Protocol

Title: Biomarkers for Event-driven PrEP Adherence

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TITLE OF PROJECT: Biomarkers for Event-driven PrEP Adherence
Short title: ED-PrEP Biomarkers

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Rationale: Men who have sex with men (MSM) continue to be disproportionately affected by HIV. The majority of HIV infections among MSM occur through exposure to the rectal mucosa during condomless receptive anal intercourse (CRAI). To aid in prevention, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) are recommended for MSM who may be exposed to HIV. Current CDC recommendations for PrEP are to take the combination anti-HIV drug, tenofovir+emtricibatine (TDF/FTC), on a daily basis for the duration of someone's HIV risk exposure period, which could be months or years. For PEP, a three-drug anti-HIV medication is recommended within 72 hours of a possible exposure for a 28-day course by CDC. While PrEP and PEP are efficacious, both the daily dosing of PrEP and the 28 day course of PEP limit their utility in practice, as many users find long term adherence to these regimens to be difficult. Therefore, short course regimens taken around the time of sex (On-demand or Event-Driven PrEP; ED-PrEP) are appealing to some, and WHO endorses one such ED-PrEP regimen: two doses of TDF/FTC between 2 and 24 hours before sex, one dose 24 hours after sex, and another dose 48 hours after sex. Biomarkers (e.g. tenofovir diphosphate (TFV-DP) levels from dried blood spots) to confirm self-reported adherence to daily TDF/FTC have been an important tool used to interpret the results of PrEP clinical trials and demonstration projects. However, no such biomarkers exist to validate self-reported adherence to ED-PrEP. The aim of this study is to better understand how biomarkers might be used to validate self-reported ED-PrEP use. As ED-PrEP is intended to be used infrequently, this study will determine if the accumulation of biomarkers differs depending on whether multiple ED-PrEP dosing events are sequential or intermittent.

Design: To establish biomarkers to determine adherence of ED-PrEP in MSM, investigators at Emory University will collaborate with the Center for Disease Control and Prevention (CDC) to conduct a clinical trial of up to 40 MSM aged 18-59 with measurement of anti-retroviral drug concentrations in various body compartment sites. We plan to enroll participants who are HIV negative and at low risk for HIV and are not currently (or have no current plans) taking PEP or pre- exposure prophylaxis (PrEP). We will enroll participants in one of 4 study arms where they will be given the aforementioned 2-1-1 dosing of TDF/FTC.

We will recruit participants through existing research databases at the Hope Clinic and the Rollins School of Public Health, Research Match, and Clinical Data Warehouse. Internet and paper advertisements, and community venues will also be used. At the first study visit, eligibility will be determined and screening blood work (approximately 24 mL), including an HIV test, will be performed. Participants will receive doses of the drug in clinic or will provide documentation of taking doses of the drug at home. During visits, all participants will undergo blood collection (approximately 24 mL or 5 teaspoons of blood will be obtained), a urine sample, and finger stick will be collected. At certain visits, hair sampling will also be collected.

Duration: The duration of this study is 1 year. Participants will be considered 'on study' for no more than 24 weeks.

Sample Size: For this protocol we will recruit 80 HIV-negative MSM (age 18-59) who meet eligibility criteria outlined in the protocol, to ensure completion of 40 participants.

Population: The population to be studied in this protocol are healthy HIV negative MSM at low risk of HIV infection who currently do not desire daily PrEP and are willing to perform study procedures. We will recruit participants through existing research databases at the Hope Clinic and the Rollins School of Public Health, through internet and paper advertisements, and community venues as is currently the process for Dr. Kelley's ongoing research protocols.

LAY SUMMARY:

Men who have sex with men (MSM) continue to be disproportionately affected by HIV. In 2014, MSM made up approximately 2% of the U.S. population but accounted for 70% of the new HIV infections (CDC)(2). The majority of MSM acquire HIV after exposure to the rectal mucosa through receptive anal intercourse without condoms. Pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) are recommended for MSM who may be exposed to HIV to prevent infection. Current recommendations for PrEP are to take the combination anti-HIV drug, tenofovir+emtricibatine (TDF/FTC), on a daily basis for the duration of someone's HIV risk exposure period, which could be months or years. For PEP, a three-drug anti-HIV medication is recommended within 72 hours of a possible exposure for a 28-day course. While PrEP and PEP are effective, some people find it difficult to follow the recommended regimen. Therefore, additional short-course dosing regimens for PrEP and PEP are being implemented, such as event-driven or on-demand PrEP (ED-PrEP). This dosing regimen has patients take two doses of PrEP 2-24 hours before sex, one dose 24 hours after sex, and another dose 48 hours after sex. This proposal seeks to evaluate the usefulness of biomarkers to confirm self-reported adherence to ED-PrEP in MSM. The study drug provided in this study will not protect participants from HIV or treat any active infection.

For this protocol, we will recruit 80 HIV-negative MSM aged 18-59 in good general health. Participants will be sequentially assigned to one of 4 study arms which will determine when they will take doses of the study drug and give specimen samples. All participants will provide written informed consent at the first study visit and undergo a screening medical history and safety laboratory tests. A physical exam may also be completed. All participants will take at least 4 doses of the study drug. At study visits, participants will return to donate blood, hair, and urine samples, and a finger stick. All biologic specimens collected will be transferred to CDC on the day of collection for measurement of drug levels.

PROJECT DESCRIPTION

Public Health Relevance: Event-driven PrEP (ED-PrEP) could be an effective solution for those who struggle to take a daily regimen of PrEP to prevent HIV. This is particularly important for those who engage in sexual activities less regularly, and therefore feel daily PrEP is unnecessary or too costly. However, there are currently no biomarkers available to validate self-reported ED-PrEP adherence.

Goal: The goal of this study is to evaluate the utility of biomarkers to validate self-reported ED-PrEP dosing.

STUDY POPULATION

INCLUSION CRITERIA

1) HIV-negative person, who was assigned male at birth, who reports sex with another man in the last year, and is in good general health.
2) Aged 18-59 years
3) Not currently taking PrEP and no plans to initiate during study
4) Not currently taking PEP
5) Consistent condom use and willing to use condoms for the duration of the study
6) Able to provide informed consent in English
7) No plans for relocation in the next 4 months
8) Willing to undergo peripheral blood, urine, finger stick, and optional hair sampling.
9) Willing to use study products as directed
10) Hepatitis B surface antigen (HBsAg) must be negative (screening lab test)
11) Creatinine clearance >60 ml/min

EXCLUSION CRITERIA

1) Currently infected with hepatitis virus and/ or has liver disease
2) Current or chronic history of kidney disease or CrCl<60 ml/min
3) Continued need for, or use during the 90 days prior to enrollment, of the following medications:
    a) Systemic immunomodulatory agents
    b) Supraphysiologic doses of steroids (short course steroids less than 7 days duration, allowable at the discretion of the investigators)
    c) Chemotherapy or radiation for treatment of malignancy
    d) Experimental medications, vaccines, or biologicals
4) Intent to use HIV antiretroviral pre/post-exposure prophylaxis (PrEP or PEP) during the study, outside of the study procedures
5) Current use of hormonal therapy
6) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the patient unsuitable for the study or unable to comply with the study requirements.

PROCEDURES

Recruitment procedures

Participants will be recruited with several methods. First, the Hope Clinic maintains large databases of potential participants interested in participating in future research. Email blasts and phone calls will be made to potential participants from these databases. ResearchMatch, a secure online database used by researchers who are seeking volunteers and people who are interested in finding research/ clinical trial studies to participate in, will also be used as a recruitment source. The site will recruit from the Emory Healthcare Clinical Data Warehouse. The Clinical Data Warehouse is a repository that integrates data from clinical applications within Emory Healthcare, providing data needed for clinical reporting, research and operational support. Any contact made by email and or phone (refer to online engagement section for direct & SMS messaging script), recruiters will use one of the following scripts:

Phone call

Participants who are called will be greeted by the study staff. “Hello, my name is [ ]. I am calling from the Hope Clinic…” Staff will refer to Oral Consent and Pre-Screener.

Email

Hello my name is [ ] and I am from Emory University Hope Clinic. We are currently looking to enroll participants into a new study at the Emory University Hope Clinic. This study aims to establish biomarkers to determine adherence to on-demand PrEP which can be used to effectively prevent HIV. Study visits range from ten to twenty two visits, and you will be compensated for your time of travel and inconvenience. If you or anyone you know may be interested or have any questions about this study, please contact _____ or _____. These are the basic qualifications to participate in the study:

- You may qualify if you are:
- Age 18-59
- HIV negative man who has sex with men
- Not currently taking PrEP or PEP
- Able to consistently use condoms

Print and on-line ads will also be placed around Emory and other community settings. Finally, active recruitment will be conducted as outlined below with face-to-face and online engagements. Dr. Kelley and co-investigators have a successful track record in recruiting MSM for their research protocols utilizing all of these methods.

Volunteer contact details are collected by conducting in person face-to-face and/or online social network engagement.

Face- to-face engagements: Participants may be actively or passively recruited at community venues listed below and engaged with limited information about the study and study qualifications. Recruiters will use 1 out of 2 generalized scripts when engaging with participants (please see section B below). A site contact sheet or a tablet using SurveyGizmo will be used to populate name, phone number, and email address of interested participants.

A. Face -to- Face engagement

- **a.** Community annual events attended by MSM (e.g. Pride festivals, MSM symposium, etc.)
- **b.** Bars and Night Clubs catering towards MSM
- **c.** Community organizations serving MSM
- **d.** Sporting events
- **e.** Other community venues where MSM might visit/patronize

Online engagements: Potential participants will be engaged and supplied with limited information about the study and study qualifications via paid advertisements on social media sites and dating apps. All print and online advertisement copies will be submitted to the Emory IRB for approval prior to launching these activities. Interested participants will click a posted ad with an embedded hyperlink, which will redirect them to a short screener. This screener will capture information regarding eligibility, including HIV status, name, phone number and email. Recruiters will use information obtained from online screener to contact and schedule participant visits. Potential participants may also be engaged directly on social media to assess interest in research participation. Any contact made through direct messaging, recruiters will have a generalized script (mentioned below) to follow (script can also be used for SMS contacting, as well). We will seek permission from creator/ moderator of the private website/ group, etc. before entering an interaction if possible.

A. Online Social Network

- **f.** Dating Sites (Jack'd, Adam4Adam, Grindr, etc.)
- **g.** Social Network (Facebook, Snapchat, Instagram, etc.)
- **h.** Other online social media platforms and websites where MSM might visit/patronize

B. Script used by recruiters when engaging by direct messaging (can be used for SMS):

a. Hello, I am a recruiter for research studies at the Emory University Hope Clinic. We are currently looking for volunteers to participate in one or more of our HIV prevention research studies. Would you be interested in learning more?
Thank you,
__Insert Name and contact details here___

If contact responds affirmatively, then their contact information will be collected for a screening phone call (see phone screen script).

b. Hello, I am a recruiter for research studies at the Emory University Hope Clinic. We are currently looking for volunteers to participate our HIV prevention research studies. All enrolled volunteers will be compensated for their time, travel, and inconvenience. Would you be interested in learning more?
Thank you,
__Insert Name and contact details here___
If contact responds affirmatively, then their contact information will be collected for a screening phone call (see phone screen script).
If contact responds negatively or does not responds, no further contact will be attempted.
If contact responds negatively or does not responds, no further contact will be attempted.

c. Hello, I am a recruiter for research studies at the Emory University Hope Clinic. We are currently looking for volunteers to participate in one of our HIV prevention research studies. All enrolled volunteers will be compensated for their time, travel, and inconvenience. To learn more, please visit www.hopeclinic.emory.edu/studies/enrolling-studies.html or call 877-288-0048.
Thank you,
__Insert Name here___

If contact responds affirmatively, then their contact information will be collected for a screening phone call (see phone screen script).

If contact responds negatively or does not respond, no further contact will be attempted.
We will recruit subjects for this protocol from existing Emory University databases of MSM who have consented to be re-contacted for future research opportunities (see below).

Study visits
When possible, study activities such as questionnaires will be done remotely due to the ongoing COVID-19 pandemic.

Eligible subjects will be sequentially assigned to study arms: A, B, C & D. Our goal is to have 10 participants complete each arm.

Participants may participate in more than one study arm; however, at least 8 weeks must lapse after completion of one study arm, before entry into another. Participants who participate in more than one arm do not have to repeat the screening visit (visit 1) when starting another arm; they will begin the new arm at visit 2. However, they will be re-consented on the consent form of the new arm prior to any arm-specific study activities being performed.

Participants who are unable to donate hair will not be considered protocol deviations.

The consent process will be conducted in a private exam room at the Hope Clinic or electronically via an online e-consent platform. Copies of the consent form for this project will not be placed in individuals' medical records since this study collects sensitive information such as HIV status and sexual orientation. All participants will be provided a copy of the signed informed consent form (ICF).

ARM A (n=20; Arm will close to enrollment once 10 participants have completed study visits):

Visit 1 (screening): Eligible MSM will be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for creatinine and hepatitis B testing, as well as testing for baseline levels of study drug. A physical exam may also be completed. Participants will then be asked to return within 1-6 weeks for visit 2.

Visit 2: Participants will return to the clinic to be given their first dose of 2 pills of TDF/FTC with instructions to take the next pill 24 hours later, and document that dose with a time-stamped photograph or video.

Visit 3: Participants will return to the clinic 48 hours after first dose, and 24 hours after second dose to receive their third and final dose of one pill. After the dose is taken, approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 4: Participants will return to the clinic 24 (+/- 2 hrs) hours after their last dose at Visit 3. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 5: Participants will return to the clinic 2-5 days after their last dose at Visit 3. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 6: Participants will return to the clinic 7 (+/- 1 day) days after their last dose at Visit 3. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 7: Participants will return to the clinic 14 days (+/- 1 day) after their last dose at Visit 3. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 8: Participants will return to the clinic 21 (+/- 1 day) days after their last dose at Visit 3. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 9: Participants will return to the clinic 28 days (+/- 1 day) after their last dose at Visit 3. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with hair sample. This visit will also include urine and rectal STI screening.

ARM B (n=20; arm will close to enrollment once 10 people have completed study visits)

Visit 1 (screening): Eligible MSM will be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for creatinine and hepatitis B testing, as well as testing for baseline levels of study drug. A physical exam may also be completed. Participants will then be asked to return within 1-6 weeks for visit 2.

Visit 2: Participants will return to the clinic to receive their first set of study drug for weekly 2-1-1 dosing. The first dose of 2 pills will be taken in clinic, the next dose of 1 pill to be taken 24 hours later at home, and the last dose at home 48 hours from the first dose (24 hours after the second dose). Participants will be instructed to take their 2-1-1 dosing on the same days every week. Participants will be instructed to provide documentation of all other dosing with a time-stamped video or picture.

Visits 3-14: Participants will return after finishing their weekly 2-1-1 dose, to do their weekly convenience sampling. Approximately 24 mL of blood will be drawn, urine sample, and a finger stick will be collected. An HIV test will be completed at visits 6, 10 and 14 (once per month) along with hair samples. Urine and rectal STI screenings will be conducted at visit 10. An additional creatinine test will be done at visit 14. Participants will be provided with their medication at visits 5, 8, and 11.

Visit 15: Participants will return to the clinic to take their final dose of study drug in clinic. After the dose is taken, approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 16: Participants will return to the clinic 24 (+/- 2 hrs) hours after their last dose at Visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 17: Participants will return to the clinic 2-5 days after their last dose at Visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 18: Participants will return to the clinic 7 (+/- 1 day) days after their last dose at Visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 19: Participants will return to the clinic 14 days (+/- 1 day) after their last dose at Visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 20: Participants will return to the clinic 21 (+/- 1 day) days after their last dose at Visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 21: Participants will return to the clinic 28 days (+/- 1 day) after their last dose at Visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with a hair sample.

ARM C (n=20; arm will close to enrollment once 10 people have completed study visits)

Visit 1 (screening): Eligible MSM will provide informed consent, be questioned about their medical history, undergo a physical exam (conducted by a study clinician), a rapid HIV test, and a peripheral blood sample for a complete blood count, creatinine, coagulation test, and hepatitis B testing. Participants will then be asked to return within 1-6 weeks for visit 2.

Visit 2: Participants will return to the clinic to receive their first set of study drug for alternate week 2-1-1 dosing.. Participants will be instructed to provide documentation of all dosing with a time-stamped video or picture and provided with a calendar detailing when they should take the study drug Participants will take the first 2 pills of their 2-1-1 dosing before leaving this visit.

Visit 3-14: Participants will return to do their weekly convenience sampling. Approximately 24 mL of blood will be drawn, urine sample, and a finger stick will be collected. A rapid HIV test will be completed at visits 6, 10 and 14 (once per month) along with optional hair samples. Participants will have urine and rectal STI testing at visit 10. An additional creatinine test will be done at visit 14. Participants will be provided with their medication at visits 5, 8, and 11.

Visit 15: Participants will return to the clinic to take their final dose of study drug in clinic. After the dose is taken, approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 16: Participants will return to the clinic 24 (+/- 2 hrs) hours after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 17: Participants will return to the clinic 2-5 days after their last dose at Visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 18: Participants will return to the clinic 7 (+/- 1 day) days after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with an optional hair sample.

Visit 19: Participants will return to the clinic 14 days (+/- 1 day) after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with an optional hair sample.

Visit 20: Participants will return to the clinic 21 (+/- 1 day) days after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with an optional hair sample.

Visit 21: Participants will return to the clinic 28 days (+/- 1 day) after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with an optional hair sample.

ARM D (n=20; arm will close to enrollment once 10 participants complete study visits)

Visit 1 (screening): Eligible MSM will provide written informed consent, be questioned about their medical history, undergo a physical exam (conducted by a study clinician), a rapid HIV test, and a peripheral blood sample for creatinine and hepatitis B testing. Participants will then be asked to return within 1-6 weeks for visit 2.

Visit 2: Participants will return to the clinic to receive their first set of study drug for consecutive week 2-1-1 dosing; 8 doses of study drug for 2-1-1 dosing once per week on consecutive weeks followed by 2 consecutive weeks without dosing for 13 weeks. Participants will be instructed to provide documentation of all dosing with a time-stamped video or picture and provided with a calendar detailing when they should take the study drug. Participants will take the first 2 pills of their 2-1-1 dosing before leaving this visit.

Visit 3-14: Participants will return to do their weekly convenience sampling. Approximately 24 mL of blood will be drawn, urine sample, and a finger stick will be collected. A rapid HIV test will be completed at visits 6, 10 and 14 (once per month) along with optional hair samples. An additional creatinine test will be done at visit 14. Participants will be provided with their medication to follow this aforementioned dosing schedule at visits 5, 8, and 11.

Visit 15: Participants will return to the clinic to take their final dose of study drug in clinic. After the dose is taken, approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 16: Participants will return to the clinic 24 (+/- 2 hrs) hours after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 17: Participants will return to the clinic 2-5 days after their last dose at Visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected.

Visit 18: Participants will return to the clinic 7 (+/- 1 day) days after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with an optional hair sample.

Visit 19: Participants will return to the clinic 14 days (+/- 1 day) after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with an optional hair sample.

Visit 20: Participants will return to the clinic 21 (+/- 1 day) days after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with an optional hair sample.

Visit 21: Participants will return to the clinic 28 days (+/- 1 day) after their last dose at visit 15. Approximately 24mL of blood will be drawn, urine sample, and a finger stick will be collected, along with an optional hair sample.

Biological specimens:
Hair samples will be taken from those participants who are able to give a hair sample. 50-100 strands of hair will be taken using scissors at the above specified visits. Biologic specimens collected after the screening visit will be transferred directly to CDC for measurement of study drug levels. Specimens will be labeled with a unique ID that only the Emory study team will be able to link to identifiable information. CDC personnel will not have access to identifiable information.

Contingency visit:
Attempts to ensure adherence to the study visits will be made with telephone and/or email reminders to the participant. However, if for example, screening laboratory results are lost or are inconclusive or if a participant has been unable to adhere to study protocol, he may be rescheduled for a future date where the above visit procedures will be performed. These additional visits will be scheduled within the above visit windows.

Missed Visits:
In all arms, up to 3 missed visits (~15% of all study visits) are allowed.

Timing of procedures after dose:
The procedures conducted after dose, particularly those less than 24 hours after dose, should occur as close to the scheduled time points as possible. Protocol deviations will be filed for visits that occur outside of the target windows identified above only if the visit is conducted more than 3 hours beyond the target window defined above for each arm and visit.

Phone calls/retention contacts:
While on study, periodic phone calls, texts, or email reminders will occur between study staff and participants to ensure proper retention and adherence to study protocol.

Statistical Analysis Plan
Primary study outcome: Median (range) TFV-DP concentrations in dried blood spots will be measured at Visit 4 in Arm A and compared to TFV-DP concentrations in dried blood spots measured at Visit 16 in Arm B to compare accumulation of drug following weekly ED-PrEP dosing. In addition, TFV-DP concentrations in dried lood spots will be measured at Visit 16 in Arm C and compared to TFV-DP concentrations in dried blood spots measured at Visit 16 in Arm D to compare accumulation of drug following the different ED-PrEP dosing strategies. Differences in median drug concentrations between arms will be
analyzed with a non-parametric Wilcoxon-signed rank tests and a p-value <0.05 will be considered significant.

Other drug level outcomes will be exploratory.

Future use of specimens
Leftover biologic specimens will be stored and use for future research use at Emory University Hope Clinic or the CDC. Stored samples will only be distributed to researchers who have obtained protocol approval from an IRB (or appropriate waiver).

RISKS AND HOW MINIMIZED

HIV risk counseling
Participants that are tested for HIV to ensure eligibility will undergo HIV risk reduction counseling (e.g. increasing condom use, reducing number of partners, addressing substance abuse, etc.) by the study PI or study staff with provision of condoms and lubricant available freely at the Hope Clinic. HIV rapid testing will then be conducted with a CLIA waived product with finger-stick or whole blood from phlebotomy, depending on the test. Any participant who is found to be HIV positive on rapid testing will be referred for confirmatory testing to their local health department, community based organization that provides HIV testing, or provider of their choice. We will also assist any HIV positive participant in accessing healthcare for HIV infection as needed.

Participants will also be educated about HIV pre-exposure prophylaxis during the study by the coordinator and/or study clinician. After completion of the study, all participants who are interested in PrEP for HIV prevention will be linked to community services. A detailed listing of PrEP services available for insured and uninsured clients in Atlanta can be found at www.preplocator.org. Dr. Kelley is active in PrEP implementation in the Atlanta community and can facilitate these linkages.

Blood sample collection
The most common risks of blood sample collection are pain at the puncture site, bruising, and a feeling of lightheadedness. To minimize these risks, blood draws will be performed by trained personnel, and will be performed in a secure environment with access to first aid equipment, bandages, and trained healthcare professionals.

Risk of TDF/FTC
TDF/FTC is a combination anti-HIV medication that contains the drugs tenofovir and emtricitabine. Based on clinical trials previously conducted of TDF/FTC, the drug showed to be well tolerated (see package insert). The most common adverse events reported in clinical trials (≥ 5% incidence) included diarrhea, nausea, and headache. Additional adverse reactions occurring in less than 2% of subjects administered TDF/FTC included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression

Renal toxicity and bone density loss are rarely reported with chronic use of TDF containing products and are not expected to occur with the regimen prescribed in this protocol. Similarly, lactic acidosis and severe hepatomegaly have rarely been associated with medications in the same class as TDF and FTC.

Use of TDF/FTC can also cause flare-ups in those who have hepatitis B virus. It can cause the Hepatitis B virus to suddenly return in a worse form than before if treatment

was provided (see package insert). For this reason, it is important that participants not participate in the study if they are known to have Hepatitis B.
Acquisition of HIV drug resistance is a theoretic concern for HIV positive people taking intermittent dosing of anti-HIV medication. For this protocol, we will test participants for HIV at study entry and monitor clinically for high-risk behavior or any signs of acute HIV infection at study visits. We will only enroll participants at lower risk for HIV and who report consistent condom use. If high-risk behavior (e.g. unprotected anal intercourse with a man of unknown HIV status) or symptoms of acute HIV infection are reported, and HIV antigen/antibody test will be repeated and the participant will be counseled about the need for any follow-up testing. Clinical signs and symptoms of acute HIV infection that will be queried include: fever, fatigue, malaise, skin rash, swollen glands, oral/genital ulcers, myalgia/arthralgia(3). Dr. Kelley will review all reports of clinical signs/symptoms to determine appropriate follow-up and linkage to care as necessary. If a diagnosis of acute HIV infection is thought to be possible or determined by repeat HIV testing, the participant will be discontinued from the study.

Participants taking TDF/FTC will be counseled that they should not expect to achieve protection from HIV infection by taking drug during this study, as they will be provided a limited supply. All participants included in the study that have an interest in taking PrEP for HIV prevention, will be referred to an area PrEP provider at the termination of the study. The Hope Clinic has compiled a resource sheet of area providers that will be distributed to interested participants. All participants will be offered condoms and lubricants at every study visit.

BREACH OF CONFIDENTIALITY

All measures will be taken to ensure information provided by participants is kept confidential. Identifying paper information will be kept in a separate locked office and only accessible by the PI and study coordinator. Electronic data will be stored on the Redcap server or the Emory School of Medicine HIPPAA compliant servers, which will be accessible to the PI and study staff only. All study specimens will be labeled with a unique identifier prior to transport to CDC. Identifying information will not be shared with laboratory collaborators at the CDC and they will be unable to link the study ID to any identifying information. Any demographic data shared with CDC will also be stripped of HIPPAA identifiers prior to sharing.

BENEFITS

Subjects will not derive direct benefit from this study.

COST

There is no cost to subjects to participate in this study.

ALTERNATIVE

The alternative to participating in this study is to decide not to participate. Subjects can withdraw their consent at any time.

COMPENSATION

All participants will be compensated for their time and inconvenience of study participation. Compensation will be provided on a web-based, reloadable, debit card (ClinCard) that automates reimbursements. The ClinCard will be provided by study staff at the participants' initial visit (visit 1), and funds will be loaded after the completion of each visit.

Arm A (closed as of 7/14/21)

Participants will receive $20 for the screening visit, $20 for each study visit involving sampling procedures, to compensate for time and effort. If participants do not finish the study, we will compensate for the visits they have completed ($180 total for those who finish all study visits). Participants who complete all 9 study visits for Arm A will receive a $50 "finishing bonus" at their last visit, to improve retention in this arm.

Arms B, C & D

Participants will receive $50 for each visit they complete to compensate for time and effort. If participants do not finish the study, we will compensate for the visits they have completed ($1050 total for those who finish all study visits). Participants who complete at least 18 study visits for Arm B, C, and D (miss a maximum of 3 visits) will receive a $100 "finishing bonus" at their last visit, to improve retention in this arm.

If a contingency visit is necessary, participants will be compensated $20 for completion of a contingency study visit.

There is no charge for parking at the Hope Clinic. However, participants may be provided with a MARTA card if available.

PLAN FOR OBTAINING INFORMED CONSENT

After being screened for eligibility by the PI or study coordinator, subjects will be informed about the study and asked to sign an Emory IRB approved informed consent. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Subjects may complete the informed consent process electronically or in person. If informed consent is performed in person, subjects will be consented in a private exam room. Subjects will be given time to read the consent, ask questions and consider the risks and/or benefits to participation in this research study prior to obtaining their signature. All subjects enrolled in the study will be given a copy of their signed and dated informed consent document. This consenting process will be done by trained research staff at the Hope Clinic. If participants complete informed consent electronically, they will use an approved e-consent platform.

This will be sent to participants prior to their first visit via a secure and unique link. Participants will be given direct contact information for the study staff in order to answer any questions or concerns they may have and will electronically sign the consent form via the online platform. A copy of the consent form will be available to participants for download at the time of consent. All subjects will undergo HIV risk reduction counseling with provision of free condoms at their first in-person visit.

PROVISIONS FOR SUBJECTS FROM VULNERABLE POPULATIONS

Non-English speaking subjects or illiterate subjects will not be eligible to participate in this study.

PARTICIPATION OF WOMEN AND CHILDREN

Because this is a study of MSM, those assigned female sex at birth are not eligible. It is especially important to include MSM aged 18-21 as young MSM are at highest risk of HIV infection and research that may lead to better prevention interventions, including an HIV vaccine, are desperately needed for this group. Children younger than 18 will not be eligible.

SUBJECT PRIVACY AND DATA CONFIDENTIALITY

All subjects will provide informed consent in a private room at the Hope Clinic or on a secure electronic consenting platform.

Case report forms (CRFs) will be provided for each subject to collect demographic, behavioral, clinical, and laboratory data at study entry, and additional clinical data at the study visit. These data will be collected from the screening clinical assessment, the study entry physical examination and screening laboratory tests, and rectal biopsy visits. Subjects will be identified by the participant identification number (PID), which will be provided by the study investigator upon registration. All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain subject confidentiality. All study samples will be kept in a secure area in a limited-access laboratory facility and only the research team will have access to the samples. The samples and data will be identified only by code numbers.

Any identifiable records will be kept locked accessible only by authorized study personnel. Electronic data will be password protected and stored on the Redcap server or the Emory School of Medicine HIPAA compliant server. Biologic samples will be coded with a unique identifier and no identifiable behavioral data will be shared with laboratory investigators at CDC. Information about the subject's participation will not be shared with individuals who are not directly involved with the research subjects. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NIH, or the OHRP. Information about the subject's participation will not be shared with individuals who are not directly involved with the research subjects.

PLANS FOR SUBJECTS AT THE END OF THE PROTOCOL

Subjects will return to the standard of care at the end of the protocol. Subjects who are interested in starting PrEP will be linked to care with a community provider. In the event that study staff needs additional information, after enrollment is complete, or has additional questions pertaining to study analysis, staff will obtain consent from participant for future contact.

CLINICAL SITE MONITORING AND RECORD AVAILABILITY

The Emory University IRB, the OHRP, FDA, or other government regulatory authorities may perform clinical site monitoring. Clinical research sites monitoring may include the review of the individual participant records, including consent forms, CRFs, supporting data, laboratory specimen records, and medical records (physicians' progress notes, nurses' notes, individuals' hospital charts) to ensure protection of study participants, compliance with the protocol, and accuracy and completeness of records. The monitors may also inspect sites' regulatory files to ensure that regulatory requirements are being followed.

The investigators will make study documents (e.g., consent forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB or the OHRP for confirmation of the study data.

ADVERSE EVENT MONITORING AND REPORTING

Adverse Event Reporting

An Adverse Event (AE) as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product.

Any AE that is reported to either the investigators or their designated research associates by a study subject or by medical staff caring for the subject and which meets the criteria will be documented in the participant's chart. The reporting period for participant AEs begins at enrollment and continues until the subject either completes or withdraws from the study.

All AEs and laboratory abnormalities will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.1, July 2017, which can be found on the DAIDS RCC Web site: http://rcc.tech-res.com/tox_tables.htm.

Each AE will be assessed for relatedness to study product. Study investigators will determine AEs to be either definitely related, probably related, possibly related or not related to study product. If the adverse event is, in the investigator's opinion, possibly,

probably, or not related to study drug or procedures, then an alternate etiology will be provided by the investigator.

Related AEs ≥ Grade 3 will be included in the summary reports provided to the Medical Monitor of the study. Exceptions to expedited reporting are detailed below.
This study uses FDA approved drugs with known common side effects (please refer to the risk section of the protocol for common side effects). The following side effects will not be reported as an EAE unless it increases in severity or becomes prolonged.

Nausea: Report if severity is a Grade 3 or higher
Vomiting: Report if severity is a grade 3 or higher
Diarrhea: Report if severity is a Grade 3 or higher
Headache: Report if severity is a Grade 3 or higher
Rash: Report if severity is a Grade 3 or higher

Serious Adverse Event Reporting
Additionally, clinical investigators will monitor subjects for Serious Adverse Events (SAE) during each study visit.

A SAE is an adverse drug experience that results in any of the following outcomes:

1. Death.
2. Life-threatening situation - The subject was at risk of death at the time of the adverse event/experience. It does not refer to the hypothetical risk of death if the AE were more severe or were to progress.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant disability/incapacity - Any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life functions, including the ability to work. This is not intended to include transient interruption of daily activities.
5. Congenital anomaly/birth defects - Any structural abnormality in subject's offspring that occurs after intrauterine exposure to treatment.
6. Important medical events/experiences that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, i.e., death, a life-threatening adverse event/experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Examples of such medical events/experiences include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

In this protocol, spontaneous and elective abortions will be also be considered SAEs.

All SAEs will be reported to the Medical Monitor within 24 hours of site awareness.

Any SAE that is considered 1) unanticipated 2) related to study product AND 3) places participants at greater risk of harm than previous known is an Unanticipated Problem (UP) and will be reported to the IRB within 10 business days of study team awareness.

All other SAEs will be reported to the IRB at the time of annual review. The standard Emory IRB reporting guidelines for AE and SAE reporting, as documented at http://www.emory.edu/IRB/guidelines_adverse_event.php, will be followed.

It should however be noted that a severe adverse event /experience is not necessarily serious, as the term severe is a measure of intensity while a serious adverse event (SAE) is determined based on the aforementioned regulatory criteria.

DATA SAFETY MONITORING

Summaries of adverse events (Grades 3 or 4), and targeted AEs across study groups as well as study conduct will be reviewed regularly (in real time and summarized quarterly) by study investigators.

We will also conduct site monitoring for data quality and protocol compliance. The PI and the research coordinators will monitor for protocol compliance and data quality with periodic quality monitoring checks. In addition, we will perform self-monitoring twice yearly using the EU-Self-monitoring Tool available at http://www.ctac.emory.edu/clinical_trial_resources/Audit%20Tools.html. The PI will inform the sub-investigators and the IRB if she is provided with new safety information about the study.

STUDY DISCONTINUATION

A study participant may elect to discontinue participation in the study at any time. The study may be discontinued at any time by the IRB, the OHRP, or other government agencies as part of their duties to ensure that research subjects are protected.

BIOHAZARD CONTAINMENT

Blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products. Appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health. All infectious specimens will be transported using packaging mandated in the Code of Federal Regulations, 42 CFR Part 72.

BIOSAFETY PLAN

No specific biosafety plan is necessary for this protocol as all planned laboratory assays will fall under the existing biosafety protocols of the Hope Clinic and CDC.

REFERENCES

1. Centers for Disease Control and Prevention. Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or other Nonoccupational Exposure to HIV---United States, 2016.
2. Centers for Disease Control and Prevention. HIV Surveillance Report, 2014. 2015; 26. Available from: http://www.cdc.gov/hiv/library/reports/surveillance/.
3. US Public Health Service. Pre-exposure Prophylaxis for the Prevention of HIV Infection in the United States-2014: A Clinical Practice Guideline2014.