PROTOCOL TITLE: Multipurpose Prevention of Post-Exposure Prophylaxis Regimens (Combo-PEP)

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PRINCIPAL INVESTIGATOR:
Colleen F. Kelley MD, MPH
Associate Professor of Medicine
Division of Infectious Diseases
Department of Medicine
Emory School of Medicine
Assistant Professor of Epidemiology
Rollins School of Public Health
Email: [redacted]
Phone: [redacted]

EXTERNAL (NON-EMORY) COLLABORATORS
Richard Haaland
Centers for Disease Control and Prevention
Division of HIV/AIDS Prevention

External collaborator will submit designated protocol to The Centers for Disease Control and Preventions IRB for review and approval.

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	2.0	-Adding gift cards for food and incidentals
2	3.0	-Moved procedures from Visit 1a to 1b -Added blood collection
3	4.0	-Updated blood volume for visits -Added lab exclusion criteria

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1. Study Summary

Study Title	Multipurpose Prevention of Post-Exposure Prophylaxis Regimens (Combo-PEP)
Study Design	To determine tissue pharmacology of a single dose of doxycycline for STI PEP, investigators at Emory University will collaborate with the Centers for Disease Control and Prevention (CDC) to conduct a clinical trial of up to 20 MSM and women aged 18-59, with measurement of anti-retroviral drug and doxycycline concentrations in the rectum and vaginal regions. Study staff will plan to enroll participants who are HIV negative, at low risk for HIV and are not currently (or have no current plans) taking Post Exposure Prophylaxis (PEP) or Pre- Exposure Prophylaxis (PrEP). Enrolled participants will take a single dose of doxycycline (200mg) and Biktarvy® (200mg). Biological specimens will be collected at 10 time points during this study. Study staff 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 14 mL), including an HIV test, will be performed. Participants will receive study drug in clinic and will provide documentation of taking doses (doxycycline and Biktarvy®) of the drug at home. During all study visits, participants will undergo blood collection (approximately 14 mL or 3 teaspoons of blood will be obtained), a urine sample, and collection of vaginal and rectal secretions. At certain visits, a vaginal and cervical biopsy will be performed on women, and a rectal biopsy will be performed on men, in addition to swab procedures. Women will have the option to do a rectal biopsy, as well. A pregnancy test will be done on women of childbearing potential at their screening and biopsy visit.
Primary Objective	To determine tissue pharmacology of single dose doxycycline for STI PEP
Secondary Objective(s)	To determine the tissue pharmacology of single dose bictegravir for HIV PEP.

Research Intervention(s)/Interactions	Doxycycline (200mg) and Biktarvy® (200mg) one combined dose
Study Population	The population to be studied in this protocol are healthy HIV negative men who have sex with men (MSM) and HIV negative women (to include cisgender and trans females) at risk of HIV infection, who currently do not desire daily PrEP and are willing to undergo study procedures.
Sample Size	20 participants (10 women & 10 MSM).
Study Duration for individual participants	The duration of this study is 2 years. Participants will be considered 'on study' for no more than 8 weeks.
Study Specific Abbreviations/ Definitions	MSM—Men who have sex with men STI—sexually transmitted infection PrEP—Pre- exposure prophylaxis TAF—tenofovir alafenamide FTC—emtrictabine TDF—tenofovir disoproxil fumerate HIV—Human Immunodeficiency Virus PEP—post-exposure prophylaxis CRAI—condomless receptive anal intercourse DOX—doxycycline BIC—bictegravir CDC—Centers for Disease Control and Prevention WHO—World Health Organization ARV—antiretroviral ED-PrEP—event-driven pre-exposure prophylaxis
Funding Source (if any)	Centers for Disease Control and Prevention

2. Objectives

The purpose of this study is to determine the ability of doxycycline (200mg) and Biktarvy® (200mg) to penetrate mucosal tissues following a single oral dose and retain protective drug levels for extended periods of time.

Public Health Relevance: Event-driven PrEP (ED-PrEP) has been shown to be an effective solution for those who struggle to take a daily regimen of PrEP to prevent HIV; however, biomedical interventions for STI prevention have shown to be effective but have yet to be approved for use. There is limited data on the ability of DOX combined with ARVs to penetrate the mucosal tissues and provide protection against infection. Data regarding mucosal drug exposure will help inform development of multi-purpose event-driven dosing strategies.

Goal: The goal of this study is to understand the distribution of drug within mucosal tissues following a single oral dose of doxycycline and Biktarvy®.

3. Background

Sexually transmitted infections have been proven to increase the risk of HIV infection in men and women. Both men who have sex with men (MSM) and women 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), and among women through exposure to the vaginal mucosa regions, within the female genital tract, during condomless vaginal intercourse. To aid in prevention, pre-exposure prophylaxis (PrEP) and post-exposure prophylaxis (PEP) are recommended for HIV exposure. Current CDC recommendations for PrEP is to take the combination anti-HIV drug, tenofovir+emtricibatine (TDF/FTC or TAF/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, according to the CDC. While PrEP and PEP are efficacious, both the daily dosing of PrEP and the 28-day course of PEP limit their utility in practice, as many users find long term adherence to these regimens to be difficult. Therefore, short course regimens taken around the time of sex (On-demand or Event-Driven PrEP; ED-PrEP) are appealing to some, and WHO endorses one such ED-PrEP regimen for MSM: two doses of TDF/FTC between 2 and 24 hours before sex, one dose 24 hours after sex, and another dose 48 hours after sex. Although short course regimens have been proven to reduce one's risk of HIV infection, interventions for STI prevention have yet to be approved for use. Recent studies have shown a single dose of oral doxycycline (DOX) taken within 24 hours after having sex, can protect against STIs among MSM. A multi-purpose dosing strategy that combines DOX with ARVs could allow for a single event-driven oral dosing combination to be taken after sex for protection against HIV and other STI infections. The aim of this study is to better understand the ability of DOX, TAF, FTC, & bictegravir (BIC) to penetrate mucosal tissues after a single oral dose, and to examine how well the tissues retain protective drug levels over an extended period of time in both men and women.

4. Study Endpoints

Primary Endpoint: to compare doxycycline concentrations in rectal and vaginal biopsies collected 24 hours after a single dose.

Secondary Endpoint: The comparison of bictegravir concentrations in rectal and vaginal biopsies collected 24 hours after a single dose.

5. Study Intervention/Investigational Agent

Doxycycline
Doxycycline (DOX [200 mg]) is an oral medication used to treat or prevent infections that are strongly suspected to be caused by bacteria; it is an antimicrobial drug indicated for bacterial infections such as sexually transmitted infections.

Biktarvy
Biktarvy® (200mg) is an oral combination anti-HIV medication that contains the drugs tenofovir alafenamide, emtricitabine, and bictegravir.

Both study drugs will be stored and dispensed per manufacturer instructions by the Emory Investigational Drug Services Pharmacy Satellite location at the Hope Clinic. Prior to drug dispensing, the clinician will assess participant's medical history, and ensure the participant has no known allergies to the study drug. If a participant reports an allergy and a suitable alternative is not available, then the clinician may opt to not enroll the participant into the study.

6. Procedures Involved

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

Phone Screening (if applicable): Potential participants may be identified from Hope Clinic databases of former study participants or self-referrals after seeing study flyers, social media ads, etc. In these cases, study staff will administer a pre-screening questionnaire via phone to assess preliminary eligibility. If the results of the pre-screening questionnaire indicate that the potential participant may be eligible for this study, they will be invited to the clinic to complete the first screening visit.

Screening Visit 1a: Potential participants will be asked about their medical history, undergo a physical exam, and have a peripheral blood sample drawn (17.2 mL) for lab tests (creatinine, complete blood count, coagulation, HIV and Hepatitis B) and research tests (baseline levels of study drug). A pregnancy test will also be performed on women of childbearing potential.

Screening Visit 1b: Once all data (including screening labs) are collected, potential participants will be evaluated for eligibility. If found eligible, participants will have a blood sample drawn (2 mL), collect a self-administered rectal and/or vaginal fluid swab to test for gonorrhea and chlamydia, and provide a urine sample. If the participant tests positive for gonorrhea and/or chlamydia, the participant will be notified and referred for treatment to their primary doctor, health department, or other community STI treatment resources. Study staff will also dispense one dose of each study drug (200 mg of doxycycline and 200 mg of Biktarvy®) at this visit. Staff will provide dosing instructions to participant.

Dosing: Participants will be asked not to eat or drink anything except water after midnight the day before their scheduled dose. Participants will take both study drugs simultaneously at home approximately **1 hour before Visit 2** and will be instructed to take a timestamped photograph or videotape of themselves taking the dose. Photos and videos taken with smartphones automatically include a timestamp. Study staff will instruct participants to bring the photo/video to Visit 2 as proof of dosing. Participants will also have the option to send a text study staff at a specified number at the time of dosing if their phone does not have video/photo capabilities. Participants will be asked to abstain from receptive anal or vaginal sex from the time they take the study drug to 7 days after the biopsy procedure is completed in order to limit additional exposures (e.g. semen, douching, additional lubricants) to the rectal or vaginal mucosa.

Visit 2 (1 hour post-dose): Approximately 18 mL of blood will be drawn. Then participants will provide a urine sample and self- collect rectal or vaginal fluid swab samples.

Visit 3 (2 hours post-dose): Approximately 18 mL of blood will be drawn. Then participants will provide a urine sample and self- collect rectal or vaginal fluid swab samples.

Visit 4 (4 hours post-dose): Approximately 18 mL of blood will be drawn. Then participants will provide a urine sample and self- collect rectal or vaginal fluid swab samples.

Visit 5 (8 hours post-dose): Approximately 18 mL of blood will be drawn. Then participants will provide a urine sample and self- collect rectal or vaginal fluid swab samples.

Visit 6 (24 hours post-dose): Approximately 18 mL of blood will be drawn. If the participant has a penis, one urethral swab and one glans swab will be collected. If the participant has a vagina, a vaginal swab will be collected. A urine sample will then be collected from all participants.

Participants who have a vagina will undergo a vaginal/cervical biopsy. All other participants will undergo a rectal biopsy. Participants who complete the vaginal biopsy will have the ***option*** to also undergo the rectal biopsy at Visit 6. Once the scope (rectal) or the speculum (vaginal) is inserted, additional swabs will be inserted in the rectum or vagina to collect secretions. Then, up to 12 rectal biopsies, or 1 to 2 vaginal and 1 to 2 cervical biopsies will be collected. All participants will be informed not to place anything into the rectum or vagina and abstain from intercourse for 7 days after their biopsy procedure(s) to allow the mucosa to heal.

Vaginal and cervical tissue samples will not be collected in women who are menstruating, pregnant, or have possible cervical or vaginal infection. A pregnancy test will be administered to women of childbearing potential to ensure they are not pregnant. Visit 2 will also be scheduled 7 to 10 days after their last menstrual cycle.

Visit 7 (48 hours post-dose): Approximately 18 mL of blood will be drawn. Then participants will provide a urine sample and self- collect rectal or vaginal fluid swab samples.

Visit 8 (72 hours post-dose): Approximately 18 mL of blood will be drawn. Then participants will provide a urine sample and self- collect rectal or vaginal fluid swab samples.

Visit 9 (96 hours post-dose): Approximately 18 mL of blood will be drawn. Then participants will provide a urine sample and self- collect rectal or vaginal fluid swab samples.

Visit 10 (7 days post-dose): Approximately 18 mL of blood will be drawn. Then participants will provide a urine sample and self- collect rectal or vaginal fluid swab samples.

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 not filed for visits that occur outside of the target windows but will be noted in source documents.

Contingency visit: If needed, participants may be brought in for additional study visits. This would occur if, for example, screening laboratory results are lost or are inconclusive.

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.

Rectal Biopsy Procedures

A delegated, licensed medical professional whom the PI has trained in the procedure will complete all biopsies. Rectal biopsies will utilize 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 study staff. Similar procedures have been performed in Dr. Kelley's research protocols with no complications. Briefly, without the administration of any previous enemas or other preparation, up to 12 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, or the next study visit, whichever comes first, 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.

Vaginal and Cervical Biopsy Procedures
All vaginal and cervical biopsies will be completed using a speculum by experienced, trained clinicians. 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 other research protocols conducted at the Hope Clinic with no complications. A pelvic exam will be done prior to all vaginal and cervical biopsies to make sure it is safe to collect vaginal and cervical tissue samples. Up to two adequate ~2.4 mm thick biopsy specimens will be taken from normal-appearing vaginal mucosa using a sterilized mini tischler biopsy forceps. 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, or the next study visit, whichever comes first, study personnel will contact the subjects who donated vaginal cervical 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.

PrEP Linkage
Participants will also be educated about HIV pre-exposure prophylaxis throughout the study by trained study staff. After completion of the study, all participants who qualify and 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.

7. Data and Specimen Banking

Data collected for this study will be analyzed and stored at the Hope Clinic. After the study is completed, the de-identified, archived data may be stored for use by the researchers at the Hope Clinic and collaborative partners at The Centers for Disease Control and Prevention.

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

8. Sharing of Results with Participants

Study results, including results of laboratory tests and genetic tests, will not be shared with the participants. If abnormalities deemed to be clinically significant are discovered during the

procedure and/or from the safety labs, such as positive chlamydia or gonorrhea tests, these results will be discussed with the participant and a referral will be made to a primary care physician or specialist as needed.

9. Study Timelines

- Participants will be considered on study for no more than 8 weeks.
- The duration anticipated to enroll all study participants is 1 year.
- The estimated date for the investigators to complete this study is 2 years.

10. Inclusion and Exclusion Criteria

Inclusion Criteria

1) HIV negative person, who was assigned male or female at birth, who reports sex with another man in the last year and is in good general health
2) Aged 18-59 years
3) Not currently taking PrEP and no plans to initiate during study
4) Not currently taking PEP
5) Not currently taking doxycycline or other tetracycline-derived antibiotics and no plans to initiate during the study
6) Willing to use condoms consistently for the duration of the study
7) Able to provide informed consent in English
8) No plans for relocation in the next 4 months
9) Willing to undergo peripheral blood, urine, rectal or vaginal secretion collection, and a rectal or vaginal and cervical biopsy procedure
10) Willing to use study products as directed
11) Hepatitis B surface antigen (HBsAg) negative (screening lab test)
12) Creatinine clearance >60 ml/min

Exclusion Criteria

1) Currently infected with hepatitis virus and/ or has liver disease
2) Current or chronic history of kidney disease or CrCl<60 ml/min
3) Continued need for, or use during the 90 days prior to enrollment, of the following medications:
    a) Systemic immunomodulatory agents
    b) Supraphysiologic doses of steroids (short course steroids less than 7 days duration, allowable at the discretion of the investigators)
    c) Chemotherapy or radiation for treatment of malignancy
    d) Experimental medications, vaccines, or biologicals
4) Intent to use HIV antiretroviral pre/post-exposure prophylaxis (PrEP or PEP) during the study, outside of the study procedures
5) Intent to use doxycycline or other tetracycline-derived antibiotics during the course of the study, outside of the study procedures
6) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the patient unsuitable for the study or unable to comply with the study requirements
7) Not pregnant and no plans on getting pregnant throughout the duration of the study
8) Known allergic reaction to study drugs.
9) Significant laboratory abnormalities at baseline visit for rectal biopsies, 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

This study will not include any of the vulnerable populations listed below.

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

11. Vulnerable Populations

This research will not involve human fetuses, neonates, prisoners, minors or cognitively impaired adults.

12. Local Number of Participants

This study will enroll a total of 20 participants (10 MSM and 10 women) at Emory. In order to enroll all 20 participants, it is anticipated that 40 will sign consent and be screened.

13. Recruitment Methods

Dr. Kelley and co-investigators have a successful track record in recruiting MSM for their research protocols utilizing all of the recruitment methods detailed below. All recruitment materials will be IRB-approved prior to use.

Databases

The Hope Clinic maintains a large database of people who have previously expressed interest in participating in future research. Additionally, the study team will use existing Emory University databases, including Research Match and the Emory Healthcare Clinical Data Warehouse, who have consented to be contacted about research opportunities.

Email blasts and phone calls will be made to potential participants from these databases.

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. A site contact sheet or a tablet using SurveyGizmo will be used to populate name, phone number, and email address of interested participants. Examples of locations used for face-to-face engagement are listed below:

a. Community annual events attended by study population
b. Bars and Night Clubs catering towards MSM
c. Community organizations serving study population
d. Sporting events
e. Community venues

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. Interested participants will click a posted ad with an embedded hyperlink, which will redirect them to a short screener. This screener will capture information regarding eligibility, including HIV status, name, phone number and email. Recruiters will use information obtained from online screener to contact and schedule participant visits. Potential participants may also be engaged directly on social media to assess interest in research participation. Any contact made through direct

messaging, will follow the general script below. We will seek permission from creator/ moderator of the private website/ group, etc. before entering an interaction if possible.

a. Dating Sites (Tinder, Bumble, Jack'd, Adam4Adam, Grindr, etc.)
b. Social Network (Facebook, Snapchat, Instagram, etc.)
c. Other online social media platforms and websites where study population might visit/patronize
d. Craigslist

Print Ads and Listservs
In order to reach a wider audience, print ads will be placed around Emory and other community settings. Study staff will also utilize listservs run by our community partners to disseminate recruitment materials.

Recruitment Scripts
Phone Call Script
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 in combination with doxycycline are absorbed into different body tissues and may be considered for future STI prevention regimens in the future. The study will consist of ten visits, and you will be compensated for your time of travel and inconvenience. If you or anyone you know may be interested or have any questions about this study, please contact _____ or _____. These are the basic qualifications to participate in the study:

- You may qualify if you are:
- Age 18-59
- HIV negative person, who was assigned male or female at birth (including trans females), who reports sex with another man in the last year, and is in good general health
- Not currently taking PrEP, PEP, doxycycline or other tetracycline-derived antibiotic
- Willing to use condoms if instructed to do so
- 1 or more sexual partners in the last 6 months

Direct Messaging via Social Media or Text

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).

   If contact responds negatively or does not responds, no further contact will be attempted.

b. Hello, I am a recruiter for research studies at the Emory University Hope Clinic. We are currently looking for volunteers to participate in 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.

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 [insert website] or call [insert phone number].

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.

14. Withdrawal of Participants

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. Participants are free to withdraw from participation in the study at any time upon request. Under certain circumstances, an individual participant may be terminated from participation in this study. Specific events that will result in early termination include:

- Participant refuses further participation
- Participant relocates prior to completion of the biopsy visit
- If any laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the appropriate Case Report Form (CRF).

15. Risks to Participants

Rectal Biopsies

For this proposed work, there are some risks. Risks associated with lower gastrointestinal endoscopy performed for clinical purposes include colitis from chemicals for endoscope sterilization, bowel perforation, bleeding, diverticulitis, and infection. A delegated, licensed medical professional whom the PI has trained in the procedure will complete all biopsies. To minimize risks, rigid proctoscopy, rather than flexible sigmoidoscopy or colonoscopy, will be used in this study and the number of biopsies taken will be limited to 12. Colonoscopy has been shown to be associated with a still low, but significantly greater risk of complications than rectosigmoidoscopy[10]. 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[10, 11] including a combined 144,832 clinically indicated procedures, the incidence of serious complications ranged from 0.06 to 0.8% utilizing flexible sigmoidoscopy. 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[12,13] including a combined 3,011 procedures and a median of eight[14] and 17 biopsies[13], respectively, there was only one serious complication, for an incidence of approximately 0.33%. More relevant to the present protocol, in a study of subjects undergoing endoscopic procedures exclusively for research purposes[76], 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. Thus, the risk of serious complications from the proposed study procedures, even with up to 12 biopsy specimens, is expected to be very low. Of note, Dr. Kelley has performed >400 such procedures for other research protocols at the Hope Clinic with zero complications.

There is theoretical risk of increased acquisition of HIV or other infection if an HIV negative study participant is exposed soon after the rectal biopsy procedure (i.e. while the mucosal surface is damaged). Similarly, transmission risk from an HIV positive participant to sexual partners may also be heightened with mucosal bleeding. Therefore, study subjects will be counseled not to engage in anal intercourse for 1 week after the 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 designated study personnel will be able to access information to identify specimens of individual participants.

Any abnormalities discovered during the procedure and/or from the safety labs conducted will be discussed with the participant, and a referral will made to a primary care physician, gastroenterologist or other specialist as needed.

Vaginal and Cervical Biopsies

As with rectal biopsies, there are risk associated with cervical and vaginal biopsies. These risks include pain, discomfort, a persistent odor, bleeding, and infection. If bleeding occurs that cannot be stopped by applying pressure, medication will be used, such as monsel's solution and paste, to stop it. Silver nitrate has a gray color that can cause gray flecks in the vaginal discharge after the biopsy is completed. All female participants will be notified of this expected side effect.

A delegated, licensed medical professional who has trained in the procedure will complete all biopsies.

To minimize some of these risks, study staff will limit the collection to a maximum of two vaginal and two cervical samples. Study subjects will be instructed to take over-the-counter pain medication before and/or after the procedure, such as Tylenol, if not contraindicated. Subjects will be instructed on how to care for the area and to contact the PI or their medical care provider if any of the aforementioned risk occur and persist.

The procedure is not anticipated to be associated with any deleterious impact on participants' health or well-being.

Doxycycline
Doxycycline (DOX) is a medication used to treat or prevent infections that are strongly suspected to be caused by bacteria. DOX is an antimicrobial drug indicated for bacteria infections such as sexually transmitted infections. The most common adverse reaction reported is diarrhea. Other adverse reactions include vomiting, nausea, dysphagia, and inflammatory lesions. Additional adverse reactions that are rare and not expected to occur with a one-dose regimen prescribed in this protocol include hepatotoxicity, exfoliative dermatitis (skin), rise in BUN levels, hypersensitivity reactions, hemolytic anemia, neutropenia, and eosinophilia.

The medication provided in this study is not for treatment or prevention of HIV and other STI infections. Participants who are interested in pre-exposure prophylaxis (PrEP) after this study ends, will be referred to a medical provider who can prescribe PrEP.

To protect against possible side effects of the study drug, women who are pregnant or nursing a child may not take part in this study. If a female participant becomes pregnant, there may be risks to the participant, the embryo, or fetus. These risks are not yet known. Women of childbearing potential will be asked to provide a urine pregnancy test to ensure they are not pregnant, prior to administering drug. Women of childbearing ability will discuss contraceptive methods to use throughout the study and may be asked to abstain throughout the duration of the study. If the participant becomes pregnant during the study, they must inform the study doctor immediately. Pregnant women will be excluded or removed from the study.

Biktarvy® (TAF/FTC/BIC)
Biktarvy® is a combination anti-HIV medication that contains the drugs tenofovir alafenamide, emtricitabine, and bictegravir. Based on clinical trials previously conducted of Biktarvy®, the drug showed to be well tolerated (see package insert). The most common adverse events reported in clinical trials ($\geq$ 5% incidence) included diarrhea, nausea, and headache. Additional adverse reactions occurring in less than 2% of subjects administered Biktarvy® 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 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 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 1-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, study staff 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. 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, study staff 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 or vaginal sex from the time they take the study drug to 7 days after the biopsy procedure is completed in order to limit additional exposures (e.g. semen, douching, additional lubricants) to the rectal or vaginal mucosa. Participants taking Biktarvy® 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.

Blood Sample Risks
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.

16. Potential Benefits to Participants
Subjects are not expected to derive direct benefit from this study.

17. Compensation to Participants
All participants will be compensated for their time and inconvenience of study participation according to the schedule below:

- Screening 1a: $25
- Screening 1b: $20
- Follow-Up Visits: $50 x 8 = $400
- Rectal/Vaginal Biopsy Visit: $125
- Optional Rectal Biopsy (Women Only): $50
- Unscheduled Visit (if needed): $20
- Total: $570

If participants do not finish the study, they will be compensated for the visits they have completed.

Because Visits 2-5 take place over a span of 8 hours, we will provide participants with a $15 gift card while they wait, for food and/or incidentals.

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.

There is no charge for parking at the Hope Clinic. However, participants may be provided with a MARTA card or other transportation resource (e.g. rideshare), if available.

18. Data Management and Confidentiality

Confidentiality

Case report forms (CRFs) will be used to collect demographic, behavioral, clinical, and laboratory data at study visits. Upon enrollment, each participant will be assigned a unique Participant Identification (PID) number. All laboratory specimens, CRFs, reports, and other records that leave the site will be identified only with by the assigned PID. All study samples and records (both identifiable and not identifiable) will be kept in a secure area in a limited-access facility that only authorized study personnel have access to. Electronic data will be password protected and stored in REDCap or other Emory-sponsored HIPAA-compliant system. Information about the subject's participation will not be shared with individuals who are not directly involved with participants. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the FDA, the NIH, the CDC or OHRP.

Quality Assurance Data Monitoring
Hope Clinic QA staff will monitor data periodically for data quality and protocol compliance. Twice yearly, study staff will conduct a systematic review of study data using the Emory University-Self-monitoring Tool available at http://www.ctac.emory.edu/clinical_trial_resources/Audit%20Tools.html.

Statistical Analysis Plan
Primary Outcomes: Comparison of doxycycline concentrations in blood and tissue between men and women. Plasma doxycycline concentrations at 24 hours will be compared between men and women using a Wilcoxon test. Median rectal and vaginal swab doxycycline concentrations collected at 24 hours after dosing will be compared using a Wilcoxon test. Median rectal and cervical tissues doxycycline concentrations collected at 24 hours after dosing will be compared using a Wilcoxon test. P-values less than 0.05 will be considered significant.

Exploratory Outcomes: Comparison of TAF, FTC, and BIC concentrations in blood and tissue between men and women. Plasma TAF, FTC, and BIC concentrations at 24 hours will be compared between men and women using a Wilcoxon test. Median rectal and vaginal swab TAF, FTC, and BIC concentrations collected at 24 hours after dosing will be compared using a Wilcoxon test. Median rectal and cervical tissue TAF, FTC, and BIC concentrations collected at 24 hours after dosing will be compared using a Wilcoxon test. P-values less than 0.05 will be considered significant.

19. Provisions to Monitor the Data to Ensure the Safety of Participants

Adverse Events
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 (Visit 2) and continues until the subject either completes or withdraws from the study.

All AEs and laboratory abnormalities will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version

2.1, July 2017, which can be found on the DAIDS RCC Web site: http://rcc.tech-res.com/tox_tables.htm.

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

Related AEs ≥ Grade 3 will be included in the summary reports provided to the Medical Monitor of the study. Exceptions to expedited reporting are detailed below.

This study uses FDA approved drugs with known common side effects (please refer to the risk section of the protocol for common side effects). The following side effects will not be reported as an EAE unless it increases in severity or becomes prolonged.

Nausea: Report if severity is a Grade 3 or higher

Vomiting: Report if severity is a grade 3 or higher

Diarrhea: Report if severity is a Grade 3 or higher

Rash: Report if severity is a Grade 3 or higher

Serious Adverse Events

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

2. Death.
3. 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.
4. Inpatient hospitalization or prolongation of existing hospitalization.
5. 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.
6. Congenital anomaly/birth defects - Any structural abnormality in subject's offspring that occurs after intrauterine exposure to treatment.
7. 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.

The reporting period for participant SAEs begins at enrollment (Visit 2) and continues until the subject either completes or withdraws from the study. All SAEs will be reported to the Medical Monitor within 24 hours of site awareness and reported to the IRB per its policies.

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
AEs ≥ Grade 3 or 4 and targeted AEs will be reviewed in real time by study investigators.

Medical Monitor
A medical monitor will be assigned to this study for the purpose of safety oversight. The medical monitor will be notified of all SAEs within 24 hours of site awareness and receive quarterly summary reports of all AEs meeting the previously described criteria.

20. Provisions to Protect the Privacy Interests of Participants

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 study staff members. Electronic data will be stored on the Redcap server or Emory School of Medicine HIPPAA compliant servers, which will be accessible to the study staff only. All study specimens will be labeled with a unique identifier prior to transport to CDC. Identifying information will not be shared with laboratory collaborators at the CDC and they will be unable to link the study ID to any identifying information. Any demographic data shared with CDC will also be stripped of HIPAA identifiers prior to sharing.

21. Economic Burden to Participants

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

22. Consent Process

The consent process will be conducted in a private exam room at the Hope Clinic or electronically via an online e-consent platform (DocuSign) by trained and delegated study staff. The IRB-approved consent form will describe the purpose of the study, procedures, and the risks and benefits of participation. Study staff will review each section of the informed consent with potential participants either in person or remotely (via phone or Zoom). 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. Potential participants may 'pause' the consenting process to review the consent form on their own time to think about participating, discuss with family and friends, etc. Participants will be given direct contact information for the study staff in order to answer any questions or concerns they may have. Once signed, all participants will be provided a either a paper or electronic copy of the signed informed consent form (ICF).

Non-English-Speaking Participants: Non-English-speaking subjects will not be enrolled in this study because the study team does not have the resources to enroll and routinely accommodate non-English speaking participants.
Participants who are not yet adults (infants, children, teenagers) Participants who are under the age of 18 will not be enrolled in this study.
Cognitively Impaired Adults Cognitively impaired adults in this study will not be enrolled.
Adults Unable to Consent: Adults who are unable to provide consent for themselves will not be enrolled in this study.

23. Setting
All participant visit will be conducted in a clinic setting at the Hope Clinic.

24. Resources Available
The Hope Clinic routinely meets enrollment goals and has existing partnerships that serve as resources for new potential participants. The study team does not anticipate any issues with recruiting the 40 participants for this study.

The Hope Clinic of Emory University is a free-standing medical research building located in Decatur, GA, and is easily accessible by vehicle or public transportation. There are 8 examination rooms on the top floor in which to see participants. The bottom floor houses the sample processing and storage laboratory. At all times there is a clinician in the clinic available to study staff (all clinicians are on all studies). Should a medical emergency arise, the clinician will manage the immediate situation. The Hope Clinic is located across the street from Emory Decatur Hospital. If needed, Hope Clinic staff would call 911 and have the participant transported there for care.

All study staff have completed all Emory University institutional required research trainings. Prior to working on the study, each staff member is trained thoroughly on each protocol and it's supporting documents. There is a dedicated regulatory coordinator who ensures all training and delegation is completed appropriately for each study.

25. Multi-Site Research when Emory is the Lead Site
Not applicable.

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Table 1. Schedule of Activities

	Visit 1a	Visit 1b	Dose	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10
Timepoint	-42 to 0 days	-42 to 0 days	0 hr	1 hr	2 hrs	4 hrs	8 hrs	24 hrs	48 hrs	72 hrs	96 hrs	7 days
Window	-	-	-	±30 min	±30 min	±30 min	±30 min	±1 hr	±1 hr	±1 hr	±1 hr	±1 hr
Informed Consent	X											
Physical Exam	X											
Medical History	X											
Eligibility		X										
Dose Administration			X									
Pregnancy Test	X							X				
Urine Sample	X			X	X	X	X	X	X	X	X	X
Self-Collected Rectal/Vaginal Swabs		X		X	X	X	X		X	X	X	X
Staff-Collected Urethral/Glans/ Vaginal Swabs								X				
Rectal/Vaginal Biopsy								X				
Blood Volume	17.2 mL	2 mL	18 mL	18 mL	18 mL	18 mL	18 mL	18 mL	18 mL	18 mL	18 mL	18 mL