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Short title: On-Demand PEP

Principal Investigator:

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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, taken around the time of HIV exposure (peri-PrEP), are absorbed into different body compartments, including mucosal tissues, as they may be considered for peri-PrEP regimens in the future. The study drug provided in this study will not protect participants from HIV or treat any active infection.

Design: To address the absorption 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 62 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 Pre- drug arm (control) first. After the completion of pre- drug arm, we will then begin enrollment sequentially in Arm A, followed by Arm B and finally Arm C. Arms A, B, and C will be broken down into two (2) different sub-groups, which will determine the timing of when the participant will undergo a rectal swab and biopsy procedure (Arm A: groups A.1 and A.2; Arm B: groups B.1 and B.2; and Arm C: groups C.1 and C.2). Arm D will include a single time point specimen collection. 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 with a single dose of Genvoya® (fixed-dose combination anti-retroviral drug containing tenofovir alafenamide, emtricitabine, elvitegravir, and cobicistat), and instructed to take the dose at home with documentation by digital, time-stamped photo or video. At the third study visit, which will occur at the Hope Clinic 24hrs after home dosing, participants will be given another single dose of Genvoya. 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 (visit 4 and visit 5). During visits 4 and 5, all participants will undergo blood collection (approximately 24 mL 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, some of which will be used for STI testing . Each participant will also undergo a single time-point (depending on study arm assignment—either visit 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 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; however, at least 6 weeks must lapse after completion of 1 study arm before entry into another. Men who participate in more than one arm will not be consented again and 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 62 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 unprotected receptive anal intercourse. 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, taken around the time of HIV exposure (peri-PrEP), are absorbed into different body compartments, including mucosal tissues, as they may be considered for peri-PrEP regimens in the future.

For this protocol, we will recruit 62 HIV-negative MSM aged 18-49. We plan to complete enrollment for the pre- drug (control) arm first. After the completion of the pre- drug arm, we will continue to enroll sequentially in each arm until all arms are filled (Pre-drug, then Arm A, then Arm B, then Arm C, then Arm D). All participants will provide written informed consent at the first study visit and undergo a screening medical history, physical exam, and safety laboratory tests. All biologic specimens collected will be transferred to CDC on the day of collection for measurement of drug levels.

Participants (up to n=6) enrolled in the pre-drug arm will not receive any drug. At visit 2, they will undergo blood, urine, penile swab, cheek swab, rectal swab and rectal biopsy collection.

Participants (up to n=16) enrolled in Arm A will be provided with a single dose of Genvoya®, at study visit 2, and instructed to take the dose at home which they will document with a smartphone photo or video time/date stamp. Participants will return to the clinic 24hrs after taking home dose for visit 3 when participants will be given another single dose of Genvoya. Specimen collection including blood, urine, urethral swab, penile swab, and cheek swab will be collected 2hrs after taking the medication in the clinic (visit 4), and 48hrs after taking the medication in the clinic (visit 5). In addition, participants will be sequentially assigned to undergo rectal swab and biopsy procedure at a single time point, at visit 4 (sub-group A.1) OR visit 5 (sub-group A.2). Participants will also be asked to provide an optional semen specimen within 2hrs of their biopsy procedure to further evaluate drug levels. All participants will undergo only one rectal swab and biopsy procedure.

Participants (up to n=16) enrolled in Arm B will be provided with a single dose of Genvoya®, at study visit 2, and instructed to take the dose at home which they will document with a smartphone photo or video time/date stamp. Participants will return to the clinic 24hrs after taking home dose for visit 3 when participants will be given another single dose of Genvoya. Specimen collection including blood, urine, urethral swab, penile swab, and cheek swab will be collected 4 hours after taking the medication in the clinic (visit 4), and 72hrs after taking the medication in the clinic (visit 5). In addition,

participants will be sequentially assigned to undergo rectal swab and biopsy procedure at a single time point, at visit 4 (sub-group B.1) OR visit 5 (sub-group B.2). Participants will also be asked to provide an optional semen specimen within 2hrs of their biopsy procedure to further evaluate drug levels. All participants will undergo only one rectal swab and biopsy procedure.

Participants (up to n=16) enrolled in Arm C will be provided with a single dose of Genvoya®, at study visit 2, and instructed to take the dose at home which they will document with a smartphone photo or video time/date stamp. Participants will return to the clinic 24hrs after taking home dose, for visit 3, at which time, participants will be given another single dose of Genvoya. Specimen collection including blood, urine, urethral swab, penile swab, and cheek swab will be collected 24hrs after taking the medication in the clinic (visit 4), and 96hrs after taking the medication in the clinic (visit 5). In addition, participants will be sequentially assigned to undergo rectal swab and biopsy procedure at a single time point, at visit 4 (sub-group C.1) OR visit 5 (sub-group C.2). Participants will also be asked to provide an optional semen specimen within 2hrs of their biopsy procedure to further evaluate drug levels. All participants will undergo only one rectal swab and biopsy procedure.

Participants (up to n=8) enrolled in Arm D will be provided with a single dose of Genvoya®, at study visit 2, and instructed to take the dose at home which they will document with a smartphone photo or video time/date stamp. Participants will return to the clinic 24hrs after taking home dose, for visit 3, at which time, participants will be given another single dose of Genvoya. Specimen collection including blood, urine, urethral swab, penile swab, and cheek swab will be collected 8hrs after taking the medication in the clinic (visit 4). All participants assigned to Arm D will undergo rectal swab and biopsy sampling at 8hrs after taking the medication in the clinic. Participants will also be asked to provide an optional semen specimen within 2hrs of their biopsy procedure to further evaluate drug levels. All participants will undergo only one rectal swab and biopsy procedure.

After collection, biologic specimens will be picked up by the CDC and immediately transported to the Division of HIV/AIDS Prevention Laboratory Branch for processing. The lab at CDC will measure the levels of tenofovir alafenamide, emtricitabine, elvtiaegravir, and cobicistat in the different biologic specimens. Comparison of assay results between the study arms will help in determining the ability of the different anti-HIV drugs to be taken up by different body tissues, including at the site of possible HIV exposure.

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---peri-PrEP.

Goal: To assess the pharmacokinetics and tissue distribution of anti-HIV drugs after taking a single dose of Genvoya®.

STUDY POPULATION

A total of up to 62 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 62 men will likely result in study completion for 31 men.

INCLUSION CRITERIA FOR MSM

1) HIV-negative man who reports receptive anal sex with another man 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, or vaginal perforation, 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 that also metabolizes Genvoya 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

B. For face- to- face engagement recruiters will use one of the following scripts when interacting with participants.

a. “Hello, my name is _____, I am a recruiter for the Hope Clinic at Emory University. We are currently seeking volunteers to participate in one of our HIV prevention research studies. If you have a moment, would you be interested in hearing more? If not, maybe you would like to leave us your contact information to speak at another time or take one of our flyers for future reference, thank you for your time. Enjoy your day.”

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.
or

b. "We are here from the Emory University Hope Clinic. We would like to talk to you about volunteering in HIV prevention studies. There are several studies that you may be eligible for [give brief description of current studies]. If you would like further information, either I or another recruiter can give you a call at a time that's convenient for you. Can I take your name and number? Thanks for your time."

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.

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. 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 or dating sites 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

c. Dating Sites (Jack'd, Adam4Adam, Grindr, etc.)

d. Social Network (Facebook, Snapchat, Instagram, etc.)

e. 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

Eligible Subjects will be sequentially assigned to study arms. We will assign participants to **Pre- drug arm** (control) first. Once this arm is filled, we will enroll participants in **Arm A**. 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.** After the previously mentioned arms are filled, we will enroll participants in **Arm D.**

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. Men who participate in more than one arm or subgroup, will not be consented again and 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) upon departure.

Pre-Drug Arm (up to n=6; enrollment for this Arm will close once 3 men complete their biopsy visit):

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 a complete blood count, creatinine, coagulation test, and hepatitis B**.** Participants will then be asked to return within 1- 6 weeks for visit 2.

Visit 2: Visit will occur within 1-6 weeks after the screening visit. 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, 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 be asked to provide an optional single semen sample, which will be collected at home, no more than 2hrs prior to or after the biopsy visit.

After 3 men complete the pre-drug arm, subsequent participants will be sequentially assigned to Arm A, B, C or D.

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

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

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 a complete blood count, creatinine, coagulation test, and hepatitis B**.** Participants will then be asked to return within 1- 6 weeks for visit 2.

Visit 2**:** Participants will be given a one- day supply of Genvoya®. Staff will provide instructions to participant on when to take dose at home. Participants will be asked to dose **24hrs before visit 3** and will be instructed to photograph or videotape themselves taking 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 after home dose. During this visit, drugs will be dispensed to participants, and they will be instructed to take one dose of Genvoya®. Men will be dosed on-site (time of dose will be recorded) and asked to return in 2hrs. Procedures should be done as close to 2hrs as possible with a +/- 1 hour window.

Visit 4: Visit 4 takes place 2hrs (+/- 1 hour) after on-site 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, 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 be asked to provide an optional single semen sample, which will be collected at home, no more than 2hrs before/after to biopsy visit.

Visit 5: Visit 5 takes place 48hrs (+/- 1 hour) after on-site 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.

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

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 a complete blood count, creatinine, coagulation test, and hepatitis B**.** Participants will then be asked to return within 1- 6 weeks for visit 2.

Visit 2: Participants will be given a one- day supply of Genvoya®. Staff will provide instructions to participant on when to take dose at home. Participants will be asked to dose **24hrs before visit 3** and will be instructed to videotape or photograph themselves taking dose with the timestamp included. Study staff will instruct participants to bring the video/photo 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 capabilities.

Visit 3: Visit 3 takes place 24hrs after home dose. During this visit, drugs will be dispensed to participants, and they will be instructed to take one dose of Genvoya®. Men will be dosed on-site (time of dose will be recorded) and asked to return in 2hrs. Procedures should be done as close to 2hrs as possible with a +/- 1 hour window.

Visit 4: Visit 4 takes place 2hrs (+/- 1 hour) after on-site 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.

Visit 5: Visit 5 takes place 48hrs (+/- 1 hour) after on-site 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, 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 be asked to provide an optional single semen sample, which will be collected at home, 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 men complete their biopsy visits for subgroup B.1, subsequent men will be enrolled into sub-group B.2. A total of 8 men must complete all study visits for this arm.

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

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 a complete blood count, creatinine, coagulation test, and hepatitis B**.** Participants will then be asked to return within 1- 6 weeks for visit 2.

Visit 2**:** Participants will be given a one- day supply of Genvoya®. Staff will provide instructions to participant on when to take dose at home. Participants will be asked to dose **24hrs before visit 3** and will be instructed to videotape or photograph themselves taking dose with the timestamp included. Study staff will instruct participants to bring the video/photo 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 capabilities.

Visit 3: Visit 3 takes place 24hrs after home dose. During this visit, drugs will be dispensed to participants, and they will be instructed to take one dose of Genvoya®. Men will be dosed on-site (time of dose will be recorded) and asked to return in 4hrs. Procedures should be done as close to 4hrs as possible with a +/- 1 hour window.

Visit 4: Visit 4 takes place 4hrs (+/- 1 hour) after on-site 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, 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 be asked to provide an optional single semen sample, which will be collected at home, no more than 2hrs before/after the biopsy visit.

Visit 5: Visit 5 takes place 72hrs (+/- 1 hour) after on-site 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.

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

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 a complete blood count, creatinine, coagulation test, and hepatitis B**.** Participants will then be asked to return within 1- 6 weeks for visit 2.

Visit 2: Participants will be given a one- day supply of Genvoya®. Staff will provide instructions to participant on when to take dose at home. Participants will be asked to dose **24hrs before visit 3** and will be instructed to videotape or photograph themselves taking dose with the timestamp included. Study staff will instruct participants to bring the video/photo 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 capabilities.

Visit 3**:** Visit 3 takes place 24hrs after home dose. During this visit, drugs will be dispensed to participants, and they will be instructed to take one dose of Genvoya®. Men will be dosed on-site (time of dose will be recorded) and asked to return in 4hrs. Procedures should be done as close to 4hrs as possible with a +/- 1 hour window.

Visit 4: Visit 4 takes place 4hrs (+/- 1 hour) after on-site 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.

Visit 5: Visit 5 takes place 72hrs (+/- 1 hour) after on-site 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, 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 be asked to provide an optional single semen sample, which will be collected at home, 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 men complete their biopsy visits for subgroup C.1, subsequent men will be enrolled into sub-group C.2. A total of 8 men must complete all study visits for this arm.

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

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 a complete blood count, creatinine, coagulation test, and hepatitis B**.** Participants will then be asked to return within 1- 6 weeks for visit 2.

Visit 2: Participants will be given a one- day supply of Genvoya®. Staff will provide instructions to participant on when to take dose at home. Participants will be asked to dose **24hrs before visit 3** and will be instructed to videotape or photograph themselves taking dose with the timestamp included. Study staff will instruct participants to bring the video/photo 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 capabilities.

Visit 3: Visit 3 takes place 24hrs after home dose. During this visit, drugs will be dispensed to participants, and they will be instructed to take one dose of Genvoya®. Men will be dosed on-site (time of dose will be recorded) and asked to return in 24hrs. Procedures should be done as close to 24hrs as possible with a +/- 1 hour window.

Visit 4: Visit 4 takes place 24hrs (+/- 1 hour) after on-site 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, 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 be asked to provide an optional single semen sample, which will be collected at home, no more than 2hrs before/after the biopsy visit.

Visit 5: Visit 5 takes place 96hrs (+/- 1 hour) after on-site 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.

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

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 a complete blood count, creatinine, coagulation test, and hepatitis B**.** Participants will then be asked to return within 1- 6 weeks for visit 2.

Visit 2: Participants will be given a one- day supply of Genvoya®. Staff will provide instructions to participant on when to take dose at home. Participants will be asked to dose **24hrs before visit 3** and will be instructed to videotape or photograph themselves taking dose with the timestamp included. Study staff will instruct participants to bring the video/photo 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 capabilities.

Visit 3: Visit 3 takes place 24hrs after home dose. During this visit, drugs will be dispensed to participants, and they will be instructed to take one dose of Genvoya®. Men will be dosed on-site (time of dose will be recorded) and asked to return in 24hrs. Procedures should be done as close to 24hrs as possible with a +/- 1 hour window.

Visit 4: Visit 4 takes place 24hrs (+/- 1 hour) after on-site 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.

Visit 5: Visit 5 takes place 96hrs (+/- 1 hour) after on-site 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, 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 be asked to provide an optional single semen sample, which will be collected at home, no more than 2hrs before/after the biopsy visit.

Arm D (n=8; enrollment will close once 4 men complete their biopsy visit):

***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 a complete blood count, creatinine, coagulation test, and hepatitis B**.** Participants will then be asked to return within 1- 6 weeks for visit 2.

Visit 2: Participants will be given a one- day supply of Genvoya®. Staff will provide instructions to participant on when to take dose at home. Participants will be asked to dose **24hrs before visit 3** and will be instructed to videotape or photograph themselves taking dose with the timestamp included. Study staff will instruct participants to bring the video/photo 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 capabilities.

Visit 3: Visit 3 takes place 24hrs after home dose. During this visit, drugs will be dispensed to participants, and they will be instructed to take one dose of Genvoya®. Men will be dosed on-site (time of dose will be recorded) and asked to return in 8hrs. Procedures should be done as close to 8hrs as possible with a +/- 1 hour window.

Visit 4*:* Visit 4 takes place 8hrs (+/- 1 hour) after on-site 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, 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 be asked to provide an optional single semen sample, which will be collected at home, no more than 2hrs before/after the biopsy visit.

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>All participants who will 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 rectal biopsies will be performed 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 experienced gastroenterologist at Emory University. All biopsies will be completed by either the PI or a delegated, licensed medical professional whom the PI has trained in the procedure. 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 by Dr. Kelley >300 times for other research protocols with no complications. Briefly, without the administration of any previous enemas or other preparation, 8-10 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.

Semen collection:

After participants have taken study dose in clinic, they will be asked to obtain an optional semen sample 2hrs before or after the scheduled rectal biopsy or procedure 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, the semen sample can still be accepted.

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 Genvoya®

Genvoya® is a combination anti-HIV medication that contains the drugs tenofovir alafenamide, emtricitabine, elvitegravir, and cobicistat. Based on clinical trials previously conducted of Genvoya®, the drug showed to be well tolerated (see package insert). According to participants, the most common side effect shown was nausea with diarrhea being the second most common side effect. Of those who reported this adverse event, 0.9% and 1.5 % discontinued treatment regardless of the severity (see package insert). Adverse events associated with Genvoya® can include a transient decrease in renal function and slight decreases in bone mineral density. There is also a possibility of lactic acidosis, which can be hard to identify during early stages. These effects occur with prolonged use of the medication and are not expected to occur with the limited 2-day dosing in this protocol.

Genvoya® 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 men 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 men for HIV at study entry and monitor clinically for high-risk behavior or any signs of acute HIV infection at study visits.

Men 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. Men taking Genvoya® 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 men 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 biopsies will be completed by either the PI or a delegated, licensed medical professional whom the PI has trained in the procedure. 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.

For Pre-drug Arm, study participants will be compensated $25 for visit 1 and $125 for visit 2. Participants who enter into Arm A, Arm B, and Arm C will be compensated $25 for visit 1, $20 for visit 2, $20 for visit 3, and $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. Participants in Arm D will be compensated $25 for visit 1, $20 for visit 2, $20 for visit 3, and $125 for visits in which a rectal biopsy procedure is performed.

If a semen sample is provided, participants will be compensated an additional $20.

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. All subjects will undergo HIV risk reduction counseling with provision of free condoms.

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, women 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 events (AEs) ≥ Grade 3 will be reported on an expedited basis at the standard level during the protocol-defined expedited adverse event (EAE) Reporting Period, which is the entire study duration for an individual subject (from study enrollment until study completion or discontinuation of the subject from study participation for any reason).

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 AE 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

AE Reporting

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 addition, clinical investigators will monitor subjects for Serious adverse events (SAE) Unanticipated problems (UP) during each study visit. Any SAE that is judge related to study product or UP will be reported to the IRB within 5 days of the event. 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.

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.
7. Spontaneous and elective abortions will be reported to the Emory IRB as serious adverse events.

8. Severity of AEs will be rated according to the following definitions:

Mild: The adverse event is transient and easily tolerated by the subject.

Moderate: The adverse event causes the subject discomfort and interrupts the subject's normal activities.

Severe: The adverse event causes considerable interference with the subject's normal activities and may be incapacitating or life-threatening.

The following definitions will be used to assess the relationship of the AE to study drugs or procedures:

Probably Related: An adverse event has a strong temporal relationship to study drug or recurs on re-challenge, and another etiology is unlikely or significantly less likely.

Possibly Related: An adverse event has a strong temporal relationship to the study drug, and an alternative etiology is equally or less likely compared to the potential relationship to study drug.

Probably Not Related: An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.

Not Related: An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has much more likely alternative etiology).

If the adverse event is in, the investigator's opinion, possibly or probably related, or not related to study drug or procedures, then an alternate etiology will be provided by the investigator.

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.

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 1.0, December 2004, which can be found on the DAIDS RCC Web site: http://rcc.tech-res.com/tox_tables.htm.

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. Any SAE that is judged related to study product or UP will be reported to the IRB within 5 days of the event. 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.

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 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. Study 2 – Peri PrEP Dosing (n=62)

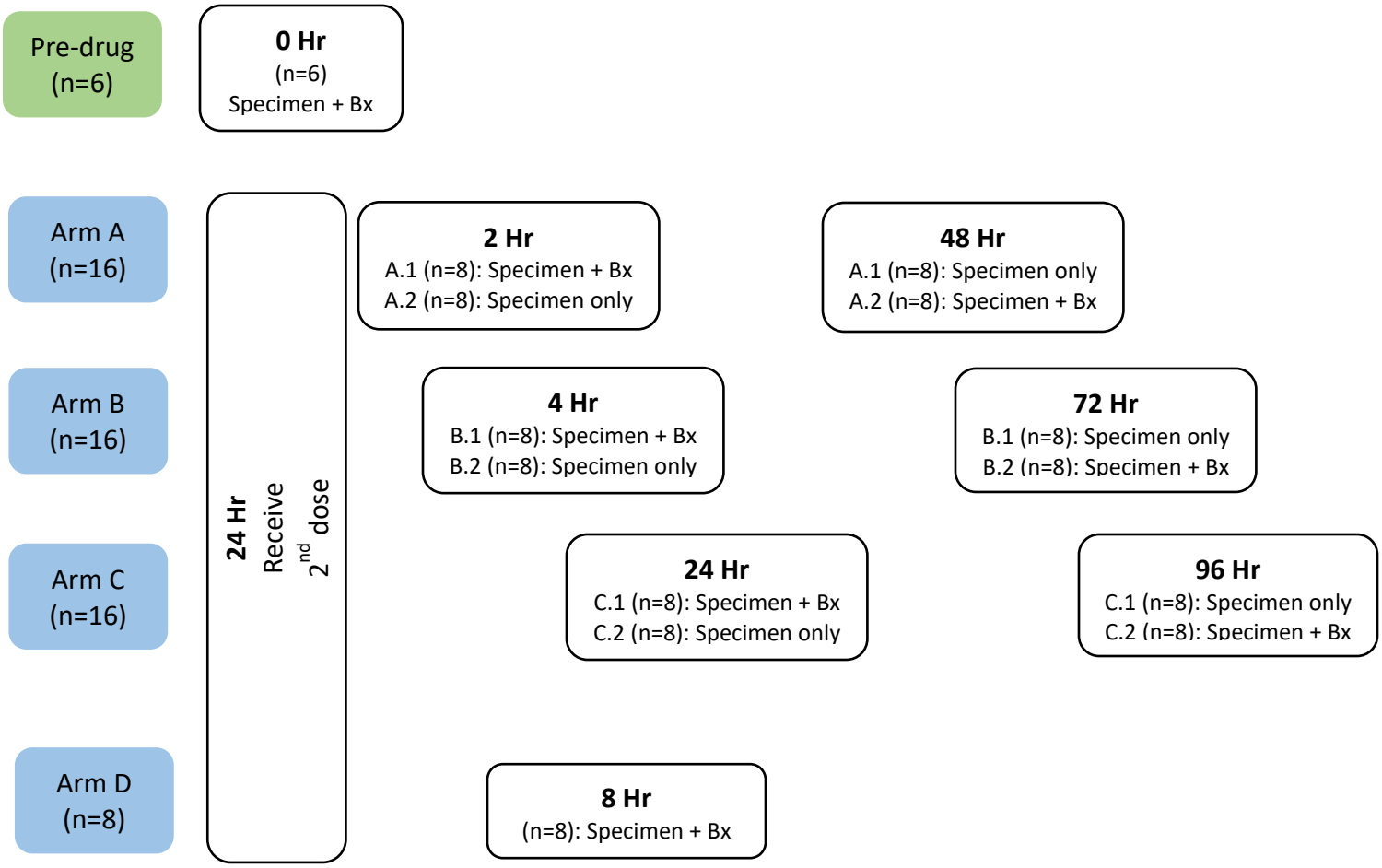
Objective: Determine pharmacokinetics of a combination of NRTIs + INSTI in mucosal tissues following on-demand peri-exposure prophylaxis regimen

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

1st dose recorded observed dosing, 2nd dose observed in clinic

Timing of specimen collection begins following 2nd dose

Each participant has 1 biopsy visit and 1 non-biopsy visit (Except Pre-Drug & Arm D)



	All Specimen Visits	Biopsy Visits
Specimens Collected	Blood (2 CPT, 1 EDTA) Urine Penile/Urethral Swabs Cheek Swab	*Standard collection* + Rectal Swabs (x2) Rectal Biopsies (x10) Aptima Swab-Rectal STI Testing Semen