ART Persistence: Antiretroviral Drug Persistence in Different Body Compartments in HIV Negative Men Who Have Sex With Men

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TITLE OF PROJECT: Antiretroviral drug persistence in different body compartments in HIV negative men who have sex with men

Short title: ART Persistence

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ABSTRACT

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 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 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, additional short-course dosing regimens for PrEP and PEP are being considered for future development. This proposal seeks to understand how other anti-HIV medications are absorbed into different body compartments, including mucosal tissues, and for how long they persist in those body compartments. Anti-HIV medications with good mucosal tissue levels that persist over time may be considered for testing in future clinical trials of PrEP or PEP regimens. The study drug provided in this study will not protect participants from HIV or treat any active infection.

Design: To address the absorption and persistence of anti-retroviral drugs by mucosal tissues 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 56 MSM aged 18-49 with measurement of anti-retroviral drug concentrations in various body compartment sites of possible HIV exposure. We plan to enroll men who are HIV negative that engage in receptive anal intercourse (RAI) and are not currently (or have no current plans) taking PEP or pre- exposure prophylaxis (PrEP). We will enroll participants in one of 3 study arms where they will be given 2 doses of the oral fixed dose combination anti-HIV medication Biktarvy® (TAF/FTC/BIC) separated by 24 hours. Depending on study arm (A, B, C), participants will undergo body compartment sampling at different time points including, blood, urine, optional semen, oral swabs, penile swabs, and rectal biopsy collections.

Participants will undergo rectal biopsy collection at 1 study timepoint while other biologic specimens will be collected at 3 study time points. 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 15 mL), including a rapid HIV test, will be performed. At the second study visit, participants will be provided two doses TAF/FTC/BIC. The first does will be observed in clinic. They will be instructed to take the second dose at home with documentation by digital, time-stamped photo or video.

Depending on which study arm the participant is sequentially assigned to, the participant will be asked to return to the Hope Clinic at different time points to complete the remaining visits (visits 3, 4, 5). During visits 3-5, all participants will undergo blood collection (approximately 2 tablespoons of blood will be obtained), an oral cheek swab, urethral swab, 1 pre- wet and 1 dry penile swabs, and a urine sample will be collected. Each participant will also undergo a single time-point (depending on study arm assignment—either visit 3 or 4 or 5) rectal secretion collection with swabs and wicks, a swab for rectal STI testing, and a rectal biopsy via rigid sigmoidoscopy. All participants will have urine tested for STIs from one time point. All participants will be asked to abstain from receptive anal intercourse for 7 days after biopsy procedures to allow the mucosa to heal.

Participants will also be asked to provide an optional single semen specimen on the day of rectal sampling to further evaluate drug levels. All biologic specimens will be transferred to CDC within 4 hours of collection for measurement of antiretroviral drug levels.

Participants may participate in more than one study arm or subgroup; however, at least 6 weeks must lapse after completion of 1 study arm or subgroup before entry into another. Men who participate in more than one arm will be consented on the arm-specific consent form prior to starting study activities, but do not have to repeat the screening visit (visit 1) when starting another arm; they will begin the new arm at visit 2.

Duration: The duration of this study is 2 years. Participants will be considered 'on-study' for no more than 12 weeks.

Sample size: For this protocol we will recruit 56 HIV-negative MSM (age 18- 49) who meet eligibility criteria outlined in the protocol.

Population: The population to be studied in this protocol are healthy HIV negative MSM who are engaging in receptive anal intercourse (RAI) 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 considered for future development. The study drug provided in this study will not protect participants from HIV or treat any active infection. This proposal seeks to understand how other anti-HIV medications are absorbed and how long they persist in different body compartments, including mucosal tissues, as they may be considered for PrEP or PEP regimens in the future.

For this protocol, we will recruit 56 HIV-negative MSM aged 18-49 in good general health. Participants will be sequentially assigned to one of 3 study arms which will dictate the timing of subsequent study visits. 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. At the beginning of the study, all participants will take 2 doses of the anti-HIV regimen tenofovir+emtricitabine+bictegrativir (TAF/FTC/BIC). At subsequent study visits (visit times defined by the protocol), participants will return to donate blood, oral swabs, penile swabs, and urine. At one study visit (visit defined by the protocol), participants will undergo a rectal biopsy procedure and provide a semen specimen. All biologic specimens collected will be transferred to CDC on the day of collection for measurement of drug levels.

PROJECT DESCRIPTION

Public Health Relevance: Information about new anti-HIV agents and how they are absorbed by different body sites will better inform scientists about the potential of new agents to be used around the time of HIV exposure for HIV prevention.

Goal: To assess the pharmacokinetics and tissue distribution of anti-HIV drugs after taking 2 doses of TAF/FTC/BIC.

STUDY POPULATION

A total of up to 56 HIV-negative MSM aged 18-49 will be recruited from existing Emory University study databases of MSM who have agreed to future contact about research opportunities. We will also recruit men from community engagement events conducted by Hope Clinic recruiters, from print and on-line advertisements, and from social media. Research recruiters at the Hope Clinic are experienced in recruiting this population for

research studies, including those with rectal biopsies, and do not anticipate problems. Dr. Kelley has conducted several similar studies before and does not anticipate any problems with recruiting the target population. Based on our previous studies, we expect a percentage of men will not complete all study visits, therefore the sample size of up to 56 men will ensure study completion for at least 28 men.

INCLUSION CRITERIA FOR MSM

1) HIV-negative person assigned male sex at birth who reports receptive anal sex with another person assigned male sex at birth in the last 6 months
2) Aged 18-49 years
3) Not currently taking PrEP and no plans to initiate during study
4) Not currently taking PEP
5) Able to provide informed consent in English
6) No plans for relocation in the next 3 months
7) Willing to undergo peripheral blood, penile swabs, urine, and rectal biopsy sampling
8) Willing to use study products as directed
9) Willing to abstain from receptive anal intercourse 3 days prior to starting study product and for the duration of the study and for 7 days after any rectal biopsy procedure.
10) Hepatitis B surface antigen (HBsAg) must be negative (screening lab test)
11) Creatine clearance >60 ml/min

EXCLUSION CRITERIA

1) History of inflammatory bowel disease or other inflammatory, infiltrative, infectious or vascular condition involving the lower gastrointestinal tract that, in the judgment of the investigators, may be worsened by study procedures or may significantly distort the anatomy of the distal large bowel
2) Currently infected with hepatitis virus and/ or have liver disease
3) Current or chronic history of kidney disease
4) Significant laboratory abnormalities at baseline visit, including but not limited to:
    a) Hgb ≤ 10 g/dL
    b) PTT > 1.5x ULN or INR > 1.5x ULN
    c) Platelet count <100,000
    d) Creatinine clearance <60
    e) HBsAg reactive
5) Any known medical condition that, in the judgment of the investigators, increases the risk of local or systemic complications of endoscopic procedures or pelvic examination, including but not limited to:

   a) Uncontrolled or severe cardiac arrhythmia
   b) Recent major abdominal, cardiothoracic, or neurological surgery
   c) History of uncontrolled bleeding diathesis
   d) History of colonic, rectal, fistula, or malignancy
   e) History or evidence on clinical examination of ulcerative, suppurative, or proliferative lesions of the anorectal mucosa, or untreated sexually transmitted disease with mucosal involvement
6) Continued need for, or use during the 14 days prior to enrollment, of the following medications:
   a) Aspirin or more than 4 doses of NSAIDs
   b) Warfarin, heparin (low-molecular weight or unfractionated), platelet aggregation inhibitors, or fibrinolytic agents
   c) Any form of rectally administered agent besides lubricants or douching used for sexual intercourse
7) 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) Experimental medications, vaccines, or biologicals
8) Intent to use HIV antiretroviral pre/post-exposure prophylaxis (PrEP or PEP) during the study, outside of the study procedures
9) Symptoms of an untreated rectal sexually transmitted infection (e.g. rectal pain, discharge, bleeding, etc.)
10) Current use of hormonal therapy
11) 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.
12) Participants taking potent inhibitors (e.g. itraconazole, diltiazem) or inducers (e.g. rifampin, phenytoin) of the CYP3A4 enzyme will be excluded from the study.

PROCEDURES

Recruitment procedures

Participants will be recruited with several methods. First, the Hope Clinic maintains large databases of volunteers interested in participating in future research. Email blasts and phone calls will be made to potential volunteers 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. 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 understand how certain HIV medications are absorbed into different body tissues and may be considered for future HIV prevention regimens in the future. Study visits range from two to four 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 18-49
- HIV negative man who has sex with men
- HIV transgender woman who has sex with men who is not taking hormone therapy
- Not currently taking PrEP or PEP
- Willing to undergo rectal biopsy sampling

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 icapture/redcap application will be used to populate name, phone number, email address, and physical 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. Volunteers 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 and interaction.

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 [redacted]

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. After the completion of **Arm A**, study staff will start enrollment for **Arm B**. After the completion of **Arm B,** study staff will start enrollment for **Arm C.**

Participants may participate in more than one study arm or subgroup; however, at least 6 weeks must lapse after completion of one study arm or subgroup, before entry into another. Participants who participate in more than one arm or subgroup, will be consented on the arm-specific consent form prior to completing study activities, but do not have to repeat the screening visit (visit 1) when starting another arm or subgroup; they will begin the new arm at visit 2.

The consent process will be conducted in a private exam room at the Hope Clinic. 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 (up to n=24 maximum enrolled):
Participants will be sequentially assigned to groups A.1, A.2, A.3. Once 4 participants complete their biopsy visits for subgroup A.1, subsequent participants will be enrolled into sub-group A.2 and then A.3. A total of 12 participants must complete all study visits for this arm.
Group A.1 (n=8; enrollment will close once 4 participants complete their biopsy visit):

Visit 1(screening)*:* Eligible MSM will provide written informed consent, be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for a complete blood count, creatinine, coagulation test, and hepatitis B testing**.** 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 be given 2 doses of TAF/FTC/BIC. The first dose will be observed in clinic. Staff will provide instructions to participant on when to take dose the second dose at home (i.e. 24 hours after the first dose). Participants will be instructed to photograph or videotape themselves taking the second dose with the timestamp included with their smartphone. Study staff will instruct participants to bring the photo/video to their next visit to provide proof of dosing. Participants will also have the option to send a text to a specified number with the time and date of dose if their phone device does not have video/photo capabilities.

Visit 3: Visit 3 takes place 2hrs (+/- 1 hr) after the first/in-clinic dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are

complete, participants will be asked to provide a urine sample (some of which will be used for gonorrhea and chlamydia testing), then the practitioner (Principal investigator or Co- investigator) will collect rectal secretion samples by using two swabs and insert an aptima swab for rectal gonorrhea and chlamydia testing, before the participant undergoes a rectal biopsy via rigid sigmoidoscopy.

Participants will also provide a single optional semen sample, which will be collected at home or the clinic, no more than 2hrs before/after the biopsy visit.

Visit 4: Visit 4 takes place 48hrs (+/- 1 hour) after the in-clinic first dose and 24 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Visit 5: Visit 4 takes place 96hrs (+/- 1 hour) after the in-clinic first dose and 72 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Group A.2 (up to n=8; enrollment will close once 4 participants complete their biopsy visit):

Visit 1(screening)*:* Eligible MSM will provide written informed consent, be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for a complete blood count, creatinine, coagulation test, and hepatitis B testing**.** 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 be given 2 doses of TAF/FTC/BIC. The first dose will be observed in clinic. Staff will provide instructions to participant on when to take dose the second dose at home (i.e. 24 hours after the first dose). Participants will be instructed to photograph or videotape themselves taking the second dose with the timestamp included with their smartphone. Study staff will instruct participants to bring the photo/video to their next visit to provide proof of dosing. Participants will also have the option to send a text to a specified number with the time and date of dose if their phone device does not have video/photo capabilities.

Visit 3: Visit 3 takes place 2hrs (+/- 1 hr) after the first/in-clinic dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are

complete, participants will be asked to provide a urine sample (some of which will be used for gonorrhea and chlamydia testing).

Visit 4: Visit 4 takes place 48hrs (+/- 1 hour) after the in-clinic first dose and 24 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swabs and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample, then the practitioner (Principal investigator or Co- investigator) will collect rectal secretion samples by using two swabs and insert an aptima swab for rectal gonorrhea and chlamydia testing, before the participant undergoes a rectal biopsy via rigid sigmoidoscopy.

Participants will also provide a single optional semen sample, which will be collected at home or the clinic, no more than 2hrs before/after the biopsy visit.

Visit 5: Visit 4 takes place 96hrs (+/- 1 hour) after the in-clinic first dose and 72 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Group A.3 (up to n=8; enrollment will close once 4 participants complete their biopsy visit):

Visit 1(screening)*:* Eligible MSM will provide written informed consent, be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for a complete blood count, creatinine, coagulation test, and hepatitis B testing**.** 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 be given 2 doses of TAF/FTC/BIC. The first dose will be observed in clinic. Staff will provide instructions to participant on when to take dose the second dose at home (i.e. 24 hours after the first dose). Participants will be instructed to photograph or videotape themselves taking the second dose with the timestamp included with their smartphone. Study staff will instruct participants to bring the photo/video to their next visit to provide proof of dosing. Participants will also have the option to send a text to a specified number with the time and date of dose if their phone device does not have video/photo capabilities.

Visit 3: Visit 3 takes place 2hrs (+/- 1 hr) after the first/in-clinic dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are

complete, participants will be asked to provide a urine sample (some of which will be used for gonorrhea and chlamydia testing).

Visit 4: Visit 4 takes place 48hrs (+/- 1 hour) after the in-clinic first dose and 24 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Visit 5: Visit 4 takes place 96hrs (+/- 1 hour) after the in-clinic first dose and 72 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample, then the practitioner (Principal investigator or Co- investigator) will collect rectal secretion samples by using two swabs and insert an aptima swab for rectal gonorrhea and chlamydia testing, before the participant undergoes a rectal biopsy via rigid sigmoidoscopy.

Participants will also provide a single optional semen sample, which will be collected at home or the clinic, no more than 2hrs before/after the biopsy visit.

Arm B (up to n=16 maximum enrolled):
Participants will be sequentially assigned to groups B.1 and B.2. Once 4 participants complete their biopsy visits for subgroup B.1, subsequent participants will be enrolled into sub-group B.2. A total of 8 participants must complete all study visits for this arm.

Group B.1 (n=8; enrollment will close once 4 participants complete their biopsy visit):

Visit 1(screening)*:* Eligible MSM will provide written informed consent, be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for a complete blood count, creatinine, coagulation test, and hepatitis B testing**.** 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 be given 2 doses of TAF/FTC/BIC. The first dose will be observed in clinic. Staff will provide instructions to participant on when to take dose the second dose at home (i.e. 24 hours after the first dose). Participants will be instructed to photograph or videotape themselves taking the second dose with the timestamp included with their smartphone. Study staff will instruct participants to bring the photo/video to their next visit to provide proof of dosing. Participants will also have the option to send a text to a specified number with the time and date of dose if their phone device does not have video/photo capabilities.

Visit 3: Visit 3 takes place 4hrs (+/- 1 hr) after the first/in-clinic dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample (some of which will be used for gonorrhea and chlamydia testing), then the practitioner (Principal investigator or Co- investigator) will collect rectal secretion samples by using two swabs and insert an aptima swab for rectal gonorrhea and chlamydia testing, before the participant undergoes a rectal biopsy via rigid sigmoidoscopy.

Participants will also provide a single optional semen sample, which will be collected at home or the clinic, no more than 2hrs before/after the biopsy visit.

Visit 4: Visit 4 takes place 26hrs (+/- 1 hour) after the in-clinic first dose and 2 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Visit 5: Visit 4 takes place 120hrs (+/- 1 hour) after the in-clinic first dose and 96 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Group B.2 (n=8; enrollment will close once 4 participants complete their biopsy visit):

Visit 1(screening)*:* Eligible MSM will provide written informed consent, be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for a complete blood count, creatinine, coagulation test, and hepatitis B testing**.** 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 be given 2 doses of TAF/FTC/BIC. The first dose will be observed in clinic. Staff will provide instructions to participant on when to take dose the second dose at home (i.e. 24 hours after the first dose). Participants will be instructed to photograph or videotape themselves taking the second dose with the timestamp included with their smartphone. Study staff will instruct participants to bring the photo/video to their next visit to provide proof of dosing. Participants will also have the option to send a text to a specified number with the time and date of dose if their phone device does not have video/photo capabilities.

Visit 3: Visit 3 takes place 4hrs (+/- 1 hr) after the first/in-clinic dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile

swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample (some of which will be used for gonorrhea and chlamydia testing).

Visit 4: Visit 4 takes place 26hrs (+/- 1 hour) after the in-clinic first dose and 2 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Visit 5: Visit 4 takes place 120hrs (+/- 1 hour) after the in-clinic first dose and 96 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample, then the practitioner (Principal investigator or Co- investigator) will collect rectal secretion samples by using two swabs and insert an aptima swab for rectal gonorrhea and chlamydia testing, before the participant undergoes a rectal biopsy via rigid sigmoidoscopy.

Participants will also provide a single optional semen sample, which will be collected at home or the clinic, no more than 2hrs before/after the biopsy visit.

Arm C (up to n=16 maximum enrolled):
Participants will be sequentially assigned to groups C.1 and C.2. Once 4 participants complete their biopsy visits for subgroup C.1, subsequent participants will be enrolled into sub-group C.2. A total of 8 participants must complete all study visits for this arm.

Group C.1 (n=8; enrollment will close once 4 participants complete their biopsy visit):

Visit 1(screening)*:* Eligible MSM will provide written informed consent, be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for a complete blood count, creatinine, coagulation test, and hepatitis B testing**.** 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 be given 2 doses of TAF/FTC/BIC. The first dose will be observed in clinic. If participant is in clinic for their visit 3 (24hrs after first dose), study staff will instruct participant to take dose immediately at the start of visit. If participant is late to visit, but still within the +/- 1hr window, study staff will provide instructions to participant on when to take the second dose at home (i.e. 24 hours after the first dose). Participants will be instructed to photograph or videotape themselves taking the second dose with the timestamp included with their smartphone. Study staff will instruct

participants to bring the photo/video to their next visit to provide proof of dosing. Participants will also have the option to send a text to a specified number with the time and date of dose if their phone device does not have video/photo capabilities.

Visit 3: Visit 3 takes place 24hrs (+/- 1 hr) after the first/in-clinic dose. If the participant did not dose at home, study staff will instruct participant to take dose after in clinic study procedures are performed. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample (some of which will be used for gonorrhea and chlamydia testing), then the practitioner (Principal investigator or Co- investigator) will collect rectal secretion samples by using two swabs and insert an aptima swab for rectal gonorrhea and chlamydia testing, before the participant undergoes a rectal biopsy via rigid sigmoidoscopy.

Participants will also provide a single optional semen sample, which will be collected at home, no more than 2hrs before/after the biopsy visit.

Visit 4: Visit 4 takes place 28hrs (+/- 1 hour) after the in-clinic first dose and 4 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Visit 5: Visit 4 takes place 72hrs (+/- 1 hour) after the in-clinic first dose and 48hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Group C.2 (n=8; enrollment will close once 4 participants complete their biopsy visit):

Visit 1(screening)*:* Eligible MSM will provide written informed consent, be questioned about their medical history, undergo an HIV test, and a peripheral blood sample for a complete blood count, creatinine, coagulation test, and hepatitis B testing. 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 be given 2 doses of TAF/FTC/BIC. The first dose will be observed in clinic. If participant is in clinic for their visit 3 (24hrs after first dose), study staff will instruct participant to take dose immediately at the start of visit. If participant is late to visit, but still within the +/- 1hr window, study staff will provide instructions to participant on when to take dose the second dose at home (i.e. 24 hours after the first

dose). Participants will be instructed to photograph or videotape themselves taking the second dose with the timestamp included with their smartphone. Study staff will instruct participants to bring the photo/video to their next visit to provide proof of dosing. Participants will also have the option to send a text to a specified number with the time and date of dose if their phone device does not have video/photo capabilities.

Visit 3: Visit 3 takes place 24hrs (+/- 1 hr) after the first/in-clinic dose. If the participant did not dose at home, study staff will instruct participant to take dose after performing in clinic study procedures. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample (some of which will be used for gonorrhea and chlamydia testing).

Visit 4: Visit 4 takes place 28hrs (+/- 1 hour) after the in-clinic first dose and 4 hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample.

Visit 5: Visit 4 takes place 72hrs (+/- 1 hour) after the in-clinic first dose and 48hours after the at-home second dose. Approximately 24 mL of blood will be drawn, an oral cheek swab, 1 pre- wet penile swab and 1 dry penile swab, and a urethral swab will be collected. After previous swab collections are complete, participants will be asked to provide a urine sample, then the practitioner (Principal investigator or Co- investigator) will collect rectal secretion samples by using two swabs and insert an aptima swab for rectal gonorrhea and chlamydia testing, before the participant undergoes a rectal biopsy via rigid sigmoidoscopy.

Participants will also provide a single optional semen sample, which will be collected at home or the clinic, no more than 2hrs before/after the biopsy visit.

<u>All participants will be asked to abstain from receptive anal intercourse for three days prior to drug dosing and during the study protocol in order to limit additional exposures (e.g. semen, douching, additional lubricants) to the rectal mucosa.</u>

<u>All participants who undergo a rectal biopsy will be informed not to place anything into the rectum and abstain from intercourse 7 days after their rectal biopsy procedure to allow the mucosa to heal. If tested positive for gonorrhea and/or chlamydia, participant will be notified and referred to linkage for treatment.</u>

Biologic specimens:

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.

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.

<u>Rectal biopsy procedures</u>

All biopsies will be completed by either the PI or a delegated, licensed medical professional whom the PI has trained in the procedure. Rectal biopsies utilizing a disposable rigid sigmoidoscope, light source, and jumbo biopsy forceps. Dr. Kelley was trained in office based rectal biopsy procedures by Dr. Robin Rutherford, an (now retired) experienced gastroenterologist at Emory University. All biopsy procedures will be performed in an examination room at the Hope Clinic with assistance from the project coordinator or clinical research nurse. Similar procedures have been performed in Dr. Kelley's research protocols >300 times with no complications. Briefly, without the administration of any previous enemas or other preparation, up to 10 adequate ~1.0 mm thick biopsy specimens will be taken from normal-appearing rectal mucosa 10 cm above the external anal aperture using a rigid sigmoidoscope and flexible sigmoidoscopic forceps mounted on a semi-flexible rod. All biopsy specimens will be coded with a unique numeric identifier such that the CDC laboratories that receive the specimens will

be unable to link them back to the study participants. Specimens will be transported directly to CDC after the study visit.

Twenty-four to forty-eight hours after the procedure, study personnel will contact the subjects who donated rectal biopsy samples and inquire about symptoms, complications, or adverse events related to study procedures. Subjects who report symptoms suggestive of any significant complications will receive advice on seeking care and will be given referrals to appropriate healthcare professionals as needed. This follow-up may be completed over the phone or through electronic communication.

Optional semen collection:

After participants have taken study dose in clinic, they will be instructed to obtain semen sample 2hrs before or after the scheduled rectal biopsy visit. The semen will be collected by the participant at home using a provided collection cup and will be stored on ice until it is brought to the clinic. Participant will be provided towelettes for cleaning the head of the penis before masturbation is started. The sample should be collected no more than 2 hours before delivery to the clinic. The participant will be instructed to refrain from ejaculating, putting lubricants or saliva on their penis, or having insertive vaginal, anal or oral sex for at least 48 hours prior to semen collection. If these instructions are not followed, a notation will be made and the semen sample will still be accepted.

Statistical analysis plan
Median (range) drug levels (TAF and FTC and BIC) will be calculated at baseline, twenty four hours after the first dose, and 120 hours after first dose for plasma, PBMCs, and, rectal tissues. Differences in median drug levels between baseline and study visit follow-up visits will be analyzed with non-parametric Wilcoxon-signed rank tests. A p-value of <0.05 will be considered significant.

Future use of specimens
Additional biologic specimens not used for above drug level testing may be used and/or stored for future research use at Emory University Hope Clinic or the CDC.

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 men 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 TAF/FTC/BIC
TAF/FTC/BIC is a combination anti-HIV medication that contains the drugs tenofovir alafenamide, emtricitabine, and bictegravir. Based on clinical trials previously conducted of TAF/FTC/BIC, 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 TAF/FTC/BIC included vomiting, flatulence, dyspepsia, abdominal pain, rash, and depression.

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

Use of TAF/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. Nonetheless, the maximum 2-day dosing regimen for this study is unlikely to cause flare-ups in Hepatitis B even if not diagnosed.

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. 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 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. 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.

Participants will be asked to abstain from receptive anal intercourse for three days prior to drug dosing and during the study protocol in order to limit additional exposures (e.g. semen, douching, additional lubricants) to the rectal mucosa. Participants taking TAF/FTC/BIC 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.

Rigid sigmoidoscopy and biopsies

Risks associated with lower gastrointestinal endoscopy include colitis from chemicals for endoscope sterilization, bowel perforation, bleeding, diverticulitis, and infection. All procedures will be performed by Dr. Kelley or a nurse practitioner trained by Dr. Kelley. Non-physician medical providers have performed endoscopic procedures for diagnostic and therapeutic procedures for years. Many of these require mastery of flexible sigmoidoscopes, detailed anatomy of the full colon, and familiarity with sedation procedures.(4, 5) Procedures utilizing flexible instruments that access a deeper area of the colon and may or may not require sedation are more complicated and risky than the procedure detailed in this protocol which utilizes a rigid sigmoidoscope and only accesses the sigmoid colon a maximum of 15 cm from the anal verge. Therefore, it is appropriate for a trained, licensed mid-level provider to perform the procedure. Dr. Kelley's team has performed >300 similar procedures for other IRB approved protocols with zero complications.

All procedures will utilize disposable rigid sigmoidoscopes, forceps, and guides to reduce risk of infection and obviate the need for instrument sterilization between participants. To minimize risks, rigid proctoscopy, rather than flexible sigmoidoscopy or full colonoscopy, will be used in this study and the number of biopsies taken will be limited to 10. Colonoscopy has been shown to be associated with a still low, but significantly greater risk of complications than rectosigmoidoscopy.(6) The frequency of serious complications after flexible sigmoidoscopy is extremely low and complications

from rigid sigmoidoscopy are presumably even lower, but unknown. In two large studies including a combined 144,832 clinically indicated procedures, the incidence of serious complications ranged from 0.06 to 0.8% utilizing flexible sigmoidoscopy.(6, 7) Obtaining biopsies may be associated with an increased risk of complications. The best available data on the risk of multiple biopsies comes from studies of dysplasia surveillance among patients with long-standing inflammatory bowel disease, in whom large numbers of "blind" biopsies are obtained throughout the colon for early detection of malignant transformation. In two such studies including a combined 3,011 procedures and a median of eight and 17 biopsies, respectively, there was only one serious complication, for an incidence of approximately 0.33%.(8, 9) In a study of subjects undergoing endoscopic procedures exclusively for research purposes, including 64 flexible sigmoidoscopies with a mean of 25 biopsies obtained from the rectosigmoid, there were no major complications. Thirteen subjects experienced minor symptoms (self-limited bleeding and pain), which were not related to the number of biopsies.(10)

Most relevant to the current study, a summary of procedures across several Microbicide Trial Network (an NIH-funded, international network designed to develop topical agents for HIV prevention) was published in 2017.(11) This manuscript reported on the safety of 1,004 sigmoidscopy procedures with >15,000 biopsy collection from 278 research participants. Many participants underwent multiple procedures (median 3 procedures). There were no serious adverse events, and an AE related to sigmoidoscopy was reported in 1.6% of procedures. Eight of the 16 related AEs reported were abdominal pain, flatulence, bleeding, diarrhea, and bloating. Fourteen of the 16 related AEs were grade 1 and 2/16 were grade 2; median time to resolution was 1 day. The authors concluded that repeated intestinal mucosal biopsies for research purposes are safe. Thus, based on the available data, the risk of serious complications from the proposed study procedures, even with up to 10 biopsy specimens, is expected to be very low (<1:5000).

There is theoretical risk of increased acquisition of HIV or other infection if a study participant is exposed soon after the rectal biopsy procedure (i.e. while the mucosal surface is damaged). Therefore, study subjects will be counseled not to engage in anal intercourse for 1 week after the rectal biopsy procedure.

Biologic samples will be coded with a unique identifier prior to processing and storage for immunologic assays. Therefore, lab personnel will be unable to link specimens with participants. Only the PI and designated co-investigators/study personnel will be able to access information to identify specimens of individual participants.

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 coordinator 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.

Participants who enter into Arm A, Arm B, and Arm C will be compensated $25 for visit 1, $25 for visit 2, $50 for visits that include swab collections in addition to blood and urine, and $125 for visits in which a rectal biopsy procedure is performed (Total=$275 per subgroup completion).

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 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.

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 at birth are not eligible. Children 18-21 will be eligible for this study. 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.

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 AVAILABITLITY

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 beyond the two-day study follow-up period after final biopsy/ procedure visit.

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.

Additional safety monitoring will be performed annually by an independent Medical Safety Monitor. Based on the 1-year accrual expectation for the study, it is anticipated that the study will undergo 2 reviews by the Medical Safety Monitor. The first will occur approximately 6 months after the accrual of the first subject. The safety report will summarize grade 3 and 4 AEs and SAEs by study group. The Medical Safety Monitor will complete a 'final assessment' following the review of each safety report. As part of the final assessment the Medical Safety Monitor will conclude 'the study can continue as no safety concerns have been identified at the time of the review' or 'the study cannot continue as currently designed'. The final assessment by the Medical Safety Monitor will be provided to the study PI who will make the findings available as appropriate to the Emory IRB and the CDC.

In addition to the medical monitor, 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.

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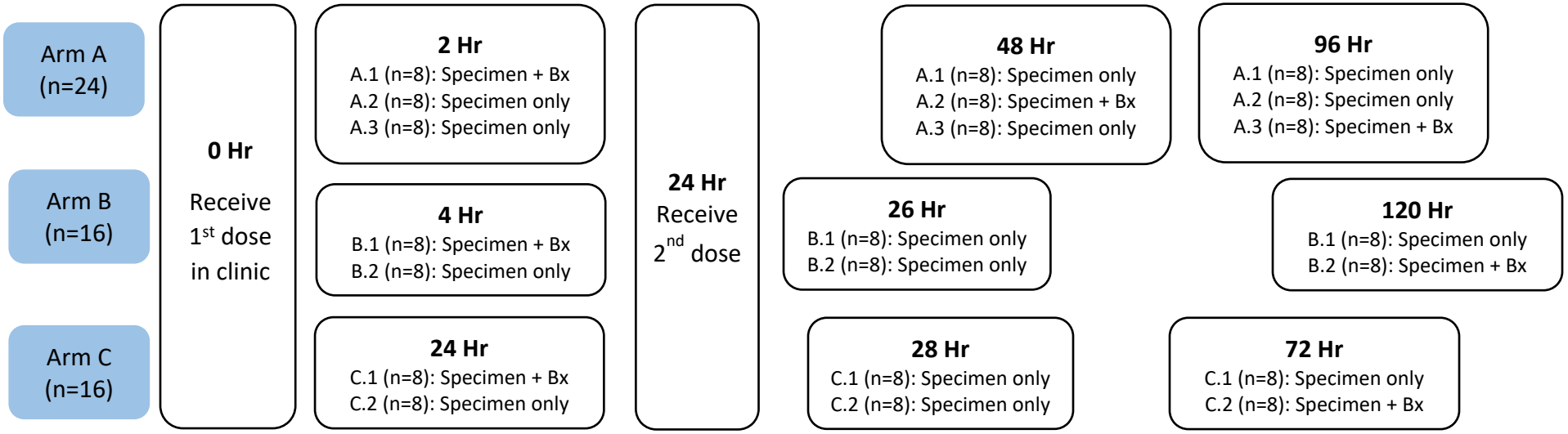
Figure 1. PEP Dosing (n=56)

Design: 2 doses of TAF/FTC/BIC given 24 hours apart

1st dose observed in clinic, 2nd dose recorded at home

Timing of specimen collection begins following 1st dose



	All Specimen Visits	Biopsy Visits
Specimen Collection	Blood (2 CPT, 1 EDTA), 5 aliquots Plasma, 2 aliquots PBMCs Urine, 4 aliquots Urethral Swab Cheek Swab, Penile Swab x2	Rectal Swabs (x2) Rectal Biopsies (x2) Aptima Swab-Rectal STI Testing Urine STI Testing Semen