Rectal Lubricant Use and Pre-Exposure Prophylaxis in Men Who Have Sex with Men

Version Date: September 26, 2016

NCT02401230

TITLE OF PROJECT: PrEP, LUBE, AND THE RECTAL MUCOSA IN MSM AT RISK OF HIV

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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 receptive anal intercourse (RAI). During RAI, many MSM will use lubricants, which can potentially cause mucosal inflammation and damage. A new HIV prevention intervention, called pre-exposure prophylaxis (PrEP), recommends that MSM at risk of HIV infection take a daily anti-HIV medication called Truvada (tenofovir/emtricitabine) which is highly effective. However, it is not known if the use of lubricant during RAI will interfere with the efficacy of PrEP for HIV prevention.

Design: To address the impact of a popular, over-the-counter gel lubricant use in MSM on PrEP, investigators at Emory University will collaborate with the Centers for Disease Control and Prevention (CDC) to conduct a randomized clinical trial of 90 MSM. Men will be randomized into a 3-arm study as follows: (1) daily oral Truvada® only, (2) daily gel lubricant applied rectally only or (3) oral Truvada® plus rectal gel lubricant application daily. This study will entail 4 study visits at the Emory University Hope Clinic. During the first visit (time 0), all men will be screened for eligibility and undergo written informed consent, physical examination, rapid HIV testing, phlebotomy for screening laboratories, and randomization. During study visit 2 prior to the initiation of study product (time 1-6 weeks), participants will undergo phlebotomy, collection of rectal secretions, and rectal biopsy via rigid sigmoidoscopy for establishment of baseline values. During study visit 3 (time 4-16 weeks), men will be dispensed and instructed on the at-home application of rectal lubricant and/or oral Truvada. During study visit 4 (time 5-26 weeks), men will return after 7 consecutive days of study product use for repeat phlebotomy, collection of rectal secretions, and rectal biopsy via rigid sigmoidoscopy. After collection, biologic specimens will be immediately transported by courier to CDC (laboratory of Clyde Hart) for processing. Specimens will be processed immediately for *ex vivo* laboratory assays that will include PrEP drug concentrations, inflammatory cytokine levels, HIV target cell measurement and characterization by flow cytometry, and *in vitro* HIV infection assays. Comparison of assay results among the 3 study arms should determine if rectal lubricant usage reduces PrEP drug concentrations, increases inflammation, or increases the proportion or susceptibility of HIV target cells in the rectal mucosa.

Duration: The duration of this study is 2 years. Participants will be considered ‘on-study’ for no more than 26 weeks.

Sample size: For this protocol we will recruit 90 HIV-negative MSM who meet eligibility criteria outlined in the protocol.

Population: The population to be studied in this protocol is HIV negative MSM who meet eligibility criteria and are willing to perform study procedures. These men will be recruited from existing databases of MSM who have agreed to be contacted for future studies, and from internet and paper advertisements currently used routinely by the Hope Clinic for study

recruitment.

LAY SUMMARY

Men who have sex with men (MSM) continue to be disproportionately affected by HIV. Over 60% of new HIV infections in the US occur among MSM. The majority of HIV infections among MSM occur through exposure to the rectal mucosa during receptive anal intercourse (RAI). During RAI, products such as lubricants are often used to reduce friction. However, lubricants, especially hyperosmolar lubricants, have been shown to cause inflammation in the rectum. Pre-exposure prophylaxis (PrEP) is a new HIV prevention method that is recommended by CDC and WHO for MSM at risk of HIV infection. PrEP entails taking an anti-HIV medication (Truvada; tenofovir/emtricitabine) on a daily basis to prevent HIV infection. However, it is unclear whether the inflammation caused by rectal lubricant usage during RAI will result in rectal tissues with increased numbers of HIV target cells, or reduced PrEP drug levels, such that PrEP is no longer able to prevent HIV infection for MSM using rectal lubricants. This study is designed to examine whether the use of rectal lubricants could affect the efficacy of PrEP for MSM.

For this protocol, we will recruit HIV-negative MSM aged 18-49 who are willing to adhere to study procedures. There will be 4 study visits conducted over a maximum 6-month period. The first visit will be a screening visit where eligibility is determined, written informed consent is obtained, screening tests are performed, and men will be randomized to one of three study groups: 1. Use of rectal over the counter gel lubricant alone; 2. Use of oral Truvada alone; or 3. Use of rectal gel lubricant and oral Truvada. The second study visit will occur 1-6 weeks after the screening visit. During the second study visit, men will undergo a blood draw and rigid sigmoidoscopy for collection of baseline rectal secretions and biopsies. The third study visit will occur at least 3 weeks after the second study visit (4-16 weeks after the screening visit). During the 3rd study visit, men will be given lubricant and/or Truvada and instructed on their use for 7 consecutive days before study visit 4. Study visit 4 will occur at least 4 weeks after study visit 2 (5-26 weeks after the screening visit). During study visit 4, men will again undergo a blood draw and undergo a rigid sigmoidoscopy for collection of rectal secretions and biopsy samples post use of product(s) for 7 days just prior to visit. All specimens will be transported directly to the laboratory of Clyde Hart, PhD at CDC where multiple immune assays are planned to determine if the use of lubricant may affect how well PrEP works.

PROJECT DESCRIPTION

The efficacy reported in clinical studies of daily oral dosing of Truvada® or tenofovir to prevent HIV infection in MSM indicates the potential for PrEP to greatly reduce HIV infections within these high-risk populations. CDC recently released clinical practice guidelines recommending PrEP for MSM at risk of HIV infection.[1] However, the impact of rectal lubricant use on factors that could impact PrEP effectiveness in MSM is unclear. Recent studies suggest that lubricant application can increase epithelial damage and expression of inflammatory makers in human rectal tissue explants and epithelial cell cultures, and in macaque monkey rectal models without increasing their rates of HIV or SHIV infection, respectively.[2-4] In contrast, consistent rectal lubricant use has been shown to increase acquisition of non-HIV STDs in a cohort of MSM in the USA.[5] Additionally, studies from the TDF2 Study have suggested that ratios of intracellular tenofovir to natural substrate are reduced in the presence of immune cell activation. Together, these studies raise the concern that while MSM taking oral PrEP may be protected from HIV acquisition, regular use of rectal lubricants may abrogate the protection provided by PrEP due to increased epithelial damage, inflammation and immune activation.

To address the impact of a popular, over the counter, gel lubricant use in the rectum in MSM on PrEP, investigators at Emory University will collaborate with Dr. Clyde Hart at the CDC to recruit and randomize 90 MSM into a three-arm study of PrEP and lubricants: (1) daily oral Truvada® for 7 days, (2) daily gel lubricant applied rectally for 7 days or (3) oral Truvada® plus rectal gel lubricant application daily for 7 days. At CDC, *ex vivo* laboratory assays will be used to evaluate the impact of rectal lubricant use on oral PrEP's effectiveness. Blood, rectal secretions and rectal biopsies obtained by rigid sigmoidoscopy (at approximately 8 -10 cm from the anal verge) will be collected from men in all three study arms at least 21 days prior to initiation of treatment and immediately following 7 days of consecutive use of assigned product. Specimens will be processed immediately for *ex vivo* laboratory assays at CDC. Blood plasma and PBMCs will be used to measure extracellular and intracellular drug concentrations as well as intracellular concentrations of the natural dNTP substrates to assess adherence to oral Truvada® and to compare changes in the ratio of drug to natural substrate in peripheral blood. Rectal secretions from all participants will be analyzed to measure changes in soluble immunological cytokines in the presence of gel lubricant usage that may indicate associated increases in inflammation. Rectal lymphocytes will be isolated from the rectal biopsies collected from each man and analyzed for concentrations of intracellular tenofovir and emtricitabine as well as natural substrates, dATP and dCTP, to evaluate the potential for gel lubricant to alter the ratio of antiretroviral drug to natural substrate in the rectal mucosa. Additionally, rectal lymphocytes from 10 participants in each arm will be characterized using multicolor flow cytometry to observe potential changes in the proportion and activation state of HIV target cells within the rectal mucosa. Rectal lymphocytes from the remaining 10 participants in each arm will be subjected to *in vitro* infection with HIV to test for changes in the susceptibility to virus infection in the presence of gel lubricant usage.

These studies should provide important laboratory results to help inform policy and public health officials as to usage of hyperosmolar rectal lubricants in concert with oral PrEP. Pharmacological analyses will provide important data as to whether lubricant usage diminishes the ratio of drug to substrate in HIV target cells in the rectum that may reduce PrEP effectiveness. Immunological studies will help us understand whether lubricant usage

increases inflammation and the concentrations of HIV target cells in the rectum of men taking oral PrEP. The *ex vivo* virus infection assays described here will provide a surrogate measure of whether lubricant usage increases susceptibility to rectal infection with HIV for men taking oral PrEP. Together the combination of these studies should help determine if rectal lubricant usage may abrogate the potential anti-HIV benefits of oral PrEP.

Public Health Relevance: Information about the impact of rectal lubricant use in men who have sex with men will better inform policy makers and the public to make important choices regarding the safety of rectal lubricant usage in the presence of pre-exposure prophylaxis.

Goal: To determine if PrEP efficacy can be abrogated by use of rectal lubricants in MSM.

STUDY POPULATION

A total of 70 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 print and on-line advertisements. Research recruiters at the Hope Clinic and the Rollins School of Public Health are experienced in recruiting this population for research studies, including those with rectal biopsies, and do not anticipate problems. Dr. Kelley is currently conducting an Emory IRB approved study of the effects of unprotected anal intercourse on the rectal mucosa. This study involves recruiting a similar population to undergo repeated rectal biopsy procedures that are timed with sexual intercourse. We expect approximately 10-15% of men will not complete the study, therefore the sample size of 70 men will likely result in study completion for 60 men.

INCLUSION CRITERIA FOR MSM

1) HIV-negative man who reports receptive anal sex with another man in the last 6 months aged 18-49 years
2) Male to female transgender women who are not currently taking hormonal therapy or plan to take hormonal therapy for the duration of the study
3) Not currently taking PrEP and no plans to initiate during study
4) Able to provide informed consent in English
5) No plans for relocation in the next 6 months
6) Willing to undergo peripheral blood and rectal biopsy sampling
7) Willing to use study products as directed
8) Willing to abstain from receptive anal intercourse 3 days prior to study visit 2 and 10 days prior to study visit 4.
9) Willing to abstain from receptive anal intercourse for 1 week after study visits 2 and 4.

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) 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
3) 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 or vaginal mucosa, or untreated sexually transmitted disease with mucosal involvement
4) 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 products lubricants or douching used for sexual intercourse
5) 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
   c) Experimental medications, vaccines, or biologicals
6) Intent to use HIV antiretroviral pre-exposure prophylaxis (PrEP) during the study, outside of the study procedures
7) Symptoms of an untreated rectal sexually transmitted infection (e.g. rectal pain, discharge, bleeding, etc.)
8) Current use of hormonal therapy
9) Any other clinical condition or prior therapy that, in the opinion of the investigator, would make the patient unsuitable for the study or unable to comply with the study requirements.

PROCEDURES

Recruitment procedures

We will recruit subjects for this protocol from 2 existing databases of MSM who have consented to be re-contacted for future research opportunities (see below). We will also recruit men with print and on-line (e.g. Facebook) advertisements as have been utilized for

other studies conducted by the Emory investigative team. We will submit all print and online advertisement copy to the Emory IRB for approval prior to launching these activities.

1) The Hope Clinic at Emory University maintains a large study database of research participants that have agreed to be re-contacted for future research studies. Due to the nature of ongoing studies at the Hope Clinic, a large proportion of these participants are MSM. We will utilize this study database to recruit both MSM who are engaging in URAI and men who have never engaged in anal sex. Men will be contacted by phone or email and screened by phone with the eligibility criteria for this protocol. Men who are eligible will be scheduled for a screening visit.

2) PRISM Health (research group in the Rollins School of Public health, Dr. Kelley is a member of this group) maintains large study databases of MSM who have participated in previous research studies and have consented for future contact. Men will be contacted by phone or email and screened by phone with the eligibility criteria for this protocol. Men who are eligible will be scheduled for a screening visit.

Study visits

Visit 1 (screening):

This study will be comprised of 4 study visits over a minimum 6 week period and maximum 6 month period.

During the screening visit, eligible MSM will provide written informed consent after all their questions are answered in a private exam room at the Hope Clinic. Subjects will also receive an approved HIPAA statement and will be informed about the way their protected health information will be used and stored. Copies of the consent/HIPAA 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.

After provision of informed consent, a medical history and physical examination will be conducted by the PI to evaluate for exclusion criteria. A rapid HIV test with finger stick whole blood (OraQuick or INSTI) will be performed by the PI or study coordinator who will be certified in HIV counseling and testing to confirm eligibility. Peripheral blood will be drawn for a complete blood count and coagulation tests. Finally, MSM will be randomized to one of three study arms:

Arm 1. Use of rectal gel lubricant alone for 7 days prior to study visit 4.

Arm 2. Use of PrEP alone for 7 days prior to study visit 4

Arm 3. Use of both rectal gel lubricant and PreP for 7 days prior to study visit 4.

This study will not be blinded, so both investigator and participant will be aware of randomization assignment. Participants will be asked to abstain from receptive anal intercourse for at least 3 days prior to study visit 2.

Visit 2:

Study visit 2 will occur 1-6 weeks after the screening visit. During visit 2, the participant will undergo a 60mL peripheral blood draw. All blood 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. Finally, rigid sigmoidoscopy (described further below) will be performed and, rectal secretions will be collected with Dacron swabs, and 8-12 rectal biopsies will be collected. An additional swab will be collected for testing for gonorrhea, chlamydia, and HSV-2 DNA to be performed by CDC. If positive for gonorrhea or chlamydia, men will be referred for care at their private physician's office, the health department, or AID Atlanta for treatment. HSV-2 results will not be returned to participants given the unclear clinical utility of HSV-2 serology in the absence of active disease. All men will be instructed to place nothing in the rectum and to abstain from sex for 7 days after the procedure to allow the mucosa to heal. Men will be given a follow-up appointment for visit 3 which will occur 3-16 weeks after visit 2.

Visit 3:

Study visit 3 will occur a minimum of 3 weeks (maximum 16 weeks) after study visit 2 in order to allow full healing of the rectal mucosa after biopsy and some flexibility in clinic scheduling. During visit 3, the study group assignment will be reviewed and participants will be provided applicators pre-filled with 5ml of a popular, over the counter gel lubricant and/or Truvada. Truvada will be dispensed through the Emory Investigational Drug Service. MSM assigned to study arms 1 and 3 will be instructed to insert 5mL of rectal lubricant with the study-provided pre-filled applicator once daily for 7 consecutive days prior to their scheduled study visit 4. MSM assigned to study arms 2 and 3 will be dispensed 7 days of Truvada from the Emory Investigational Drug Service and instructed on daily dosing for 7 consecutive days prior to their scheduled study visit 4. Of note, MSM in study group 3 will use rectal gel lubricant and Truvada during the same 7-day period. MSM will be requested to abstain from receptive anal intercourse while on study product (Truvada and/or lubricant).

Visit 4:

Study visit 4 will occur a minimum of 1 week after study visit 3 and a maximum of 26 weeks from the screening visit. As above, men will be provided an appointment for study visit 4 during study visit 3. They will be instructed to use study product based on arm assignment for 7 consecutive days prior to the study visit 4 appointment. During study visit 4, the participant will undergo a 60mL peripheral blood draw. A urine sample will be collected from participants randomized to an arm containing Truvada. This sample will be used to at CDC to develop an assay to detect Truvada in the urine. All 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. Finally, rigid sigmoidoscopy (described further below) will be performed and, rectal secretions will be collected with Dacron swabs, and 8-12 rectal biopsies will be collected. An additional swab will be collected for testing for gonorrhea, chlamydia, and HSV-2 DNA to be performed by CDC. If positive for gonorrhea or chlamydia, men will be referred for care at their private physician's office, the health department, or AID Atlanta for treatment. HSV-2 results will not be returned to participants given the unclear clinical utility of HSV-2 serology in the absence of active disease. All men will be instructed to place nothing in the rectum and to abstain from sex for 7 days after the procedure to allow the mucosa to heal.

Contingency visit:

Attempts to ensure adherence to the study visits will be made with telephone and/or email reminders to the participant. However, if 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.

Phone calls/retention contacts:

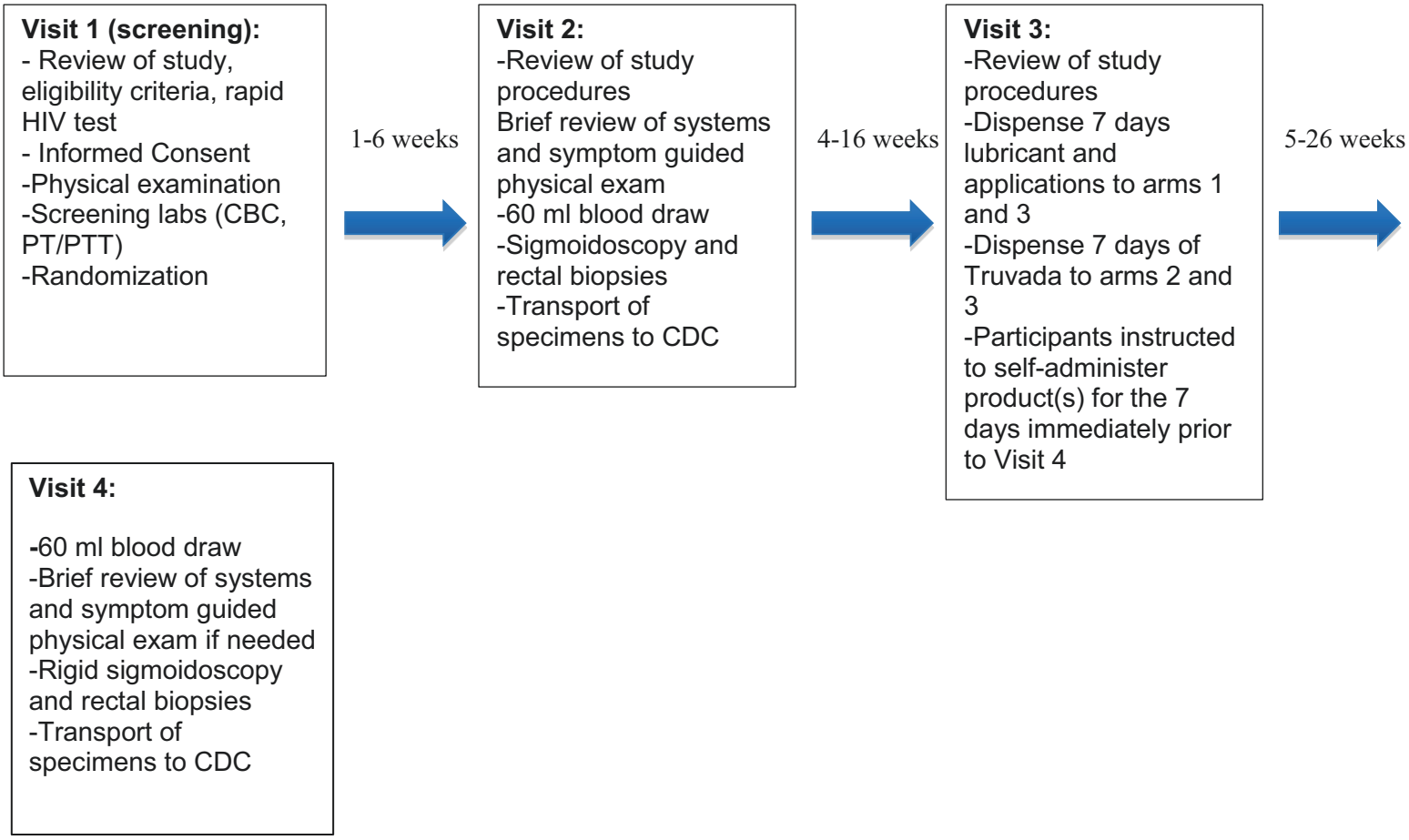
While on study, periodic phone calls, texts, or email reminders will occur between study staff and participants to ensure proper retention and adherence to study protocol.

<u>Rectal biopsy procedures</u>

Dr. Kelley or a to-be-named mid-level provider who is trained and supervised by Dr. Kelley (see below) will be performing all rectal biopsies utilizing a disposable rigid sigmoidoscope, light source, and jumbo biopsy forceps. Dr. Kelley was trained in office based rectal biopsy procedures by Dr. Robin Rutherford, an experienced gastroenterologist at Emory University. All biopsy procedures will be performed in an examination room at the Hope Clinic with assistance from the project coordinator or clinical research nurse. Dr. Kelley has personally completed more than 50 rectal biopsy procedures for another Emory IRB approved study protocol at the Hope Clinic with zero complications. Briefly, without the administration of any previous enemas or other preparation, 8-12 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, study personnel will interview 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.

Figure 1. Summary of study visits.



RISKS AND HOW MINIMIZED

HIV risk counseling

Participants will undergo HIV risk reduction counseling and testing by the study PI or study staff that have been trained in HIV risk reduction counseling and testing. Any participant who is found to be HIV positive on rapid testing will be referred for confirmatory testing to their local health department, AID Atlanta, or provider of their choice. We will also assist any HIV positive participant in accessing healthcare for HIV infection as needed.

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.

Risks of Truvada for PrEP

In clinical trials of PrEP for MSM, the drug was well tolerated[6]. Nausea was more common among participants taking the medication than among those taking placebo (9% vs. 5%). There were no differences in severe or life-threatening adverse laboratory events between the active and placebo group. Adverse events associated with tenofovir can include a transient decrease in renal function and slight decreases in bone mineral density. Both of these effects occur with prolonged use of the medication and are not expected to occur with the limited 7-day dosing in this protocol.[1]

Acquisition of HIV drug resistance is a theoretic concern for those taking Truvada for PrEP. However, clinical trials have shown this to be a very rare event except in those who were 'acutely' infected with HIV at the time of study enrollment. In the iPrex study, there was no drug resistant virus detected in 100 MSM who became infected after enrollment. Of the ten men who were identified retrospectively to be acutely infected with HIV at enrollment, drug resistance was detected in 2/2 of men in the active drug arm and 1/8 of men in the placebo arm[6]. 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[1]. 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.

Men will be asked to abstain from receptive anal intercourse while using PrEP and/or lubricant during the study protocol in order to limit additional exposures (e.g. semen, douching, additional lubricants) to the rectal mucosa. Men taking PrEP will be counseled that they should not expect to achieve protection from HIV infection by taking PrEP during this study as it is a limited, 7-day course. All men included in the study have a 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.

Risks of rectal lubricant application

Personal lubricants are commonly used during sexual intercourse to reduce friction between body parts. Multiple lubricants are available over the counter in local pharmacies. The FDA designates personal lubricants as medical devices, therefore there is no requirement for human safety testing prior to marketing.[4] There have been a handful of studies that suggest personal lubricants, particularly hyperosmolar lubricants (e.g. Astroglide brand), can damage human tissues and potentially increase susceptibility to HIV or other STDs.[2,3,5] Clearly, more research is needed into this question of lubricant safety and HIV transmission. This study is designed to answer some of these outstanding questions. To minimize the risk of rectal lubricant application, we will counsel all participants about the possibility of tissue damage with the use of lubricants and recommend use of condoms for all sexual acts to reduce transmission of HIV and other STDs. In addition, we will ask men to abstain from receptive anal intercourse for the one week period when they are using study product and for 1 week after both rectal biopsy procedures (visits 2 and 4).

Rigid sigmoidoscopy and biopsies

Risks associated with lower gastrointestinal endoscopy include colitis from chemicals for endoscope sterilization, bowel perforation, bleeding, diverticulitis, and infection. All procedures will be performed by Dr. Kelley or a mid-level provider trained and supervised by Dr. Kelley. Non-physician medical providers have performed endoscopic procedures for diagnostic and therapeutic procedures for years. Many of these require mastery of flexible sigmoidoscopes, detailed anatomy of the full colon, and familiarity with sedation procedures.[7,8] 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 15-20 cm from the anal verge. Therefore, it is appropriate for a licensed mid-level provider to perform the procedure after completing a training period under the supervision of Dr. Kelley. The training period for the mid-level provider will include a minimum of 10 directly observed (by Dr. Kelley) rectal biopsy procedures.

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 12. Colonoscopy has been shown to be associated with a still low, but significantly greater risk of complications than rectosigmoidoscopy[9]. 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[9,10] 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[11,12] including a combined 3,011 procedures and a median of eight[12] and 17 biopsies[11], 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[13], 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.

Non-physician medical providers have performed endoscopic procedures for diagnostic and therapeutic procedures for years. Many of these require mastery of flexible sigmoidoscope, anatomy of the full colon, and familiarity with sedation procedures.[7,8] 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. Therefore, it is appropriate for a licensed mid-level provider to perform the procedure after appropriate training and under the supervision of Dr. Kelley. The training period for the mid-level provider will include a minimum of 10 directly observed (by Dr. Kelley) rectal biopsy procedures.

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 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.

BREECH 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 server, 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. In the event that confidentiality is accidentally breached, the event will be reported to Emory IRB officials who are then required to report to the IRB director and/or the IRB Chair any instances of which they are aware that involve a use or disclosure of information in violation of the confidentiality obligations set forth in the Confidentiality and Non-Disclosure Agreement, HIPAA Regulations or HIPAA Privacy and/or Security Policies. The IRB Director and IRB Chair shall, in turn, report the breach to the Emory University HIPAA Privacy Officer within the Office of Research Compliance. The Emory IRB shall take such steps as are appropriate to mitigate any damage

that may have been caused by the breach and to take corrective action as necessary in order to ensure that a similar breach does not occur in the future.

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 the time and inconvenience of study participation.

Study participants will be compensated $25 for visits 1 and 3. They will be compensated $125 for visits 2 and 4 as these visits contain rectal biopsy procedures.

If a contingency visit is necessary, participants will be compensated $20 for the incomplete study visit and the above amount when the missed visit is completed.

There is no charge for parking at the Hope Clinic.

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 HIPPAA 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 or as identified in the HIPAA consent.

PLANS FOR SUBJECTS AT THE END OF THE PROTOCOL

Subjects will return to the standard of care at the end of the protocol.

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) 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).

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 AEs during each study visit. Any AE will be reported to the Emory University IRB within 10 days of the event, and any serious adverse event (SAE) will be reported to the IRB within 24-48 hours 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. All AEs will be followed to satisfactory clinical resolution.

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 AE will be reported to the Emory University IRB within 10 days of the event, and any SAE will be reported to the IRB within 24-48 hours 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 DCC will work with the Medical Safety Monitor to 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 NIH.

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

As the of 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 immunologic and genetic assays will fall under the existing biosafety protocols of the Hope Clinic and CDC.

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