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ePrEP: Testing an electronic PrEP initiation and maintenance home care system to promote PrEP among adolescent MSM

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ATN 159 - ePrEP: Testing an electronic PrEP initiation and maintenance home care system to promote PrEP among adolescent MSM

SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Investigator of Record: _____
Print/Type

Signed: _____ Date: _____

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TABLE OF CONTENTS

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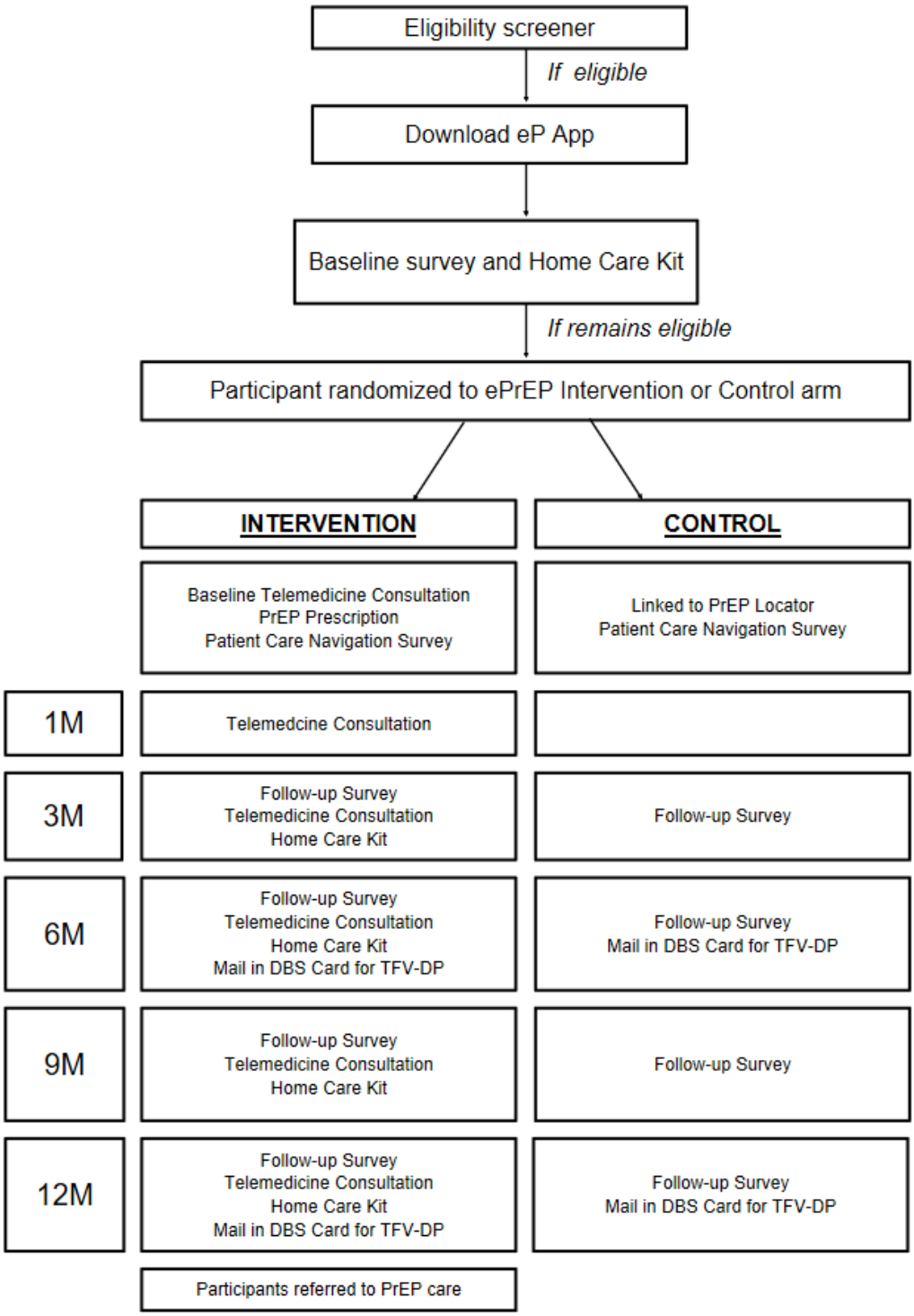
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AC	Analytic Core
ACTG	AIDS Clinical Trials Group
ACASI	Audio Computer Assisted Self Interview
AIDS	Acquired Immunodeficiency Syndrome
API	Application Programming Interface
ATN	Adolescent Medicine Trials Network for HIV/AIDS Interventions
BMSM	Black men who have sex with men
CASI	Computer assisted self-interview
CFR	Code of Federal Regulations
CRF	Case Report Form
DBS	Dried Blood Spot
DHHS	U.S. Department of Health and Human Services
EC	Ethics Committee
EDC	Electronic Data Capture system
ePrEP	Study intervention
FTC/TAF	Emtricitabine/tenofovir alafenamide
FTC/TDF	Emtricitabine/tenofovir disoproxil fumarate
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HSP	Human Subjects Protection
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MC	Management Core
MSM	Men who have sex with men
NCHS	National Center for Health Statistics
NICHD	National Institute of Child Health and Development
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
OHRP	Office of Human Research Protection
PI	Principal Investigator
PrEP	Pre-Exposure Prophylaxis
QNS	Query and Notification System
RDC	Remote data capture
SID	Study Identification
SRV	Subject Recruitment Venue
SSL	Secure Socket Layer
SUS	System Usability Scale
TC	Technology Core
TFV-DP	Tenofovir diphosphate
YMSM	Young men who have sex with men

STUDY ABSTRACT

DESIGN:	A two-arm randomized controlled trial (RCT) among young men who have sex with men (MSM) in Georgia, Mississippi, and North Carolina. Participants randomized to the intervention will receive the ePrEP home care system for telemedicine PrEP care that includes initiation and maintenance in care. The ePrEP home care system consists of a smartphone application (app) for video-based telemedicine PrEP consultations with a clinician, messaging and remote tracking system, and behavioral risk surveys that are complemented by home specimen collection kits. Home kits allow for remote testing for standard laboratory tests for PrEP care. Participants randomized to the control condition will be referred to their nearest PrEP provider to receive standard of care. Both groups will conduct quarterly surveys through an electronic interface and home specimen collection of dried blood spots for detection of medication at 6 and 12 months after randomization.
DURATION:	Participants will remain in the study for 12 months after randomization.
SAMPLE SIZE:	240 participants (120 intervention, 120 control)
POPULATION:	Age 18-29, HIV-negative, MSM, from Alabama, Georgia, Mississippi, and North Carolina, targeting 50% recruitment of highly impacted groups of Black or Latino MSM.
STRATIFICATION:	1:1 randomization, each site will enroll ~80 participants. Participants will be stratified by site.
DATA COLLECTION:	A secure electronic survey platform will be used to collect participant data through quarterly surveys. All laboratory tests will be conducted in CLIA-certified laboratories, including the test for the primary study outcome. App paradata will be collected within the study app. Data regarding PrEP care interactions between study clinicians and staff will be collected through the study app. Case report form data will be collected using an electronic data capture system. Interviews will be audio-recorded and professionally transcribed.
OBJECTIVES	1) To assess protective levels of PrEP for those randomized to ePrEP system versus those assigned to the standard of care (control) condition, as determined by a biomarker for TFV-DP. 2) To conduct additional assessments to contextualize trial results and facilitate appropriate scale-up.

STUDY DESIGN OR SCHEMA



1.0 INTRODUCTION

1.1 Background

In 2015, MSM continued to account for two-thirds of new HIV cases in the United States.[1] Within this elevated risk group, Black MSM and young MSM aged 15-24 bear disproportionate burdens,[1] and represent priority populations for intervention. Rural and peri-urban areas across the Southeast do not have substantial access to PrEP providers.[2] The National Center for Health Statistics (NCHS) classifies counties into six levels of urbanicity: the two smaller levels contain no PrEP providers in Georgia, despite these areas containing a substantial MSM population (>20,000).[3] Home-based care has the potential to quickly make PrEP services available to the large number of MSM in rural and small town areas who currently lack access.

PrEP scale-up in the US may also be limited by the availability of clinic space and time. A home-based PrEP support system could address some patient concerns regarding PrEP uptake. One limitation of PrEP is the heavy burden of follow-up visits borne by patients, including indirect cost (i.e. absence from paid work, need for child-care) and direct cost (i.e. transport, co-payments)[4] that could lead to problems with PrEP adherence.[5, 6] The home care system for PrEP is comprised of inexpensive, commonly available laboratory supplies such as finger prick devices, swabs, and microtubes. Patient self-completion surveys that simulate clinician visit typical questions may allow for clinicians to have a higher volume of patients due to time savings. Given these inputs, the home care system has the potential to be cost saving, depending in part on the level of human resources required to maintain patients in home care.

Past efforts to address PrEP uptake or adherence for YMSM have been conducted predominately in urban areas, and the most successful programs have been approaches tailored for urban YMSM. The premise for the study is that a tailored approach for YMSM using telemedicine, addressing known barriers of transportation, access to providers, and privacy, is most likely to yield high levels of PrEP initiation and persistence in care.

Using a smartphone application (app), participants assigned to the intervention will receive and maintain a PrEP prescription without needing to leave their home (excepting pharmacy pick-up or initiation laboratory testing for Hepatitis B in some cases) – achieved through app-based surveys/screenings, telemedicine consultations, and home specimen self-collection.

1.2 Rationale

1.2.1 Young, Black, and Latino MSM are at high and elevated risk for HIV, and PrEP has been demonstrated to prevent HIV transmission.

In 2015, MSM continue to account for two-thirds of new HIV cases in the United States.[1] Within this elevated risk group, Black MSM (10,315/26,645, 39%) and young MSM aged 15-24 (7,150/26,645, 27%) bear disproportionate burdens.[1] PrEP has high effectiveness: in international settings PROUD[7] found 86% reduction in anticipated infections. In domestic settings, follow-up of Kaiser Permanente patients in the San Francisco Bay area found no new cases of HIV among patients prescribed PrEP.[8]

1.2.2 PrEP provision in rural and small town areas is limited, despite having substantial populations of MSM

A national database of PrEP-prescribing clinics, developed by the authors, indicates a substantial lack of PrEP providers in rural areas. Using standard classification of counties in Georgia, the

least urban categories (noncore and micropolitan) counties had no PrEP clinics, despite these areas containing >20,500 MSM,[3] with the patient population spread across hundreds of miles. In practice, this translates to 'PrEP deserts' that have no near providers.

1.2.3 HIV prevalence is high among MSM residing in rural areas.

People residing in areas classified as not being a part of a metropolitan statistical area accounted for 18% (7068/40022) of new HIV diagnoses in the US in 2013.[1] HIV prevalence among MSM in rural counties is high, with many counties exceeding 15% prevalence.[9]

2.0 STUDY OBJECTIVES

2.1 Primary Objective:

Assess protective levels of PrEP for those randomized to the ePrEP system versus those assigned to the standard of care (control) condition, as determined by a biomarker for TFV-DP.

2.2 Secondary Objective:

Conduct additional assessments to contextualize trial results and facilitate appropriate scale-up:

Aim 2.1 Adjusted analyses of the primary outcome (protective levels of PrEP) that control for potential residual confounding, and analyses of secondary outcomes including components of PrEP care continuum.

Aim 2.2 Exploratory analyses of intervention effectiveness across subgroups, and analysis of potential mediators of initiation or persistence in PrEP care across both study arms, such as self-efficacy, urbanicity, or clinical eligibility.

Aim 2.3 Conduct a series of in-depth interviews with participants regarding their experiences along the PrEP care cascade, and with key informants regarding their experiences with ePrEP.

2.3 Additional Analyses:

Conduct cost-effectiveness and cost-utility analyses of the ePrEP intervention.

2.4 Study Hypotheses/Research Questions

Those assigned to the ePrEP intervention will be further along the PrEP care continuum, with protective levels of PrEP (the primary outcome) higher among those assigned to ePrEP.

3.0 STUDY DESIGN

PrEP-naïve MSM will be recruited into the study, with a focus on Black and Latino MSM, targeted to make up half of all participants. A screening will be conducted online and involve a screening consent and questions to determine initial eligibility. This will be followed by a full consent (if eligible), a baseline survey, and the return of self-collected specimens for testing to determine clinical PrEP eligibility. Those eligible for the study will be enrolled into the trial and randomized to either intervention (ePrEP) or control (standard of care). Participants assigned to the ePrEP intervention (n=120) will have a baseline teleconsultation with a site study clinician who will be responsible for prescribing PrEP as indicated.[10] Intervention participants will be offered telemedicine consultations at 1, 3, 6, 9 and 12 months, and will complete quarterly home specimen collection for laboratory tests recommended by CDC at each time period. The study

virtual visits consist of surveys, specimen collection, and telemedicine consultation. Those assigned to the control condition (n=120) will be referred to a publicly available website that geolocates the nearest PrEP provider, www.PrEPLocator.org. Both conditions will have identical TFV-DP kit collection for primary outcome assessments (6 and 12 months) and app-based surveys for secondary outcomes assessments across all study periods (baseline, 3, 6, 9, and 12 months).

The three study sites will be staffed by clinicians who will conduct telemedicine consultations and supporting staff who will address participant care needs such as referrals for treatment. Study recruitment, retention communication, and tracking will be handled by staff at the Emory University site.

3.1 Study Population

A total of 240 young MSM (aged 18-29) will be enrolled and randomized into the study. All participants, at the time of screening, must live in one of the four study site states (AL, GA, MS, NC). The study will target enrollment of 50% Black or Latino MSM.

3.2 Sample Size

240 total participants, with 120 assigned to intervention and 120 assigned to control.

3.3 Study Randomization and Stratification

An electronic data capture system (EDC) will be used to stratify randomization by site to decrease the likelihood of Type I error[11] due to the expected association between covariates and study outcome. Randomization will be accomplished within the study data management platform; within each stratum, the data system will produce a sequential block randomization list. This list will automatically populate the appropriate study arm assignment in iDataFax at the time each new participant is randomized at any of the three study sites.

4.0 SELECTION AND ENROLLMENT OF STUDY PARTICIPANTS

Eligibility assessment includes the inclusion and exclusion criteria listed below. To maintain eligibility participants must complete the baseline survey modules within one week of initiating them. Inclusion/exclusion criteria that address PrEP eligibility are guided by CDC and WHO criteria.[12],[13, 14]

4.1 Inclusion Criteria

- Assigned male at birth
- Age 18-29 (inclusive)
- Live in a study state (GA, MS, NC, AL)
- Able to provide informed consent and complete survey instruments in English
- Willing to provide complete contact information (including 2 alternate contacts)
- Able and willing to provide ID verification for viewing confirmation only
- Laboratory confirmed HIV negative
- Owns an iOS or Android smartphone capable of running the study app

- Male sex partners in past 6 months or clinician discretion of epidemiologic context of HIV risk[14]
- Behaviorally indicated for PrEP :
    - History of inconsistent or no condom use with more than one partner
    - History of inconsistent or no condom use with one partner who is not mutually monogamous
    - Any STI diagnosed in past 6 months
    - Commercial sex work
    - African American MSM reporting anal sex in the past 6 months*[13]
    - Clinician discretion based on epidemiologic context of HIV risk [14]
- Willing to take FDA-approved daily oral PrEP
- Willing to use study-provided PrEP navigation services
- Willing to self-collect specimens

4.2 Exclusion Criteria

- HIV positive (self-report or laboratory confirmed)
- Chronic Hepatitis B or no verification of hepatitis B vaccination
- Currently enrolled in any HIV prevention trial (biomedical)
- Currently taking oral PrEP based on self-report
- Creatinine clearance <60 ml/min based on the Cockcroft-Gault equation
- Symptoms of acute HIV infection within the prior 30 days
- Contraindications to taking oral PrEP
- Personal diagnosis or family history of hemophilia
- Health insurance with Kaiser Permanente (unable to prescribe PrEP through the study)
- Investigator discretion to exclude anyone whose best interest is not to participate
- Evidence of fraudulent participation, such as duplicate IP address, multiple screening attempts, duplicate emails, etc

4.3 Recruitment

Participants will be recruited using advertisements on social media platforms and geospatial sexual networking apps. Targeted recruitment, based on interest and participant location using 5-digit ZIP codes for these platforms, will display advertisements to men in geographic areas that would indicate potential eligibility for the study. The methods of advertising for the study will include banner advertisements and brief electronic messages. Retargeting methods may be used send ads to people who clicked initially but did not complete the screener. Additional participants may be recruited from referral from other participants, research studies, or research screeners; only individuals who have indicated willingness to be contacted regarding future research studies will be contacted. Secondary recruitment methods may include flyers at events or places such as clinics, organizations, colleges, or local establishments where youth may congregate. We will also follow respondent-driven sampling (RDS) methods and use a long-chain referral method to supplement recruitment.

* As defined by WHO guidelines of including populations at "substantial risk".

4.4 Screening

Potential participants who respond to recruitment procedures will be directed to a webpage that includes a brief introduction script and a self-administered online screener. Those who click on the electronic ad or who receive an email will be directed to the brief online consent and screener to determine eligibility. The online screener will be hosted on a secure electronic survey platform, and will include the eligibility script, consent to be screened, and screener questions. A link to a PrEP informational video will be included in the screener. Participants may also opt to have screening conducted verbally over the phone. For those who meet eligibility criteria for this first screening procedure, personal contact information will be requested and recorded, including the first name, e-mail, and phone number of the participant.

There will be no identifying information collected from participants determined to be ineligible at screening. Therefore, it is possible these individuals could rescreen without the knowledge of study staff. We will seek to minimize fraudulent participation through re-screen attempts. Participants deemed behaviorally eligible at screening will provide their name and contact information. Participant name, email address and phone number will be automatically checked for duplicates for the app to be downloaded. Staff will check for duplicates by assessing participant photo or other ID through study app and other mechanisms. Results of assessment will be recorded on the eligibility checklist. For security, once participant ID is verified, the uploaded document will be permanently deleted from the system. Rescreens explicitly allowable by the protocol will be noted and considered for eligibility.

4.5 Informed Consent

Participants will complete a brief consent for the screening survey. Then, participants who are eligible based on screening will be provided an electronic study consent on a secure electronic survey platform, with study staff available by phone to answer any questions during business hours. The consent form describes all study procedures, including confidentiality and privacy, information about potential risks, discomforts, benefits of participation, and information regarding who they can contact with further questions. It also states that participation is voluntary, that participants may decide not to take part or to withdraw from the study at any time without penalty or loss of any benefit to which they might otherwise be entitled, and that study participation is in no way related to being able to access or continue getting care or services at any participating study site. Participants can refuse to answer any question, and can withdraw from the study at any time. Participants will provide consent using an electronic method to document signature on the electronic consent form. Informed consent must be obtained before any study procedures are performed. The consent form will only be available in English. Informed consent verification will be completed over the phone with study staff prior to baseline visit procedures. Timeline for consent is contingent on the timeline of study activities as described in section 5.1. Participants will be asked to sign a new consent if activities are not completed within the specified timeline.

5.0 STUDY PROCEDURES

5.1 Enrollment Procedures

There will be two stages of eligibility assessment: screening (including behavioral assessment screening) and clinical eligibility screening in which the study clinician determines whether the participant is eligible to take PrEP. Each procedure below must be completed prior to moving to the next procedure.

1. Participants who respond to an electronic ad will complete a brief online consent for screening. (Section 4.5)
2. Participants will complete screening (the first stage of eligibility) and if eligible will complete a full study consent (Sections 4.4 and 4.5).
3. Participants will be called to verify eligibility and consent.
4. Participants may be scheduled to consult with clinician regarding HIV risk and PrEP eligibility.
5. Participants will be given instructions to download the study app (through GooglePlay or Apple Store), and create a personal account for the app on their mobile devices. (Section 5.4)
6. Staff will affirm non-fraudulent participation by assessing participant photo or other ID through study app and other mechanisms and record results on the eligibility checklist.
7. Staff will notify participants to complete the Baseline survey through the app.
8. Staff will send participants a home test kit to self-collect specimens and return them via mailer. (Section 5.5)
9. Staff will check state immunization records for Hepatitis B or refer participants to testing.
10. Participants determined to be behaviorally and clinically eligible for the clinical trial will be enrolled and randomized. (Section 5.3)

Participants must complete enrollment procedures according to the following schedule. If activities are not completed by the specified timeframe, participants will be asked to repeat the appropriate previous step. Participants should download the app within 2 weeks of completing the Screener. After downloading the app, participants should complete the baseline survey and return the home test kit within 4 weeks. Lab results will be returned within 2 weeks after the kits are received by the study. The maximum time for enrollment procedures, that does not trigger repeat of some study steps, is 8 weeks prior to randomization.

5.2 Locator/Contact Information

Once consented and enrolled, designated site study staff will verify the contact information the participant provided in the behavioral eligibility screener. Information to be verified will include the already provided working phone number(s) and valid email address(es). Additionally, participants will provide valid contact information for two alternate contacts, which may include family members and/or friends who can be called in the event the participant cannot be reached by phone or email. We will also record whether participants are willing or not willing to receive voice and text messages using the contact information provided. Study staff will not leave messages unless expressly permitted to do so by the participant. If permission is given to leave messages, site staff will assure participants that messages left with a family member or friend will only ask the participant to contact study staff and will not include any protected health information or information related to study participation.

The contact information will not contain any study data and will be kept secure, separate from study records where able, with access limited to designated site research personnel. Site staff will maintain contact information collected in the web-based platform retention and scheduling database.

For potential participants that provide contact information, but do not download the app, we will maintain a database for follow up.

5.3 Randomization Procedures

Upon completion of all eligibility assessments (online behavioral screening, baseline survey and clinical), participants will be randomized to either intervention (ePrEP, n=120) or control (standard of care, n=120). Participants will be randomized using iDataFax. Randomization will be stratified by study site (AL, GA, MS, NC) to decrease the likelihood of Type I error due to the expected association between covariates and study outcome.

5.4 Intervention

5.4.1 ePrEP System

The ePrEP system is a mobile health intervention designed to allow participants to initiate and maintain PrEP care from their homes. A unified and secure, web-based platform hosts the study app and management portals, allowing for a single database to populate information across these study interfaces. Laboratory testing is accomplished through 'home test kits' consisting of instructions and materials to allow participants to self-collect specimens and return them to a central laboratory for appropriate testing. The intervention fully complies with the standard of care PrEP provision practices outlined in the CDC/US Public Health Service guidance.[12]

Study App:
The study app, eP, serves as the primary participant-facing component of the intervention. The eP app, which will be downloaded on participants' phones, includes many features to facilitate remote care. Electronic messaging features provide a means for participants to communicate with their clinical care team through secure messages, or send documentation needed for PrEP navigation through secure photos. Surveys are hosted in the app, and used to populate key forms and answer key clinical questions such as medication adherence. Automated notifications of progress and appointment reminders are sent, seeking to facilitate engagement in care. A timeline-based view shows progress in care, and next steps such as upcoming virtual visits or home test kits to be completed. Telemedicine consultations with study clinicians will occur within the app through secure video, and scheduling of these consultations will be accomplished through a calendaring function. A preferences function will allow participants to alter their profile such as changing preferred pharmacy or home shipping address. Some of the app features, particularly messaging and survey functionalities, will also be used to incorporate components of interaction that are specific to research study participation. The app is hosted in a secure environment, compliant with all relevant security protocols, and will use password protected entry to enhance privacy. (Section 7.3.4)

The eP app has two versions: one for the intervention group and one for the control group. When participants first download the app, they will only be able to see the initial parts of the app needed for study initiation: baseline survey modules and home test kit tracking. Once the participant is randomized, their version of the app will open up to show them the timeline of the study visits information based on the group they are assigned. The intervention group will be able to see and use all components of the eP app. The control group will only be able to see the parts of the app that are applicable to research: surveys, tracking home test specimens (the mail-in DBS card for TFV-DP), and messaging functionality for communication with study staff.

Management portals:

- *Administrator portal*: Study staff will manage participant interactions through a web-based interface that exchanges data directly with the eP app. Study staff will use the participant management system to securely exchange messages with participants using the eP app. The participant management system will have a dashboard to manage and track participant completion of study-related activities, such as survey completion or scheduling of telemedicine consultations.
- *Clinician portal:* Clinicians will view clinically-relevant participant information in a web-based interface that exchanges data with the administrator interface and the eP app. Participant information viewable to clinicians will include lab results and participant self-reports of sexual behavior, PrEP adherence, and PrEP side effects. A calendaring function will be used by clinicians to make time slots available for telemedicine consultations so that participants can schedule through the eP app. Telemedicine consultation data, including clinician notes, will be collected in the clinician interface for each telemedicine consultation.

Home Test Kit:

ePrEP will use a mail-based specimen self-collection system that has previously been pilot-tested.[16] Participants will receive a plain box via standard mail that includes instructions and materials for each specimen to be collected. Participants will be provided with video and written instructions as well as a call-in help line for the home collection system (during business hours). After specimen collection, participants will enclose them in a prepaid mailer to be sent directly to the lab. Testing of all specimens will be performed at CLIA-certified laboratories using FDA-approved tests. (Section 5.5)

Telemedicine:

The eP app includes a secure video component that will allow for study telemedicine consultations between study clinicians and participants. This will allow study clinicians to evaluate participants at standard, quarterly prescribing intervals for PrEP. Participants may also ask questions of their study clinician using the eP secure messaging system.

5.4.2 PrEP Initiation/Continuation

If laboratory, clinical and behavioral survey results do not show contraindications to PrEP initiation/continuation, the study clinician will initiate or renew the PrEP prescription. Eligible participants will be initiated with a 3-month prescription for FTC/TDF or FTC/TAF by the site study clinician. Standard PrEP financial navigation services will be delivered by study staff trained in order to ensure uniformity of intervention provision. The navigation will use Gilead medication assistance and co-pay access programs, in addition to state-specific programs, to facilitate access to PrEP at low or no cost to participants. We will seek to make home delivery of PrEP prescriptions from pharmacies available. If a participant's insurance does not allow for the home delivery, participants will pick up PrEP from their preferred local pharmacy. Enrolled participants not on PrEP, due to discontinuation or never having initiated, will continue participation in the scheduled research assessments. With clinician guidance, such participants can choose to uptake PrEP at any point during the study.

5.4.3 PrEP Discontinuation / Restart

Regular study interactions include telemedicine consultation, surveys, and messaging with staff. If through any of these interactions a participant reports a gap of not taking PrEP for ≥10 days, this will be defined as a PrEP discontinuation. Participants who have discontinued PrEP will be

allowed to re-initiate during the study with clinical re-evaluation and repeat HIV testing. An additional creatinine test will not be needed as long as previous results were within acceptable range in the past 6 months. Reasons for discontinuing or restarting will be captured.

5.4.4 Research Staff Training

Study staff and clinicians will complete HSP and GCP training. Staff will be trained on using the ePrEP web-based portal for participant management, and on eP app functionality. Study clinicians will discuss case scenarios for PrEP patients for more standardized approaches to specific scenarios seen by PrEP clinicians.

5.4.5 Intervention Monitoring/Quality Control

The principal investigator will monitor data collection throughout the study, will ensure that protocols and procedures are followed, all adverse event reports are reviewed (if any), confidentiality procedures are implemented, and the UNC IRB is alerted if unexpected concerns arise. The study may also be subject to a quality assurance audit by the sponsor or its designees, as well as inspection by appropriate regulatory authorities.

5.5 Laboratory Procedures

All study lab tests will be conducted at CLIA-certified laboratories using FDA-approved tests. Participants will self-collect whole blood in microtubes from finger prick for creatinine and syphilis (using antibody test with reflexive RPR) tests. Whole blood collected on dried blood spot (DBS) cards will be used for HIV testing. Pharyngeal swabs, rectal swabs and a urine sample will be collected for gonorrhea and chlamydia testing. Hepatitis B surface antigen will be tested either through Quest/LabCorp, local health department, or self-collect. Participants may be referred to local testing services, if needed. The Alabama Department of Public Health, Georgia Department of Public Health, Mississippi State Department of Health, and the North Carolina Department of Health and Human Services will be notified of confirmed positive results in accordance with state public health reporting laws, a procedure that will be explained to participants at consent.

Baseline testing: All participants will be tested for HIV, syphilis, creatinine, gonorrhea, chlamydia, and Hepatitis B.

Follow-up testing: Intervention participants will be tested for HIV, syphilis, gonorrhea, and chlamydia quarterly. Creatinine will be tested at months 3 and 9. All participants are scheduled to return DBS cards for TFV-DP testing at months 6 and 12.

5.5.1 HIV Testing

HIV testing may be conducted on either whole blood or DBS. 4th generation HIV tests will be conducted using DBS cards that participants self-collect through finger prick. Standard of care 3rd generation tests may be run if unable to conduct 4th gen test on DBS sample. Specimens with a reactive result on the antibody-based test will undergo confirmatory testing per established protocols on DBS specimens. If confirmed, results will be returned to participants by study staff experienced in HIV care linkage.

5.5.2 STI Testing

All participants will be tested for syphilis and pharyngeal, urethral, and rectal gonorrhea and chlamydia at Baseline. Intervention participants will be tested for syphilis gonorrhea, and chlamydia (pharyngeal, urethral and rectal) at quarterly follow-up virtual visits. Reflexive RPR titer will be conducted if the syphilis antibody test is reactive. Hepatitis B surface antigen will be tested to determine chronic hepatitis B status at Baseline.

5.5.3 Safety Labs

Creatinine will be checked at Baseline, in order to calculate creatinine clearance for eligibility determination. Creatinine testing will be repeated at months 3 and 9 in accordance with CDC guidance. Creatinine will be tested from participant self-collected whole blood specimens using a point-of-care machine. Creatinine clearance will be calculated using the Cockcroft-Gault equation, with participant's self-reported weight at baseline. If creatinine clearance <60 ml/min on follow-up testing, the prescribing physician will make an assessment and recommendation regarding whether the participant will need repeat testing and/or temporary or permanent discontinuation of PrEP.

5.5.4 Dried Blood Spots

Participants will be informed of expectations regarding specimen collection at baseline. DBS cards will be sent to both intervention and control participants for primary outcome assessment at 6 months and 12 months. Spots will be collected on a filter paper card and dried for ≥4 hours prior to mailing. Once returned to the lab, the primary outcome assessment DBS specimens will be stored in a laboratory freezer at -20˚C until they are batch tested for TFV-DP levels at the UNC Kashuba Lab. The Kashuba Laboratory will also measure emtricitabine-triphosphate (FTC-TP) from the DBS cards for secondary analyses.

5.5.5 Referrals

In the case of an initial (4^{th} gen) positive HIV test done through the study, participants will be instructed to discontinue PrEP dosing. Participants testing positive will be referred for study-provided HIV confirmatory testing. Upon receipt of positive HIV confirmatory test results, the linkage to care process will be initiated within two business days. For changes in creatinine clearance, study clinicians will consider discontinuing PrEP for any participants with calculated creatinine clearance below 60 ml/min. As needed, the linkage to care process for low creatinine results will be initiated within two business days. For positive STI tests, participants will have PrEP prescriptions initiated or renewed, and be referred to STI treatment at a local agency. Site study staff will follow-up with participants testing positive for STI to encourage participants to seek appropriate care. Laboratory test results will be provided to participant providers if requested and authorized to release.

6.0 MEASURES

6.1 Behavioral Measures

6.1.1 Pre-entry or screening measures

- Screener for Behavioral Eligibility: The screener asks basic demographic questions and behavioral eligibility questions.

6.1.2 Pre-intervention (baseline) measures

- Baseline Survey: The baseline survey will include questions in the domains of demographics, sexual history, potential correlates of initiating and maintaining in PrEP care, mental health, and stigma. To continue to be eligible for randomization, all survey modules must be completed within a week of starting the first module. After completing the baseline survey (and if clinically eligible) participant will be randomized into control or intervention arm.

6.1.3 On-Study measures

- 1-Month CRF: Intervention participants will have a telemedicine consultation with study staff or clinician to assess experiences one month after initiating PrEP. CRF will record adherence and side effects.
- Surveys for participants in both arms at months 3, 6, 9 and 12: categories include sexual behavior, PrEP cascade, and the validated system usability scale (SUS).

6.1.4 Premature Discontinuation/Off-Study measures

Participants will be asked to answer several brief questions, to be recorded on a CRF, documenting reasons for study withdrawal.

6.2 Clinical and Laboratory Evaluations

6.2.1 Baseline measures

- Home Test Kit: HIV, and Creatinine tests will determine clinical eligibility for the study.

6.2.2 On-Study measures

- *HIV:* 4th generation HIV tests will be conducted using whole blood specimen. HIV testing will be conducted quarterly.
- *DBS:* TFV-DP levels will be assessed at months 6 and 12 to gain an understanding of participant adherence to their PrEP regime. These research outcome results will not be returned to the participants or clinicians.

7.0 DATA COLLECTION AND SITE MONITORING

7.1 Development of Protocol and Case Report Forms

The Protocol Team, in collaboration with the Management Core (MC) and Analytic Core (AC), is responsible for the development of this protocol and the Case Report Forms (CRFs) needed to collect the information required to implement this protocol.

7.2 Data Records

Participant-related study information will be identified through a study ID number (SID) and participant code (participant first initial and two-digit day of birth) on all participant CRFs and survey data. SID will be used wherever possible in place of personally-identifying information.

Source documents, such as laboratory results, the clinician dashboard, and CRFs, will be accessible only to the study staff and study clinicians on a role-based standard.
SIDs will not be entered into the mobile app and instead a unique app ID will be assigned to each participant and used when logging into the app. These unique App IDs will be provided by the developer. Participant locator/contact information will be stored securely in the web-based interface (Section 7.3.4).

7.3 Data Collection

7.3.1 CRFs

Study monitoring data, including information about eligibility and monitoring untoward effects, will be collected on CRFs. CRFs will be completed electronically through iDataFax. All CRFs will be distributed to study staff through iDataFax.

7.3.2 Electronic Surveys

Self-administered surveys at Baseline, 3, 6, 9 and 12 month virtual visits will be completed by participants on personal devices via surveys hosted on a secure electronic platform. Data collected using electronic surveys will remain confidential and be stored on a secure electronic platform, accessed by an application programming interface (API) to populate the eP app and administrative portals. The platform API is linked to the eP app allowing participants to take survey's on their personal devices. SID will be used in order to link the interview responses to the participant's CRF data.

The survey will be an embedded webpage, hosted on the study's electronic survey platform, which appears to participants to be a seamless component of the eP app. The survey will be split into multiple modules to ease participant burden imposed by long surveys.

7.3.4 Data Security

Electronic Survey Data Security
Utilizing a role-based standard, authorized users will be granted unique login names and passwords to access survey data on the survey platform servers. To ensure data privacy, as soon as data is entered (in real-time), it will be encrypted during transmission to the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) Analytic Core (AC) using Secure Socket Layer (SSL) technology. When downloaded, the data is stored in a secure database on an AC server within the AC data center. SSL encryption will be used for transfers of information online and data will be stored in the secure, HIPAA-compliant servers of SurveyGizmo. The Emory AC team maintains a business partner HIPAA agreement with SurveyGizmo.

Participant management system data security
The ePrEP participant management system has two components: a back-end "office" that is an interface for administrators and clinicians to manage participants and store data, and a participant-facing mobile app called eP. Emory University holds Business Associate Agreements (BAA) with all components interacting with the app and hosting servers including Microsoft Azure, Zoom, and SurveyGizmo to ensure HIPAA compliance.

The back-end office participant management system, hosted in the cloud, interacts with a custom, secure API developed to communicate data to and from the server. It also interacts with a HIPAA-compliant video conferencing service, Zoom. Both connections are over a secure connection. The cryptographic algorithm the ePrEP participant management system uses is the AES 256 algorithm, with the key hardcoded on the server side. The system uses SSL to communicate with the API. The key size is 128 bits. The system only includes API authentication; there is no other hard-coded information that exists within the system.

Users and devices will be authenticated through the eP app using form authentication through a unique user ID and password, or through login authentication that uses ID and password settings from Facebook or Google. The app will provide no data to Facebook/Google, and vice versa; instead the app will simply use the Facebook/Google system to authenticate the appropriate user to allow for log-in to the eP app. Once an authentication system is established, the eP app will allow users to log in with TouchID if it is enabled on their phone.

All relevant compliance requirements are met by the eP app, including HIPAA compliance, and security measures for personal health information including auto log out feature. All API's for the eP application are HIPAA compliant. Sensitive data including participant's demographic information (name, phone number, and email address) will be accessible in the application. The participant management system stores lab results as an encrypted database within the central Structured Queried Language (SQL) server that is secure and accessed only via authenticated administrators and clinicians. SQL is a programming language that manages data contained in relational database management systems. The lab results will not be stored in the participant mobile facing application.

7.3.5 Zoom Platform Description

For the telemedicine consultations conducted through the eP application, the study will rely on the Zoom platform. Zoom will be embedded into the eP app. Participants will use it to communicate with their ATN site study clinician in face-to-face video chat, and text based conversation. Our implementation of Zoom is HIPAA-compliant, and Emory University has entered a Business Associate Agreement (BAA) with Zoom. Zoom includes the following functions to protect users: End-to-End encryption, connects automatically using udp and tcp port 8801, 8802, and 8804 or HTTPS (port 443/TLS), encryption with the Advance Encryption Standard (AES) 256-bit algorithm. Session keys are generated with device unique hardware ID to avoid data being read from other devices. This ensures that the consultation cannot be eavesdropped or tampered with.

7.4 Data Submission

7.4.1 CRFs

Electronic CRFs in iDataFax will be used to collect key study data (e.g. randomization assignment) and to record study milestones such as study discontinuation, PrEP discontinuation and restarting, clinician decisions regarding PrEP, referrals, and adverse events (AE). AC staff will work with study investigators and the Management Core (MC) to develop CRFs.

7.4.3 Survey Data Transmission

Only authorized users, based on correct login, will be able to access and open the study surveys. To ensure data privacy, as soon as data is entered (in real-time), it will be encrypted during transmission to the AC using Secure Socket Layer technology. The data will then be immediately stored in a secure database on an AC server within the AC data center.

7.4.4 Retention Data

Study staff will track participant scheduling and retention through the administrator portal of the ePrEP system. All retention data will be stored in the cloud through HIPAA compliant Microsoft Azure. Access to this database requires user permissions and secure log in. Incremental backups of the entire database are performed regularly to create database redundancy.

7.5 Data Quality Assurance

Investigators receiving federal funding must adhere to the Code of Federal Regulations (CFR) to protect research participants and produce reliable study information. Sites participating in research sponsored by the NICHD need to have an internal quality assurance (QA) plan that will identify problems and correct errors in research study records.

7.6 Role of Data Management

The AC will provide instructions concerning the recording of study data on the CRFs, and entry of the data into iDataFax. Electronic survey results will be linked to the ePrEP participant management system back-end office used by study staff. Lab results will be entered into the participant management system back-end office. Only trained study staff will have access to the web portal dashboard and will be allowed to conduct data entry or exports.

7.7 Study Site Monitoring and Record Availability

Site monitors from the MC and AC may visit participating study sites to review a selected portion of the individual participant records, including consent forms, CRFs and supporting source documentation to ensure the protection of study subjects, compliance with the protocol, and accuracy and completeness of records. Regulatory files, as required, will also be inspected to ensure that regulatory requirements are being followed.

The site investigator will make study documents (e.g., consent forms, case report forms) *and pertinent hospital or clinic records* readily available for inspection by the local IRB, the site monitors, the NICHD, the Office of Human Research Protection (OHRP), or the sponsor's designee for confirmation of the study data.

8.0 PARTICIPANT MANAGEMENT

8.1 Tracking Participants / Follow-up

All participants will be followed prospectively for 12 months after assignment to the intervention or control conditions. Research assessments, completed at the participant's home, will be identical for intervention and control participants: surveys at 3, 6, 9, and 12 months, and DBS specimen collection and mailing at 6 and 12 months. All participants will be reminded of their upcoming assessments through the study app. All participants will be followed up for study retention regardless of whether they are actively taking PrEP and/or engaged in PrEP care.

Intervention participants will have a 1-month telemedicine consult with the ePrEP site study staff or clinician, providing an open forum to answer questions/concerns, assess side effects, adherence, behavioral risk, symptoms of acute HIV infection or STD, and provide appropriate clinical management. The intervention arm will have home test lab assessments and telemedicine consultations at 3, 6, 9 and 12 months with their ePrEP site study clinician. Participants assigned to the intervention will receive automatic reminders for scheduled ePrEP site study clinician telemedicine consultations.

Control participants will complete surveys at 3, 6, 9, and 12 months, and home DBS specimen collection and mailing at 6 and 12 months. Control participants will be sent electronic reminders to complete their research assessments. Follow-up calls may also be used for participants who need further reminding and additional follow-up.

All study virtual visits have a set window period for the participant to complete. If a participant misses a virtual visit or scheduled follow-up assessment, they will be allowed to continue in the study for the following virtual visits. They will remain on a 12-month study timeline.

8.2 Compensation

The study will compensate all participants who complete baseline procedures with $100. Participants will receive $50 for completing the baseline survey and eligibility verification steps, and $50 for sending back the home test kit. Follow-up compensation will be $40 for electronic-survey completion and $40 for DBS collection. Individuals who complete the eligibility screener may also receive up to $10. Participants who refer individuals for the study can receive $10 incentive for up to 5 referrals for a maximum of $50.

8.3 Intervening on “Social Harms"

All sites have specific policies governing the treatment of human subjects. These policies specify that medical and psychological assistance will be available in the event a participant should require further evaluation or treatment. Participants will be referred to a local clinic that is able to assist the participant further.

While participants will be informed that they may refuse to answer any question at any time, responses or reactions to certain questions may indicate distress on the part of the participants. If at any time during the study, a participant divulges that he or she is at risk for harm, including but not limited to being abused or experiencing violence, if harm is suspected or likely, or if the participant states he or she is suicidal/homicidal, measures will be taken to ensure his or her safety. Reporting will be done as appropriate to the situation and the legal statutes, and referrals will be provided to appropriate support, counseling or treatment resources.

8.4 Criteria for Premature Study Discontinuation

Participants may voluntarily withdraw from the study for any reason at any time. No further data collection will occur from the date the decision is made to permanently discontinue the subject from the study. The study investigators also may withdraw participants from the study in order to protect participant or staff safety. Study staff will record the reasons for all withdrawals. Early study discontinuation may occur for the following reasons:

- Participant has a confirmed HIV-positive test

- If the study is terminated prior to its planned end date
- If the study clinician or the PI determines it is in the participant's best interest to discontinue participation in the study
- If a participant threatens study staff

Any unexpected adverse events that meet the new safety information reporting criteria will be immediately reported to the UNC-CH IRB and the respective sites' IRBs if applicable. Study staff will complete a Study Stop form for participants who are discontinued. This form will include the date, last virtual visit completed, and reason for study discontinuation.

9.0 MONITORING UNTOWARD EFFECTS ASSOCIATED WITH OR RESULTING FROM STUDY

The study will have study clinicians prescribing FDA-approved oral PrEP, in accordance with Gilead's label indications for tenofovir disoproxil fumarate/ emtricitabine (Truvada) or emtricitabine/ tenofovir alafenamide (Descovy). The prescription of PrEP in the study will also follow guidance from the US Public Health Service and US Centers for Disease Control and Prevention. The study will not be providing study drug. Individuals will be getting prescribed medications from a local pharmacy. Side effects due to the medication will be monitored but not considered study-related adverse events.

The frequency and severity of side effects from Truvada and Descovy are listed as follows (items in bold are from the package insert):

- *Very Common (approximate incidence > 50%):* none
- *Common (approximate incidence > 25 - 50%):* none
- *Likely (approximate incidence of > 10 - 25%) and Mild to Moderate (no disruption to temporary interference with daily activities; may include prescription intervention*): **nausea, fatigue, headache, dizziness, depression, insomnia, abnormal dreams, and rash**.
- *Infrequent (approximate incidence of > 1 - 10%) and Mild to Moderate (temporary interference with daily activities; may include prescription intervention)* : **diarrhea, abdominal pain, decrease in weight**, generalized weakness, shortness of breath, increased cough, runny nose, allergic reaction, skin darkening of the palms of hands and/or soles of feet, muscle pain and weakness.
- *Rare (approximate incidence < 1%) and Severe to Life threatening*: **bone pain and bone changes**, worsening or new kidney damage or failure, liver problems, increases in pancreatic enzyme, increased triglycerides, increased creatine phosphokinase (CPK) which could mean muscle damage, lactic acidosis and severe hepatomegaly with steatosis that may result in liver failure

Site staff must first follow their own IRB's procedure for reporting and managing untoward effects.

There are two types of untoward effects to be identified: (1) those related to the participant and (2) those related to the study staff.

First, the study will catalogue any untoward effect related to the participant. All adverse events (AE) reported will be assessed by the PI for the study site in which the participant was enrolled for the severity, expectedness and relatedness. Reporting is required for occurrences including social harms, psychological distress and serious life-threatening events such as suicide attempts. These may be immediately apparent to the study staff, such as the participant's emotional upset requiring referral for counseling; or they may be delayed and reported later to study staff, such as physical harm to an individual for having participated in the study. Study staff will notify the team of these untoward effects using the iTech Query and Notification System (QNS) accessible through the iTech website (https://itechnetwork.org).

Serious adverse events (SAE) will be adverse events that result in death, are life threatening, requires or prolongs hospitalization, causes disability, or poses other significant hazards. Severity of AEs will be classified as follows: mild, moderate, and severe. Mild AEs will be events that do not require medical attention and are easily tolerated. Moderate AEs will be events that require simple and routine medical treatment and may cause some interruption to daily life. SAEs will be defined as above. AEs will also be categorized as definitely, possibly, or not related to the study. AEs that are definitely related will follow a logical causal sequence from a study activity. Possibly related events will follow a logical causal sequence from a study activity but may also be due to non-study activities. Not related events will be events that do not follow a logical causal sequence from any study activity. All adverse events require reporting to the ATN via the iTech Query system within 24 hours of becoming aware of the adverse event. Study staff will be briefed during the training on the scope of possible untoward effects and instructed to report events.

Second, study staff may encounter untoward events during virtual visits that personally affect them. Training and guidance will seek to minimize this risk. The protocol chairs should be notified of these events so that they may be immediately addressed, evaluated, and guidance modified or expanded to minimize similar risk to other staff.

A Safety Monitoring Committee (SMC) will receive standard data reports on a quarterly basis. The chair of the SMC will lead biannual calls to discuss study progress, and convene additional SMC meetings as needed based on interim reporting. The SMC will be tasked with stopping the study if the intervention proves to be significantly outperforming the standard of care, or if the inverse occurs. We will conduct one interim analysis comparing the efficacy of the intervention in the active arm to the control arm, with efficacy based on differences in trial success versus failure using the primary outcome definition (detectable Tenofovir at 12 months). We will use the O'Brien-Flemming spending function on the Z test statistic assuming a final alpha of 0.05 such that the interim Z statistic bounds are -2.96 and 2.96. If the intervention efficacy is outside those bounds, the trial will be stopped. If the intervention is significantly outperforming the standard of care, the study will seek to adjust study design and supplements to open the intervention arm. The SMC will monitor several other factors, including HIV seroconversion, changes in kidney function, behavioral disinhibition, medication adherence, persistence in PrEP care, and differential loss to follow-up.

10.0 STATISTICAL/ANALYTIC CONSIDERATIONS

10.1 Introduction

10.1.1 A total of 240 participants will be enrolled at baseline to account for a 20% expected loss to follow-up during 12-months of study follow-up.

10.1.2 Primary Outcome: The primary outcome will be detectable TFV-DP drug levels at the month 12 study virtual visit based on an intention to treat analysis. Using standard pharmacological models,[17] TFV-DP level can be used to infer the mean number of days per week PrEP is ingested over a time period of approximately 1-month preceding specimen collection. The cut point used for the primary outcome measure will be TFV-DP levels considered to be a surrogate for substantial HIV protection: >700 fmol/punch, a level indicating ≥ 4 doses per week. The intervention efficacy measure will be quantified as the difference in proportions of the intervention arm with this outcome compared to the control arm. For the power calculations, we will therefore use a two-sample comparison of proportions.

10.1.3 Secondary Outcomes: Secondary outcome measures will be harmonized, to the extent possible, with ATN measures. Safety/tolerance outcomes will include: acute HIV symptoms, medication tolerance assessed based on side effects; adherence with number of pills taken in the past week; demographic, socio-economic, and sexual behavioral risk measures derived from the National HIV Behavioral Surveillance (NHBS) instrument and our previous research instruments;[10, 18] PrEP perceptions and PrEP use adapted from the NHBS instrument as well as other sources;[10, 19] commonly used measures for depression;[20] illicit and non-prescription drug use,[21] sexual stigma,[22] HIV severity and risk perceptions,[23] HIV knowledge,[21] medication adherence self-efficacy,[24] the systems usability scale,[25, 26] healthcare coverage,[27] and use of social and geosocial networking sites.[27] We will also seek to understand rationales for those who fail to persist in PrEP, assessing perceptions of PrEP barriers and concerns.[28, 29] The Kashuba Laboratory may also measure emtricitabine-triphosphate (FTC-TP), which will allow for additional study analyses regarding recency of PrEP dosing.[30]

10.2 Power Estimates

10.2.1 All analyses will assume 80% power to detect a difference at a two-sided 5% significance level. We will also assume a 20% attrition rate in both arms, with independent censoring. Assuming that 5% of participants in the control arm are above cut-point levels of the outcome measure (Section 10.1.2), we will have sufficient power to detect a minimum detectable effect size of 13% absolute difference in the outcome measure (e.g. ≥18% of participants in the intervention arm have outcome measures above the cut-point threshold). A sensitivity analysis determined that to allow for detection of a scenario where intervention outcome level = control+20% absolute increase, our study would remain sufficiently powered with any control participant uptake level ≤15%.

10.3 Statistical Analysis Plan

10.3.1 Aim 1: Analyses of primary outcome that control for potential residual confounding, and analyses of secondary outcomes including initiation of and retention in PrEP care.

Logistic regression and log-linear models will be used to estimate the association between intervention arm and the primary study outcome, TFV-DP level. If prognostic factors associated with the outcome remain insufficiently balanced through stratified randomization, we may adjust for these factors in our models. Potential confounding factors that may be included are medication self-efficacy and motivation to take PrEP. Per protocol assessments that account for potential

changes in intervention as delivered will be conducted. For instance, this would account for participants assigned to the intervention condition opting to instead receive standard of care PrEP from a non-study clinician. A number of secondary analyses will be conducted using regression models. Intervention impact on the secondary outcomes of PrEP initiation and PrEP persistence will be determined using analogous regression models. Another secondary analysis will be to model log10 (TFV-DP levels) as the outcome variable. An additional secondary analysis will account for changes in PrEP eligibility over time, per CDC guidelines. This has the potential to detect significant smaller "sub-clinical" differences in adherence between the intervention and control study arms. Similarly, an analysis with FTC-TP will allow for a more sensitive and sub-clinical assessment of PrEP use. Other specific and aggregate measures of safety including: renal function, HIV incidence, and incident bacterial STI will be assessed.

10.3.2 Aim 2: Exploratory analyses of intervention effectiveness across subgroups, and analysis of potential mediators of initiation or persistence in PrEP care across both study arms, such as self-efficacy and urbanicity.

Heterogeneity of the intervention effects across subgroups will be explored, including that of stratification (race), and socioeconomic indicators. Understanding variables associated with success or failure in home care for PrEP will inform future research, and potentially guide clinician recommendations or policy regarding bringing PrEP to scale. For participants who seroconvert during the study, levels of TFV-DP, PrEP persistence, and other clinically-relevant study data will be analyzed.

10.4 Cost-effectiveness and Cost-utility Analysis Plan

We will employ standard methods of cost analyses, as recommended by the U.S. Panel on Cost-effectiveness Health and Medicine [31] and as adapted to HIV/AIDS programs.[32] This will be accomplished by conducting an economic analysis from the payer perspective (the cost to the party implementing the program) and societal perspective (the payer costs plus the cost to the participant for participating in the program) to estimate the cost, cost-effectiveness, and cost-utility of the intervention relative to standard of care. Comprehensive cost analysis will be conducted to assess the cost of developing and implementing the ePrEP intervention, using a micro-costing approach to estimate net costs. Cost-effectiveness analyses will include calculating the incremental cost-effectiveness ratio (ICER) for the cost per HIV infection averted compared to standard of care as: $[(Cost_{Intervention} - Cost_{StandardofCare})] / [(Infections\ Averted_{Intervention} - Infections\ Averted_{StandardofCare})]$. The health effect will be defined as the projected reduction in HIV infections over time associated with adopting the intervention relative to standard of care. The base, standard of care, model will estimate the number of infections expected in the absence of the intervention, and may vary under different assumptions of baseline and clinic-based PrEP coverage outside of the intervention.[33] In the cost-utility analysis, we will calculate the cost per quality-adjusted life year (QALY) saved. QALYs saved by averting an HIV infection will be up-to-date estimates from the literature. Sensitivity analyses (varying levels of access, coverage, and adherence and exploring the impact of generic drug pricing, one of the major determinants of PrEP cost-effectiveness.[34]) may be tested as unique intervention scenarios for the cost-effectiveness and cost-utility analyses.

10.5 Missing Data

Several procedures will be used to conduct data analysis when data for either outcomes or covariates are missing. The first step will be to assess the extent and pattern of missing data. If

data are missing for only a few cases, then data analysis will be conducted only on study participants with complete data. However, when such a strategy would result in loss of data from a substantial proportion of participants, or if this approach would lead to biased or inaccurate results, then some form of imputation may be performed for secondary analyses. The form of imputation used will depend on the nature of the data that are missing.

10.6 Qualitative Data

In-depth interviews (IDI): In-depth interviews will be conducted after completion of 12-month assessments with key participants to explore the experience of eP app users and standard of care participants over time. Participants asked to participate in IDI will have to sign a separate informed consent form and will be compensated $50 for their time. Interviews will use a timeline, activity-based approach that uses data such as history of PrEP use to prompt participant memories and create an interactive discussion between moderator and participant regarding PrEP care and care seeking experiences. Topics will include: (1) barriers and facilitators to PrEP care, (2) problems with and benefits of the ePrEP system or standard of care, (3) ways to address problems and amplify success of ePrEP or standard of care, and (4) factors that influence successful persistence in or fall-off from PrEP care. IDI's will be conducted until data saturation has been reached. Purposive sampling of study participants will include up to 15 IDI with participants maintained in PrEP care as determined by self-report of PrEP prescription (10 intervention, 5 control) and up to 15 IDI with participants not maintained in PrEP care (10 intervention, 5 control).

Analysis of IDI: Transcriptions and interviewer notes will be entered into a qualitative software to facilitate data management and analysis. Coding will be in line with the constant comparison analysis method, leveraging real-time identification of main themes, and exploring them in further depth among subsequent participants. Final analysis will compare data within and across codes and themes to answer study questions regarding ePrEP adaptation, scale-up considerations, and future research directions.

11.0 HUMAN SUBJECTS

This study will be conducted in compliance with the protocol, ICH Good Clinical Practice guidelines, and 45 CFR Part 46.

11.1 Participants' Confidentiality

All laboratory specimens, questionnaires, surveys, and reports will be identified by a coded identification number and participant code in order to maintain participant confidentiality. Participants will provide their names, mailing address and preferred contact information (email or cell phone number for SMS) into the app which will be used when ordering CareKits. Study staff will confirm shipping address with the participant before the kit is shipped. This personal information will be used only for the purposes of fulfilling the order, confirming participation in the study and returning lab testing results, and will be kept in a database with secure login requirements. All records with personally-identifying information will be kept separate from study data when practicable. In some instances, such as interactions with study clinicians, participant identifying data will be available along with study data as needed. Access to these data will be limited and role-based. Participant information will not be connected to identifying

information where possible. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by authorities specified in Section (7.7). To maximize privacy, the app's mobile phone icon is listed as "eP". The app stores require a description of the app, and we only provide vague information that will not reveal the purpose or topic of the study. The eP app is a shell for the secure, cloud-based hosting servers, and will not store any data on the mobile device. All devices must be authenticated after completing the eligibility screener and before the participant can log into the app. The app requires secure log in each time it is accessed.

Analytic Core Role in Confidentiality

Every effort will be made to ensure that study participants are protected from risks. The main risk specific to the role of the Analytic Core is breach of confidentiality.

Breach of Confidentiality: A potential risk to participants is violation of confidentiality. We will take the utmost caution to protect the confidentiality of all responses. We will minimize this risk by maintaining confidentiality and discretion throughout all research procedures and data management and analysis. All Analytic Core research staff members are required to complete ethical clearance certification regarding protection of human subjects through UNC-CH or Emory University. We also have a strong data and safety monitoring plan in place to protect participants. Adverse events will be reported to the UNC-CH and Emory IRB, individual research PI institutional IRBs and SRV site-specific IRBs using Adverse Event Reporting Forms created by the Analytic Core. Reports of serious adverse events will be sent within 24 hours of notification by the PIs. Annual updates on enrollment and retention will also be sent to the IRBs.

Participants may be concerned about the security of their data, particularly since it is collected and stored electronically. The Analytic Core has significant experience developing security protocols for Internet-based studies, and will take a variety of steps to ensure participant security, including using a dedicated server behind a firewall, encryption of data, separation of identifiers from responses when possible, and password-protected access to data. Therefore, we believe that this risk will be low.

11.2 Minimizing risk to participants

Every available step will be taken to minimize the risk of identifying/linking data being subpoenaed, stolen, or inadvertently released. Certificates of Confidentiality are automatically issued by the NIH, and will cover this study. All research staff members will be required to complete CITI ethical training regarding protection of human subjects through their relevant IRBs. All studies will have documented procedures to safeguard against the risk of the linking information being stolen by keeping such information in secure spaces to which only essential study personnel who have completed CITI certification for human subjects research ethics training (http://citiprogram.org) will have access.

11.3 Risks and Benefits

11.3.1 Risks

Risks to participants in this research study may include:

The measurements that are involved in this study require finger prick to collect blood samples. This procedure may cause local discomfort, bleeding, or bruising; rarely small clot or infection can

occur at the blood draw site. This measurement should not be considered greater than minimal risk in and of itself given its routine use in general health care delivery.

To minimize the risk of participants feeling uncomfortable about answering personal questions, we will use Computer Assisted Self Interview (CASI) methods for the study's surveys. In CASI, participants read survey questions on a mobile phone and use a combination of keyboard and touchscreen entry to input the answers themselves. In-depth interviews will be conducted through telephone or the eP app.

To minimize risks to confidentiality, we will secure study data with all appropriate physical, electronic and operational protections. Data will be stored in a physically secure environment. All data files will have encryption and strong password protection. Any identifiable data will either be stored on Emory University's secure servers or will be on fully encrypted laptops. Electronic surveys and online eligibility screening will take place on an encrypted commercial survey website, SurveyGizmo (http://www.surveygizmo.com/survey-software- features/secure-link/). This site has been used by the investigators for thousands of online surveys with MSM with no data security breaches. Access to data will be on a role-based standard; only those study staff who require access to each type of data to complete their study-related roles will be allowed access. All study staff will be trained in security and confidentiality procedures, and will sign a confidentiality agreement before receiving access to any participant data.

Procedures will be developed to minimize indirect disclosure that a participant is participating in an HIV- related research study, or a study that enrolls MSM. Participants will be asked preferred method(s) of contact. No study-related messages will ever mention HIV prevention or the nature of the research study. Additionally, all scripts for email, text message, and telephone contact with participants will be reviewed and approved by the IRB before being used for contact with participants.

We use SSL encryption for transfers of information online, and SurveyGizmo has a business partner HIPAA agreement with Emory. SurveyGizmo’s servers are HIPAA compliant. Qualitative data analysis will be conducted on a secure software program (e.g. MaxQDA, Dedoose, Atlas.ti).

All study personnel names on this application have completed training and received certification in Human Subjects Research Protection (CITI Program) and HIPAA regulations. They will continue to renew this training in compliance with institutional policies.

11.3.2 Benefits

Possible individual benefits of participation include access to HIV and STI testing at study initiation for all participants, and remote access to pre-exposure prophylaxis for HIV prevention for participants assigned to the intervention arm.

11.4 Institutional Review Board (IRB) Review and Informed Consent

This protocol, the informed consent documents and any subsequent modifications will be reviewed and approved by the IRB responsible for the oversight of the study. The informed consent will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Written informed consent will be obtained from the participant through an electronic procedure. The consent form will be kept on file on secure servers, and a copy of the consent form will be available for download by the participant.

11.5 Prisoner Participation

NICHD has concluded that this protocol does NOT meet Federal requirements governing prisoner participation in human subject research and should NOT be considered by local IRBs for the recruitment of prisoners. Subjects enrolled who subsequently become incarcerated or are placed in detention will be study stopped. If incarceration is less than 3 months, they may be able to restart study activities. Study visits cannot be conducted during the period of incarceration or detention.

11.6 45 CFR Parts 160 and 164 Standards for Privacy of Individually Identifiable Health Information ("Privacy Rule" Pursuant to the Health Insurance Portability and Accountability Act - HIPAA)

Each site is responsible for adherence to their individual institution's HIPAA policies and procedures.

11.7 Study Discontinuation

This study may be discontinued at any time by the NICHD.

12.0 PUBLICATION OF RESEARCH FINDINGS

Any presentation, abstract or manuscript will be made available for review by the study sponsors prior to submission.

13.0 BIOHAZARD CONTAINMENT

After home collection of specimen(s) for testing, participants will place the specimen collected in the provided packaging, which meets all federal regulations for shipment of Biological Substances, Category B (UN3373). Staff trained in biohazard handling will store specimens or ship them to the appropriate laboratory. Handling of specimens will be conducted in compliance with guidance from CDC, and with Federal and local laws, with OSHA blood-borne pathogens standards. *This policy includes the samples being transported by ground to the local laboratory.* Compliance will be achieved by education of personnel involved with packaging and transporting specimens.

All infectious specimens must be shipped as Diagnostic Specimens according to current IATA Shipping Guidelines for Infectious Substances Class/Div. 6.2. Refer to individual carrier guidelines (e.g. FedEx, Airborne Express) for specific instructions.

13.1 Future Storage

Participants will be asked during the consenting process if they give permission to have samples stored for future research. DBS specimens collected from participants who agree to have samples stored for future use will be stored at Emory University or contracted laboratory. Only study staff will have access to the samples. Personal identifying information will not be kept with the samples. These samples could assist with other research, such as DBS validation

measures. Participants who do not agree to have specimens stored will have specimens discarded after study lab tests are conducted.

14.0 REFERENCES

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