derived from Wilson et al.'s[23] 3-item measure, prior research on ART therapy suggests a standard deviation of approximately 20.[23] Assuming we will see the same standard deviation among PrEP users and a type-1 error rate of 5%, we have 80% power to detect a difference in adherence scores of 12.7 units between the two groups. This is approximately half of a standard deviation change, and should provide good preliminary evidence to inform future trials.

5.2. Randomization Procedures

Participants will be randomized in a 1:1 allocation to either: a) the mobile intervention of PrEP iT! in addition to usual care, or b) a control condition that consists only of usual care. The randomization sequence will be stratified by age (18-24 v. 25-29 yrs) and use blocks of four. Given the nature of the intervention, treatment allocation will not be blinded following randomization.

All study staff and participants will be unaware of randomized group allocation until enrollment and randomization procedures are completed. Following screening and enrollment, participant eligibility will be re-confirmed. After completion of the randomization CRF, the treatment allocation will be revealed within the study database. Research staff will

then instruct participants on their study group, and participants within the mobile intervention arm will be guide through setup of the PrEP iT! web application.

5.3. Analysis Plan

Feasibility of delivering the intervention will be assessed by examining the percentage of eligible people who are successfully recruited into the study and by the percentage of participants retained at each visit. Chi-square tests (or Fisher's exact test, for small cell counts) will be used to compare the intervention and control groups in the proportions of participants retained at both 3- and 6-month follow-up. We will use the following retention cut-off percentages to assess feasibility: a) 90+ = strong feasibility; b) 80-89% = acceptable feasibility; c) 70-79% = modest feasibility with a need for improvement; d) <70% = unacceptable feasibility.

Acceptability will be measured using a 10-item self-report System Usability Scale (SUS)[24] computed in the intervention arm over time (at 3- & 6-months). The average SUS score across 400 studies was 68[24] (possible range 0-100); therefore, an average score of ≥68 will be considered acceptable and ≥80 highly acceptable. We will estimate overall acceptability and changes over time. Acceptability will further be assessed by recording the frequency of *PrEP iT!* interaction (average number of uses per week) over follow-up time.

The preliminary impact of the mobile intervention will specifically be evaluated. We will focus on two adherence measures to estimate the preliminary efficacy of the *PrEP iT!* intervention. Objective adherence will be assessed via TFV-DP levels in DBS samples (n≥20 per treatment arm). TFV-DP data will be dichotomized into high levels (≥700 fmol/punch) vs low levels (<700 fmol/punch) and the difference in proportion of high levels of TFV-DP between treatment arm will be estimated using chi-square or Fisher's exact test at both 3 and 6 months. In a separate analysis, we will keep TFV-DP as a continuous variable and examine differences between control and intervention groups using T-tests and permutation tests. Second, at 3 and 6 months, we will use the validated 3-item self-report adherence measure developed by Wilson and his colleagues.[23] T-tests will compare the mean adherence score between intervention and control arm at 3 and 6 months. Permutation tests will also be used to test for treatment group differences, since they do not require distributional assumptions and are typically more robust.

6. REFERENCES:

1. Centers for Disease Control and Prevention. HIV Surveillance Report, 2016. 2017.
2. Office of National AIDS Policy. National HIV/AIDS Strategy: Update of 2014 Federal Actions to Achieve National Goals and Improve Outcomes Along the HIV Care Continuum. 2014.
3. Centers for Disease C and Prevention. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. *MMWR Morb Mortal Wkly Rep*. 2011;60:65-8.
4. Marrazzo JM, del Rio C, Holtgrave DR, Cohen MS, Kalichman SC, Mayer KH, Montaner JS, Wheeler DP, Grant RM, Grinsztejn B, Kumarasamy N, Shoptaw S, Walensky RP, Dabis F, Sugarman J, Benson CA and International Antiviral Society USAP. HIV

prevention in clinical care settings: 2014 recommendations of the International Antiviral Society-USA Panel. *JAMA*. 2014;312:390-409.
5. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapia M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernandez T, Veloso VG, Buchbinder SP, Chariyalertsak S, Schechter M, Bekker LG, Mayer KH, Kallas EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV and iPrEx Study T. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010;363:2587-99.
6. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, Henderson FL, Pathak SR, Soud FA, Chillag KL, Mutanhaurwa R, Chirwa LI, Kasonde M, Abebe D, Buliva E, Gvetadze RJ, Johnson S, Sukalac T, Thomas VT, Hart C, Johnson JA, Malotte CK, Hendrix CW, Brooks JT and Group TDFS. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med*. 2012;367:423-34.
7. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, Tappero JW, Bukusi EA, Cohen CR, Katabira E, Ronald A, Tumwesigye E, Were E, Fife KH, Kiarie J, Farquhar C, John-Stewart G, Kakia A, Odoyo J, Mucunguzi A, Nakku-Joloba E, Twesigye R, Ngure K, Apaka C, Tamooh H, Gabona F, Mujugira A, Panteleeff D, Thomas KK, Kidoguchi L, Krows M, Revall J, Morrison S, Haugen H, Emmanuel-Ogier M, Ondrejcek L, Coombs RW, Frenkel L, Hendrix C, Bumpus NN, Bangsberg D, Haberer JE, Stevens WS, Lingappa JR, Celum C and Partners Pr EPST. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med*. 2012;367:399-410.
8. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, Malahleha M, Owino F, Manongi R, Onyango J, Temu L, Monedi MC, Mak'Oketch P, Makanda M, Reblin I, Makatu SE, Saylor L, Kiernan H, Kirkendale S, Wong C, Grant R, Kashuba A, Nanda K, Mandala J, Fransen K, Deese J, Crucitti T, Mastro TD, Taylor D and Group FE-PS. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med*. 2012;367:411-22.
9. Marrazzo JM, Ramjee G, Nair GB, Palenee T, Mkhiza B, Nakabiito C and et al. Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE study (MTN 003). Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; 2013; Atlanta, GA, USA.
10. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, Chiamwongpaet S, Kitisin P, Natrujirote P, Kittimunkong S, Chuachoowong R, Gvetadze RJ, McNicholl JM, Paxton LA, Curlin ME, Hendrix CW, Vanichseni S and Bangkok Tenofovir Study G. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2013;381:2083-90.
11. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, Tremblay C, Le Gall JM, Cua E, Pasquet A, Raffi F, Pintado C, Chidiac C, Chas J, Charbonneau P, Delaugerre C, Suzan-Monti M, Loze B, Fonsart J, Peytavin G, Cheret A, Timsit J, Girard G, Lorente N, Preau M, Rooney JF, Wainberg MA, Thompson D, Rozenbaum W, Dore V, Marchand L, Simon MC, Etien N, Aboulker JP, Meyer L, Delfraissy JF and Group AIS. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med*. 2015;373:2237-46.
12. McCormack S, Dunn D and on behalf of the PROUD Study group. Pragmatic Open-Label Randomised Trial of Preexposure Prophylaxis: The PROUD Study. *22nd Conference on Retroviruses and Opportunistic Infection*. 2015;abstract #22LB.

13. Hare CB, Coll J, Ruane P, Molina J-M, Mayer KH, Jessen H, Grant R, De Wet JJ, Thompson M, Dejesus E, Ebrahimi R, Giler RM, Das M, Brainard D and McCalister S. The phase 3 DISCOVER study: daily F/TAF or F/TDF for HIV preexposure prophylaxis. *Conference on Retroviruses and Opportunistic Infections*. 2019.
14. Nunn AS, Brinkley-Rubinstein L, Oldenburg CE, Mayer KH, Mimiaga M, Patel R and Chan PA. Defining the HIV pre-exposure prophylaxis care continuum. *AIDS*. 2017;31:731-734.
15. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, Hosek S, Mosquera C, Casapia M, Montoya O, Buchbinder S, Veloso VG, Mayer K, Chariyalertsak S, Bekker LG, Kallas EG, Schechter M, Guanira J, Bushman L, Burns DN, Rooney JF, Glidden DV and iPrEx study t. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis*. 2014;14:820-9.
16. Hosek S. L, R., Rudy, B., Kapogiannis, B., Siberry, G., Rutledge, B., Liu, N., Brothers, J., Rooney, J., Wilson, C. M., and The Adolescent Trials Network for HIV/AIDS Interventions (ATN),. An HIV pre-exposure prophylaxis (PrEP) demonstration project and safety study for adolescent MSM ages 15-17 in the United States (ATN 113). . Paper presented at: 21st International AIDS Conference; 2016; Durban, South Africa.
17. Hosek SG, Rudy B, Landovitz R, Kapogiannis B, Siberry G, Rutledge B, Liu N, Brothers J, Mulligan K, Zimet G, Lally M, Mayer KH, Anderson P, Kiser J, Rooney JF and Wilson CM. An HIV Preexposure Prophylaxis Demonstration Project and Safety Study for Young MSM. *J Acquir Immune Defic Syndr*. 2017;74:21-29.
18. Venkatesh V and Bala H. Technology Acceptance Model 3 and a Research Agenda on Interventions. *Decision Sciences*. 2008;39:273-315.
19. Fisher JD, Amico KR, Fisher WA, Harman JJ, Fisher JD, Amico KR, Fisher WA and Harman JJ. The information-motivation-behavioral skills model of antiretroviral adherence and its applications. *Current HIV/AIDS reports*. 2008;5:193-203.
20. Fisher JD, Fisher WA, Amico KR and Harman JJ. *An Information-Motivation-Behavioral Skills Model of Adherence to Antiretroviral Therapy.*: Health Psychology. Vol 25(4) Jul 2006, 462-473.; 2006.
21. Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR and Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS research and human retroviruses*. 2013;29:384-390.
22. Hertzog MA. Considerations in determining sample size for pilot studies. *Res Nurs Health*. 2008;31:180-191.
23. Wilson IB, Lee Y, Michaud J, Fowler FJ, Jr. and Rogers WH. Validation of a New Three-Item Self-Report Measure for Medication Adherence. *AIDS Behav*. 2016;20:2700-2708.
24. Brooke J. SUS: A quick and dirty usability scale. In: P. W. Jordan, B. Thomas, B. A. Weerdmeester and I. McClellend, eds. *Usability Evaluation in Industry* London: Taylor and Francis 1996.
25. Rosenbaum PR. Interference Between Units in Randomized Experiments. *Journal of the American Statistical Association*. 2007;102:191-200.

APPENDIX A:

PrEP iT!: A Pilot Test of a Mobile Peer Support Intervention to Optimize PrEP Adherence and Retention in PrEP Care

IMPORTANT THINGS TO KNOW ABOUT THIS STUDY:

We are inviting you to join this research study. The purpose of the research is to understand ways in which technology can be used to support young adults who are taking pre-exposure prophylaxis (PrEP) to prevent HIV infection.

We are asking people who join this study to attend 3 study visits (in-person or online via a teleconferencing platform such as Zoom) over a period of 6 months. You may also receive access to online information, activities, and resources related to PrEP during your time in the study.

We do not know if these activities would be helpful for managing PrEP, and it is possible that they could make it worse.

You do not have to join this study. You can choose to not join the study and your participation will not affect your access to PrEP or your current healthcare for PrEP. These are the reasons you might want to join this study: 1) you may experience positive feelings about participating in a study that could lead to new ways to help persons like you manage PrEP and 2) you may learn new strategies for managing PrEP. These are the reasons you might not want to join this study: 1) it may lead to emotional discomfort; 2) there is a small risk that someone could find out that you have sex with other men or that you are on PrEP; 3) we will ask you to provide a small amount of blood through a finger prick which may be slightly painful.

We will give you details about the purposes, procedures, risks and possible benefits related to this study. We will explain other choices you have. We will also give you any other information that you need to make an informed decision about joining this study.

The following information is a more complete description of the study. Please read this description carefully. We want you to ask us any questions that will help you decide whether you want to join this study. If you join the study, we will give you a signed copy of this form to keep for reference in the future.

WHO SHOULD I CONTACT IF I HAVE QUESTIONS or Concerns?

Principal Investigator: Keith J. Horvath
SDSU Department: Psychology
Address: 5500 Campanile Drive; San Diego, CA 92182
Phone: 619-594-3346
Email: khorvath@sdsu.edu

Principal Investigator: Jason V. Baker
Institution: Hennepin Healthcare Research Institute (at Hennepin Healthcare)
Address: 701 Park Avenue (mail code G5); Minneapolis, MN 55415
Phone: 612-873-7678 (research program)
Email: Jason.baker@hcmed.org

WE ARE INVITING YOU TO JOIN THIS RESEARCH STUDY.

We are inviting you to participate in this research study because you have told us that you are on PrEP and identify as gay, bisexual or a man who has sex with men.

Up to 80 participants will be included in this study.

Research is not the same as treatment, or other medical or psychological care or therapy. The purpose of research is to answer scientific questions.

WHY ARE WE DOING THIS STUDY?

We are doing this study to find out if it is possible to provide men like you with access to online information, activities, and resources related to PrEP and, for those who agree to join the study, what they think about the website. We also want to know if men who are on PrEP find the online information, activities, and resources helpful for managing PrEP.

In the study we want to compare a group of men who are on PrEP and are provided access to a website with a group of men who are on PrEP but who are not provided access to the website. Persons who join the study have a 50% chance of being assigned to the website group and a 50% chance of being assigned to the no website group.

WHAT IS THE TIME COMMITMENT IF I JOIN THIS RESEARCH STUDY?

Your participation will last approximately 6 months. You will either come to the research office or teleconference with research staff for three (3) study visits about 3 months apart. Each visit will last about two hours. In addition, if you are randomly assigned to the website group, you will be asked to use the website during the 6 months. The amount you use the website is up to you.

The research scientist could stop your participation in the research study at any time even if you want to still be in the study. This would happen if:

- They think it is in your best interest to stop being in the study.
- You are not willing or able to do all the things needed in the study.
- The whole study stops.

If you stop being in the study, your information collected before you stopped being in the study will be included in the study unless you request that your data be removed. You may request in writing by email or calling the study Principal Investigator.

WHAT WILL I BE ASKED TO DO IN THIS RESEARCH STUDY?

To determine if you can join the study, we will ask you some questions. If your answers indicate you can participate, we will ask you to participate in the training and testing portion of this study. If you are not eligible to participate, your information will be destroyed to keep your information private.

If you choose to be in the study, you will be asked to sign this consent form before you begin the study. This initial visit will last about 120 minutes.

Study staff will collect information from your medical record chart beginning from the time you enroll in the study until the end of your study participation. We will ask you to sign a medical records release form to collect information from the clinic in which you receive your PrEP care. The study staff will collect information such as clinic visits, medical diagnoses, medication use, and laboratory results related to your PrEP care. This information will be protected in the same way the information from your medical record is protected. If you decide not to sign a medical records release form, you can still participate in this study.

After you have provided your consent, you will give the study staff a list of ways to contact you, such as your e-mail address and phone number, as well as the phone number of a relative or friend who knows how to get in contact with you. Study staff will not leave phone messages unless you give permission. The study staff will also not tell your relative or friend anything about this study, your participation in the study, or give any information about you unless you give permission. Your contact information will be used to remind you to come in for your study visits and to help you with transportation to your study visits, if needed. You also can choose not to give any information that you do not want to give. However, you will need to provide a working email in order to use the website resources, and provide a form of communication (for example, your telephone number) in order for us to communicate with you during the study.

The following is the schedule of study visits and what will be done at each visit:

Today: 1st study visit

1. You will be asked to answer questions on a computer or a tablet by yourself in an assessment room. The survey will take about 35-45 minutes and we will ask you questions about PrEP, your attitudes and feelings about PrEP, substance use, internet use, and general information about yourself (race, ethnicity, income, education).
2. If you are randomly assigned to use the website (meaning you have a 50/50 chance, like flipping a coin, of being in this group), a study staff member will give you a unique username and password for the website, and take you on a brief tour of the website. You will have the opportunity to ask questions about the website. Please use as many of the website features as possible. You may use the website on a computer, smart phone, or both.
3. If your visit is in person, we will do a finger prick to collect several drops of blood. If your visit is virtual, we will be mailing a self-collection kit that will be mailed to your home where you collect blood by pricking your finger, and then mailing the blood sample to a lab in a pre-paid mailer. Four to five drops of your blood will then be stored on a paper card until the end of the study, when it will be used to measure levels of medications that are used as PrEP. This is like getting poked with a needle and may cause discomfort.
4. You may be asked to provide additional blood draw to be stored for future research studies. This is optional and, if you agree, may result in discomfort.

About three months from today: 2nd study visit

1. You will be asked to answer questions on a computer or a tablet by yourself in an assessment room. The survey will take about 35-45 minutes and we will ask you questions about PrEP, your

attitudes and feelings about PrEP, substance use, internet use, and general information about yourself (race, ethnicity, income, education).
2. If your visit is in person, we will do a finger prick to collect several drops of blood. If your visit is virtual, we will be mailing a self-collection kit that will be mailed to your home where you collect blood by pricking your finger, and then mailing the blood sample to a lab in a pre-paid mailer. Four to five drops of your blood will then be stored on a paper card until the end of the study, when it will be used to measure levels of medications that are used as PrEP. This is like getting poked with a needle and may cause discomfort.

About six months from today: 3rd study visit

1. You will be asked to answer questions on a computer or a tablet by yourself in an assessment room. The survey will take about 35-45 minutes and we will ask you questions about PrEP, your attitudes and feelings about PrEP, substance use, internet use, and general information about yourself (race, ethnicity, income, education).
2. If your visit is in person, we will do a finger prick to collect several drops of blood. If your visit is virtual, we will be mailing a self-collection kit that will be mailed to your home where you collect blood by pricking your finger, and then mailing the blood sample to a lab in a pre-paid mailer. Four to five drops of your blood will then be stored on a paper card until the end of the study, when it will be used to measure levels of medications that are used as PrEP. This is like getting poked with a needle and may cause discomfort.
3. You may be offered the opportunity to participate in a short optional interview with clinic study staff about your experience in the study for additional compensation. This interview may be recorded so the content discussed can be captured in detail for the study. The recording will be destroyed within one month of the interview.
4. You may be asked to provide additional blood draw to be stored for future research studies. This is optional and, if you agree, may result in discomfort.

Some of your blood taken with the optional blood draw at the 1st and 3rd study visits may be stored. Your stored samples and the information collected about you during the study may be used by the study sponsor, its research partners or companies for additional testing of Tenofovir and metabolites. At the end of this study, these samples may be held in storage by Hennepin Healthcare Research Institute for up to 20 years. After 20 years, the samples will be destroyed. You can request that your samples be destroyed at any time by writing to the study doctor at the address listed on the first page of this form.

Additional Blood Specimen Collection Consent

1) Collect, store and use blood samples and data collected from the study for future research. I agree to allow my blood to be used for future research.

☐ Yes _____ *(initial)* ☐ No _____ *(initial)*

_____

Signature of Participant Date

WHAT ARE THE RISKS OR DISCOMFORTS INVOLVED IN THE RESEARCH?

- You may feel uncomfortable or embarrassed by providing information about yourself, including your PrEP use, drug use, or other information while answering surveys or speaking with research staff. You are free to provide as little or as much information as you like during the survey. If any of the topics on the survey make you uncomfortable or if you find something upsetting, you can stop at any time, and we can refer you to a counselor who may be able to help you.

- The collection of a small amount of blood through a blood draw or finger prick may cause discomfort, bruising, or bleeding. Rarely people faint as a result of this procedure.
- Potential risks of loss of confidentiality. There is some potential risk of disclosure of being on PrEP or other personal behaviors if someone sees the website on your phone, tablet, or computer. You will have a unique password-protected login to access the website and the connection will time out after a period of inactivity. The default text message is a generic text message that will serve as a weekly reminder, but will not contain any text about "medications," "dose," or "PrEP."

There is a chance that some users could engage in hostile communication in comments on the website. We will post general rules for using the website. The website will be monitored daily by research staff. Comments that are considered hostile may be removed by study staff. Additionally, if participants continue to engage in hostile communication, they may be removed from the study.

We will make every effort to protect your confidentiality, but there is a small possibility that your name, PrEP use, or sexual orientation identity could become known to others.

We may discover new information during this research study. This new information my affect whether or not you want to still be in the study. We will tell you so that you can decide if you still want to be in the research.

ARE THERE ANY BENEFITS TO PARTICIPATION?

If you join the study, you may experience positive feelings about participating in a study that could lead to new ways to help persons like you manage PrEP. You may learn new strategies for managing PrEP. However, we cannot be certain that you will receive any benefits by being in this study.

AUTHORIZATION TO DISCLOSE PROTECTED HEALTH INFORMATION

Your privacy is important to us, and we want to protect it as much as possible. By signing this form, you authorize your Study Doctors, nurses and other research assistants at Hennepin Healthcare and San Diego State University to use and disclose information created or collected in the course of your participation in this research protocol. This information might be in different places, including your original medical record, but we will only disclose information that is related to this research protocol for the purposes listed below.

This information will be given out for the proper monitoring of the study, checking the accuracy of study data, analyzing the study data, and other purposes necessary for the proper conduct and reporting of this study. If some of the information is reported in published medical journals or scientific discussions, it will be done in a way that does not directly identify you.

This information may be given to other researchers in this study, or to private entities such as academic research institutions, academic associated start-ups, and nonprofit companies. This information may also be given to state and/or federal government parties, or to regulatory authorities in the USA and other countries responsible for overseeing this research. These may include the Office for Human Research Protections, or other offices within the Department of Health and Human Services, and the Office of Human Subject Research Committee at Hennepin Healthcare.

Any information that could be used to identify you will be treated in strict confidence to the extent allowed by law. Nevertheless, some uses and disclosures of your information are necessary to conduct the study. If you agree to be part of this study, you will also be allowing the uses and disclosures of your private health information as needed for the purposes of this study as described in this consent.

"Private health information" means information that identifies you and is collected:

- during this study;

- from your past and current medical records maintained by your regular health care providers (including, if applicable, HCMC), to the extent the information is relevant to this study or to your eligibility for this study; or
- from any payment records relating to items or services furnished to you during this study.

By signing this consent, you are agreeing that your private health information may be disclosed to and used by:

- the doctors and other health care providers involved in this study;
- their staff;
- the research center (Hennepin Healthcare Research Institute);
- members of the San Diego State University Human Subjects Research Committee/Institutional Review Board;
- research staff at San Diego State University;
- the sponsor of this study and its agents; and
- representatives from the United States Government and/or Food and Drug Administration (FDA).

The findings of this study may be used for scientific meetings, written reports, and publications, but no information that could be used to identify you will be disclosed for these purposes.

Private health identifiers might be removed and the de-identified information or biospecimens used for future research or distributed to another investigator without additional informed consent from you

Once your private health information has been disclosed to a third party, federal privacy laws may no longer protect it from re-disclosure. However, anyone obtaining access to your private health information under this consent must agree to protect your information as required by this consent.

This consent to use your private health information as described above expires on December 31, 2023. However, if you later change your mind, you can revoke this consent by writing to Jason Baker, MD, MS saying that you no longer wish to allow your private health information to be used for this study. If you revoke your consent, you will no longer be able to participate in the study. Moreover, we cannot undo uses or disclosures of your private health information that have already taken place in reliance on your prior consent.

☐ **I authorize the release of HIV test results**

ARE THERE ANY ALTERNATIVES TO JOINING THIS RESEARCH STUDY?

There all no alternatives to joining this research study. However, you may choose not to participate in the research.

WILL MY INFORMATION BE PRIVATE?

Your participation in this study will be kept confidential and private as permitted by law. This includes information you provide on the survey, the audio recording of the interview, and anything you enter on the website.

Every effort will be taken to protect your identity as a participant in this study. You will not be identified by name in any study database, report or publication of this study or its results. Instead, you will be known only through a study ID number. Any data linking your name to your study ID number will be kept in a locked cabinet in a locked room at the study site, but separate from where your study records are stored. Staff members involved in this study are required to sign a form stating that they will protect and keep private all information on every person in the study.

We will keep your information private. No subjects will be identified in any report or publication about this study. However, there are things that the law does not allow us to keep private. If we think that a child or older person is being harmed, we are required to report any suspected harm to authorities. In some cases, your information in this research study could be reviewed by representatives of Hennepin Health Research Institute, San Diego State University, research sponsors, or government agencies for purposes such as quality control or safety.

At the end of the study, the electronic information from the study will be coded and stored on secure servers at the participating sites: San Diego State University, San Diego, CA and the Hennepin Healthcare Research Institute, Minneapolis MN. None of this study database information will identify you by name.

A description of this study will be available on http://clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can access this website at any time.

To help further protect your privacy, we have obtained a Certificate of Confidentiality from the U.S. Department of Health and Human Services (DHHS). It adds special protection for research information that identifies you. It says that we do not have to identify you, even under a court order or subpoena. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

Still, we may report medical information (if you need medical help), probable harm to yourself or others, or probable child abuse or neglect, and the government may see your information if it audits us. This Certificate does not mean the government approves or disapproves of our project. You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written assent/consent to receive research information, then the researchers may not use the Certificate to withhold that information.

In addition, your records may be reviewed by certain agencies or people who make sure that the study staff are doing what they are supposed to and everyone in the study is being protected. Under the guidelines of the Federal Privacy Act, the sponsoring agency at the National Institutes of Health (NIH) and San Diego State University may look at your records. If your study records are reviewed, your identity could become known to them. However, these persons are expected to maintain your individual confidentiality. This means that they will not tell others information about you or that you are in the study. De-identified information will be shared with the sponsoring agency at the NIH without obtaining additional informed consent. By signing this form, you are allowing such access.

Any paper research records will be stored in a locked office in a locked file cabinet and will only be accessible to research staff listed on the first page of this consent form. All electronic data will be encrypted and stored on a password-protected computer behind a firewall to ensure access is provided only to those involved directly in data collection or analysis.

At the end of the study, the identifying information (participants' names and contact information) is destroyed. The original data records will be archived for 7 years, and three copies of the de-identified dataset will be maintained (one working copy and two archived at different sites).

Data on what features of the website that participants in this study use will be collected and housed on physical servers residing in a secure facility that is audited to SOC3 SSAE-16 standards. The website databases and application will reside in a single tenant "private cloud" under the exclusive control of our partner, Radiant Digital. The website databases and application will be logically segmented in virtual private servers, ensuring that data may not be accessed by applications outside this project. To promote confidentiality of participant data, each participant will be assigned a study PIN login to the program during the evaluation. Users will access the system via this study PIN and an associated user-selected password. All communication between the app and server-side systems will be conducted using secure methods (e.g., SSL). All server-side systems will utilize a database-level encryption scheme to store data. No data will be collected or stored on any individual participant devices.

Your private information and bio-specimen(s) collected as part of this research study will not be used or distributed for future research studies or used for commercial profit.

The exit interview may be recorded so the content discussed can be captured in detail for the study. The recording will be destroyed within one month after the interview once the information is collected. You will only be identified on written information from the interview with a unique study ID number. The information from the recordings will not be used for any other purposes outside of this research study.

We will use the information we learn to for published articles or for presentations to other scientists. We will keep your information private. Others will not be able to identify you in those papers or presentations.

WHAT WILL HAPPEN IF I AM HURT OR INJURED WHILE I AM IN THE STUDY?

If any injury arises as a direct result of participation in this study, we will assist you in obtaining appropriate attention. If you need treatment or hospitalization because of being in this study, you are responsible for payment of the cost for that care. If you have insurance, you may bill your insurance company. You will have to pay any costs not covered by your insurance. San Diego State University, San Diego State University Research Foundation, and Hennepin Health will not pay for any care, lost wages, or provide other financial compensation. However, if you feel you have a claim that you wish to file against the State or the Foundation, please contact Graduate and Research Affairs - Division of Research Administration at (619) 594-6622 to obtain the appropriate claim forms.

DO I HAVE TO JOIN THIS STUDY?

No, you do not have to join this research study. Even if you agree to join, you can decide later that you do not want to be in the research. If you choose not to join or later decide that you do not want to be in the study, there is no penalty or loss of benefits to which you are otherwise entitled

WILL I BE TOLD ABOUT THE RESEARCH RESULTS?

If you choose to be informed, we will contact you with results of this study after the study is completed.

WILL IT COST ME ANYTHING If I Join the Research?

There are no costs if you choose to join the research study.

WILL I BE PAID IF I JOIN THE RESEARCH?

You will be compensated the following for each study activity to help cover the cost of your time:

- Enrollment visit: $50 gift card
- 3-month visit: $50 gift card
- 5-month visit: $50 gift card

If you complete all of the study activities listed above, you will receive a total of $150 in gift cards.

If you are asked to participate in an online interview during the 6-month visit and choose to do so, you will receive an additional $25 gift card incentive.

WHOM DO I CONTACT IF I HAVE QUESTIONS OR CONCERNS?

If you have questions now, please ask. If you have questions later about the research, you may contact Dr. Keith Horvath at 619-595-3346. If you have any questions about your rights as a research participant, or in the event of a research related injury, you may contact the Division of Research Affairs at San Diego State University (telephone: 619-594-6622; email: irb@sdsu.edu). At any time during the research, you can contact the IRB for questions about research rights, to discuss problems, concerns, give suggestions, or to offer input.

CONSENT TO PARTICIPATE:

The San Diego State University Institutional Review Board has approved this consent form, as signified by the Board's stamp. The IRB must review the consent form yearly. The IRB approval expires on the date indicated by the stamp in the upper right-hand corner of this document.

Your signature below indicates that the study team has explained the study to you and you have read the information in this form. You have had a chance to ask any questions you have about the research. By signing this form, you are agreeing to join the study. You have been told that you can change your mind and stop participating in the research at any time. The researcher or a member of his/her research team has provided you with a copy of this consent form. This form includes contact information about who to contact if you have questions.

The researcher or member or his/her research team has provided you with a copy of this consent form and the Authorization to Disclose Protected Health Information.

Name of Participant (please print)	Date
Signature of Participant	Date
Signature of Research Study Staff	Date