Unique Protocol ID: IRB00092488

NCT02985996

Truvada® vs. Genvoya®

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04/21/2017

TITLE OF PROJECT: Truvada® vs. Genvoya®

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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). To aid in prevention, 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 shown to be highly effective. However, current tenofovir- based regimens have shown to cause different side effects while taken. To reduce these side effects, new formulations of anti-HIV agents are being developed, but the ability of these new agents to penetrate mucosal tissues and prevent HIV infection at sites of virus exposure is unclear.

Design: To address the efficacy of the new formulated anti-HIV agents and their ability to penetrate the mucosal tissues in MSM, 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 2-arm study (forty-five men assigned to each arm) as follows: (Arm 1) daily oral Truvanda® or (Arm 2) daily oral Genvoya®. Each study arm includes 3 phases: (1) pre-drug, (2) short-course, and (3) steady state. For phase I, there will be 5 men assigned to both arm 1 and arm 2. Phases II and III will each have 20 men assigned to both arms. The study will entail 2 study visits for phase I, 3 study visits for phase II, and 4 study visits for phase III at the Emory University Hope Clinic. During **phase I**: visit 1, 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 (time 1-6 weeks after study visit 1), participant returns and a urethral swab, 2 pre- wet penile swabs, and a urine sample will be collected. Participant will then undergo a rectal biopsy via rigid sigmoidoscopy for establishment of baseline values. During **phase II**: study visit 1, men will be screened for eligibility and undergo written informed consent, physical examination, rapid HIV testing, phlebotomy (will collect 4 tablespoons) for screening laboratories, and randomization. During study visit 2 (time 1-6 weeks after study visit 1), men will be dispensed and instructed to take either one dose of Truvada® or Genvoya®. After 4 to 6 hours after dosing, a urethral swab, 2 pre- wet penile swabs, 4 tablespoons of blood, and a urine sample will be collected. During study visit 3 (time 24 hours after drug dosing), men will return after 24 hours of study product use for repeat phlebotomy, urethral and penile swabs, collection of urine and rectal secretions, and rectal biopsy via rigid sigmoidoscopy. For **phase III**: visit 1,

men will be screened for eligibility and will undergo the informed consent process. Once informed consent is signed, a physical examination will be performed, rapid HIV testing, phlebotomy for screening labs, and randomization will occur. During study visit 2 (time 1-6 weeks after study visit 1), men will be dispensed and instructed to take either Truvada® or Genvoya® for 10 days. After 3 to 5 consecutive days of dosing, participants will return for visit 3 where a urethral and penile swabs specimen, blood work, and a urine specimens will be obtained. During study visit 4 (time 10 days of consecutive drug dosing), men will return for repeat phlebotomy, urethral and penile swabs, collection of urine and rectal secretions, and rectal biopsy. 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 Truvada® and/or Genvoya® drug concentrations, inflammatory cytokine levels, HIV target cell measurement and characterization by flow cytometry, and *in vitro* HIV infection assays. Comparison of assay results between the 2 study arms will help in determining the ability of the new formulated anti-HIV drug to penetrate different body compartments at the site of possible HIV exposure.

Participants may participate in more than one phase; however, at least 8 weeks must lapse after completion of 1 study phase before entry into another. Men who participate in more than one phase will not be consented again and do not have to repeat the screening visit (visit 1) when starting another phase; they will begin the new phase at visit 2.

Duration: The duration of this study is 3 years. Participants will be considered 'on-study' for no more than 12 weeks.

Sample size: For this protocol we will recruit 90 HIV-negative MSM or transgender women who are not taking hormone therapy who meet eligibility criteria outlined in the protocol.

Population: The population to be studied in this protocol is HIV negative MSM and transgender women who are not taking hormone therapy, who meet eligibility criteria, and are willing to perform study procedures. Participants will be recruited from existing databases at Hope Clinic and the Rollins School of Public Health who have agreed to be contacted for future studies, from community recruitment events conducted by the Hope Clinic, 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) and Transgender women (TGW) who have sex with men 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 and

TGW occur through exposure to the rectal mucosa during receptive anal intercourse (RAI). 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, current tenofovir- based regimens have shown to have side effects that researchers are hoping to reduce in newly developed anti-HIV agents. This study is designed to examine the ability of these new agents to penetrate mucosal tissues and potentially prevent HIV infection during RAI exposure for MSM and TGW.

For this protocol, we will recruit HIV-negative MSM and TGW who are not on hormone therapy aged 18-49 and who are willing to adhere to study procedures. There will be 3 phases, with 2 study visits for phase I, 3 study visits for phase II, and 4 study visits for phase III that will be conducted over a maximum period of 12 weeks. Participants are allowed to participate in more than one phase if a recovery or washout period occurs 8 weeks in between each phase. The first visit for all phases (**phase I, phase II, and phase III)** 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 two study groups: 1. Use of oral Truvada®; or 2. Use of oral Genvoya®. During the second study visit (visit 2), men in **phase I** will not receive product, but will come in for blood work, urine sample, 2 pre-wet penile swabs, urethral swab, rectal swab, and rectal biopsy sampling. Participants who are in **phase II** will receive a single dose of the study product during visit 2, 1-6 weeks after the screening visit. MSM will return 4 to 6 hours after taking the drug for a urine sample. We will then collect 4 tablespoons of blood from the participants arm, in addition to, 2 pre-wet penile swabs, and a urethral swab. The third study visit will occur 24 hours from dosing time for MSM in **phase II**. Men will undergo a blood draw, urine sample, penile, urethral, and rectal swab, and rigid sigmoidoscopy for collection of rectal secretions and biopsies. Participants in **phase III** at study visit 2 will receive a 10-day supply of the study drug and will be instructed to take it for 10 consecutive days. For visit 3 in **phase III**, participants will return for a blood draw, urine collection, 2 pre-wet penile swabs, and a urethral swab to examine drug levels after 3-5 days of taking study drug. They will then return 10 days from dosage for visit 4, where blood, urine, penile, urethral, and rectal swabs will be collected, and rectal biopsy sampling will occur. All specimens will be transported directly to the laboratory of Clyde Hart, PhD at CDC where multiple immune assays are planned to determine the ability of these agents to penetrate mucosal tissues and potentially prevent HIV infection during RAI exposure.

PROJECT DESCRIPTION

Public Health Relevance: Information about new anti-HIV agents and how they penetrate through mucosal tissues will better inform scientists about the potential of new agents to be used for pre-exposure prophylaxis (PrEP).

Goal: To compare the body compartment pharmacokinetics and mucosal inflammatory effects of Truvada® vs. Genvoya®.

STUDY POPULATION

A total of 90 HIV-negative MSM aged 18-49 will be recruited from existing Emory University study databases of MSM who have agreed to future contact about research opportunities. We will also recruit men from community engagements events conducted by Hope Clinic recruiters, from print and on-line advertisements, and from social media 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 has conducted 2 similar studies before and does not anticipate any problems with recruiting the target population. Based on our previous studies, we expect approximately 20% of men will not complete all study visits, therefore the sample size of 90 men will likely result in study completion for 72 men.

INCLUSION CRITERIA FOR MSM

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

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, including but not limited to:
   a) Hgb ≤ 10 g/dL
   b) PTT > 1.5x ULN or INR > 1.5x ULN
   c) Platelet count <100,000
   d) Creatinine clearance <60

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 existing Emory University databases of MSM who have consented to be re-contacted for future research opportunities (see below). We will also recruit men with print, on-line, and social media advertisements (e.g. Facebook, Instagram, Craigslist, Grindr, etc.) as have been utilized for other studies conducted by the Emory investigative team. Volunteers may be engaged directly on social media or dating sites to assess interest in research participation. We will seek permission from creator/ moderator of the private website/ group, etc. before entering and interaction. Participants will also be recruited at community engagement events held by Hope Clinic recruiters (e.g. Pride celebrations, bars or businesses

catering to MSM). We will submit all print and online advertisement copies to the Emory IRB for approval prior to launching these activities. Also, all recruiters will use 1 of 2 generalized scripts to introduce the study when approaching potential participants (see below).

Scripts used for in person contact:

Script A.

"Hello,

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

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

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

Or

B.

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

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

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

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. Men will be contacted by phone or email and screened by phone with the eligibility criteria for this protocol. (Please see below for scripts used by recruiters when engaging by phone and/or email). Men who are eligible will be scheduled for a screening visit.

   Script used by recruiters when engaging by phone (phone calls and SMS):

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

   SMS

   Script 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.

   Script B.

   Hello, I am a recruiter for research studies at the Emory University Hope Clinic. We are currently looking for volunteers to participate our HIV prevention research studies. All enrolled volunteers will be compensated for their time, travel, and inconvenience. Would you be interested in learning more?

   Thank you,

   __Insert Name and contact details here___

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

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

or Script C.

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

Thank you,

__Insert Name here___

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

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

Script used by recruiters when engaging by 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 determine the efficiency of new anti-HIV agents to prevent HIV infection in men who have sex with men and transgender women who have sex with men. Study visits range from three to four visits, and you will be compensated for your time of travel and inconvenience. If you or anyone you know may be interested or have any questions about this study, please contact Nicole Pescatore (npescat@emory.edu) or LaShonda Hall (lashonda.l.hall@emory.edu). These are the basic qualifications to participate in the study:

1) HIV-negative men ages 18-49 years.

2) Engaged in receptive anal intercourse (bottomed) in the last 6 months.

3) Not currently taking PrEP and no current plans to initiate.

4) Willing to undergo peripheral blood draws, urethral swabs, and a rectal biopsy procedure over

a 1 week to 3 month period.

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 (refer to number 1 under recruitment for phone and email script used by recruiters). Men who are eligible will be scheduled for a screening visit.

Study visits

There are 3 phases for each study arm (Phase I Pre- drug, Phase II Short- course, and Phase III Steady state).

Visit 1

Phase I, II, and III

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 (Determine or other CLIA waved product) 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, creatinine, and coagulation tests.

Visit 2

Participants will be randomized to one of two study arms:

Arm 1. Use of Truvada®

Arm 2. Use of Genvoya®

Phase I

10 participants (5 in each study arm) will be enrolled in study phase 1.

Study visit 2 will occur 1-6 weeks after the screening visit. During visit 2, we will draw 4 tablespoons of blood from the participants arm. A urine sample as well as penile and urethral swabs will be collected from participants. These samples will be used at CDC to develop an assay to detect Truvada® and Genvoya® in the body compartments. 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. A rectal swab will be collected for testing for gonorrhea and chlamydia 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. 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.

Phase II

40 participants (20 in each study arm) will be enrolled in study phase 2.

Study visit 2 will occur 1-6 weeks after the screening visit. During visit 2, the study group assignment will be reviewed and participants will be provided with a single dose of Truvada® or Genvoya®. Drug will be dispensed through the Emory Investigational Drug Service. Depending on the study arm they were assigned to, MSM will be dispensed 1 day of Truvada® or Genvoya® and instructed on dosing for that day. Four to six hours after the drug is taken, a urine sample, 4 tablespoons of blood will be drawn from the participants arm, as well as, penile and urethral swabs will be collected from participants. These sample will be used at CDC to develop an assay to detect Truvada® and Genvoya® in the body. 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. Participants will be requested to abstain from receptive anal intercourse 3 days prior to study visit 2 and while taking study product.

Phase III

40 participants (20 in each study arm) will be enrolled in study phase 2.

Study visit 2 will occur 1-6 weeks after the screening visit. During visit 2, the study group assignment will be reviewed and participants will be provided with a 10 day supply of Truvada® or Genvoya®. Drug will be dispensed through the Emory Investigational Drug Service. Depending on the study arm they were assigned to, MSM will be dispensed 10 days of Truvada® or Genvoya® and instructed on dosing for 10 consecutive days prior to their scheduled study visit 4. MSM will be requested to abstain from receptive anal intercourse while on study product. Participants will be scheduled to return for their third study visit after taking the study product for 3-5 consecutive days.

Visit 3

Phase II

Study visit 3 will occur 24 hours after they received their study product during visit 2. During visit 3, we will draw 4 tablespoons of blood from the participants arm. A urine sample as well as penile and urethral swabs will be collected from participants. These samples will be used at CDC to develop an assay to detect Truvada® and Genvoya® in the body compartments. 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 will be performed and, rectal secretions will be collected with Dacron swabs, and 8-12 rectal biopsies will be collected. A rectal swab will be collected for testing for gonorrhea and chlamydia 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. 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.

Phase III

Study visit 3 will occur 3-5 days after they received their study product during visit 2. During this visit, we will collect a urine sample, 4 tablespoons of blood will be drawn from the participants arm, as well as, penile and urethral swabs will be collected from participants. These samples will be used at CDC to develop an assay to detect Truvada® and Genvoya® in the body. 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. MSM will be requested to abstain from receptive anal intercourse while on study product. Men will be scheduled to return for their fourth study visit after taking the product for 10 consecutive days.

Visit 4

Phase III

Study visit 4 will occur 10 days after daily dosing of the study product. During visit 4, we will draw 4 tablespoons of blood from the participants arm. A urine sample as well as penile and urethral swabs will be collected from participants. These sample will be used at CDC to develop an assay to detect Truvada® and Genvoya® in the body. 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 will be performed and, rectal secretions will be collected with Dacron swabs, and 8-12 rectal biopsies will be collected. A rectal swab will be collected for testing for gonorrhea and chlamydia. 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. 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 for example, screening laboratory results are lost or are inconclusive or if a participant has been unable to adhere to study protocol, he may be rescheduled for a future date where the above visit procedures will be performed. These additional visits will be scheduled within the above visit windows.

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.

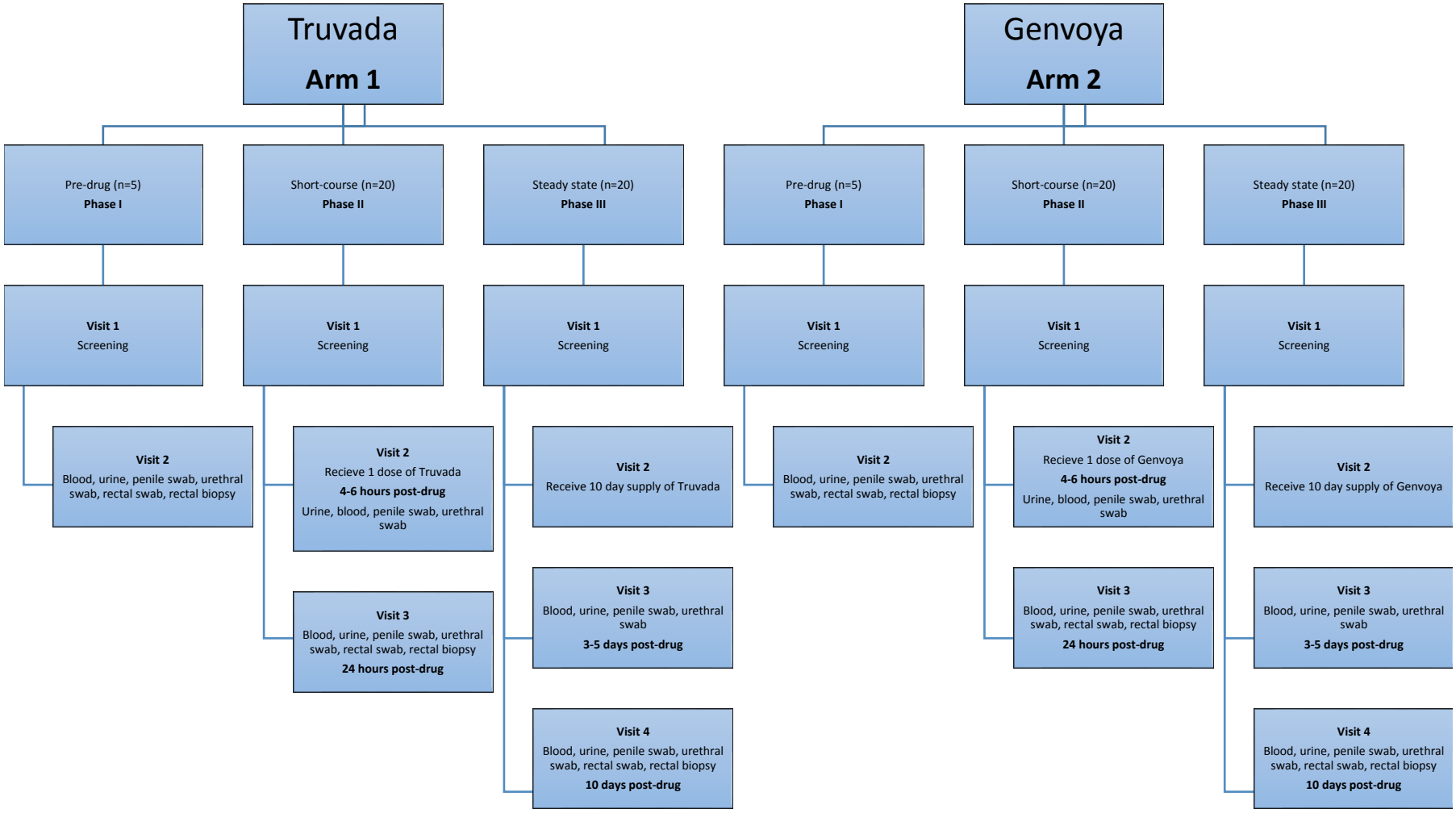
<u>Rectal biopsy procedures</u>

Dr. Kelley or Sheila Heeke FNP 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, and Dr. Kelley trained Ms. Heeke. All biopsy procedures will be performed in an examination room at the Hope Clinic with assistance from the project coordinator or clinical research nurse. Similar procedures have been performed by Dr. Kelley or Ms. Heeke >200 times for other research protocols with no 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 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.

Figure 1. Summary of study visits.



RISKS AND HOW MINIMIZED

HIV risk counseling

Participants that are tested for HIV to ensure eligibility will undergo HIV risk reduction counseling (e.g. increasing condom use, reducing number of partners, addressing substance abuse, etc.) by the study PI or study staff with provision of condoms and lubricant available freely at the Hope Clinic. HIV rapid testing will then be conducted with a CLIA waived product with finger-stick or whole blood from phlebotomy, depending on the test. Any participant who is found to be HIV positive on rapid testing will be referred for confirmatory testing to their local health department, AID Atlanta, or provider of their choice. We will also assist any HIV positive participant in accessing healthcare for HIV infection as needed. If a participant tests HIV positive prior to visit 2 or 3, they will be discontinued from the study and given the incentive for the contingency visit.

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

Blood sample collection

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

Risks of Truvada® for PrEP

Truvada® is a combination pill that contains the medications tenofovir and emtricitabine. 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] [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.

Risk of Genvoya®

Genvoya® is a combination anti-HIV medication that contains the drugs tenofovir alafenamide, emtricitabine, elvitegravir, and cobicistat. Based on clinical trials previously conducted of Genvoya®, the drug showed to be well tolerated. According to participants, the most common side effect shown was nausea with diarrhea being the second most common side effect. Of those who reported this adverse event, 0.9% and 1.5 % discontinued treatment regardless of the severity. Adverse events associated with Genvoya® can include a transient decrease in renal function and slight decreases in bone mineral density. There is also a possibility of lactic acidosis, which can be hard to identify during early stages. These effects occur with prolonged use of the medication and are not expected to occur with the limited 10-day dosing in this protocol.[7] In contrast to Truvada®, there have been no clinical trials of Genvoya® for HIV pre-exposure prophylaxis. However, similar concerns with acquisition of HIV infection and development of HIV drug resistance as discussed above also apply to Genvoya®.

Genvoya® can also cause flare-ups in those who have hepatitis B virus. It can cause the Hepatitis B virus to suddenly return in a worse form than before if treatment was provided. For this reason, it is important that participants not participate in the study if they are known to have Hepatitis B. Nonetheless, the maximum 10 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 those taking Truvada® or Genvoya® for PrEP. However, clinical trials of Truvada® for PrEP 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.[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.

Men will be asked to abstain from receptive anal intercourse while using drug during the study protocol in order to limit additional exposures (e.g. semen, douching, additional

lubricants) to the rectal mucosa. Men taking Truvada® or Genvoya® will be counseled that they should not expect to achieve protection from HIV infection by taking drug during this study, as they will be provided a limited supply. All men included in the study that have an interest in taking PrEP for HIV prevention, will be referred to an area PrEP provider at the termination of the study. The Hope Clinic has compiled a resource sheet of area providers that will be distributed to interested participants.

Rigid sigmoidoscopy and biopsies

Risks associated with lower gastrointestinal endoscopy include colitis from chemicals for endoscope sterilization, bowel perforation, bleeding, diverticulitis, and infection. All procedures will be performed by Dr. Kelley or Ms. Heeke (FNP). 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.[889] 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 [8] and only accesses the sigmoid colon a maximum of 15 cm from the anal verge. Therefore, it is appropriate for a trained, licensed mid-level provider to perform the procedure. Dr. Kelley and Ms. Heeke have performed >200 similar procedures for other IRB approved protocols with zero complications.

All procedures will utilize disposable rigid sigmoidoscopes, forceps, and guides to reduce risk of infection and obviate the need for instrument sterilization between participants. To minimize risks, rigid proctoscopy, rather than flexible sigmoidoscopy or full colonoscopy, will be used in this study and the number of biopsies taken will be limited to 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[13] and 17 biopsies[12], 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[14], 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. [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 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 including a combined 3,011 procedures and a median of eight and 17 biopsies, respectively, there was only one serious complication, for an incidence of approximately 0.33%. More relevant to the present protocol, in a study of subjects undergoing endoscopic procedures exclusively for research purposes, including 64 flexible sigmoidoscopies with a mean of 25 biopsies obtained from the rectosigmoid, there were no major complications. Thirteen subjects experienced minor symptoms (self-limited bleeding and pain), which were not related to the number of biopsies. Thus, the risk of serious complications from the proposed study procedures, even with up to 12 biopsy specimens, is expected to be very low.

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 servers, which will be accessible to the PI and study coordinator only. All study specimens will be labeled with a unique identifier prior to transport to CDC. Identifying information will not be shared with laboratory collaborators at the CDC and they will be unable to link the study ID to any identifying information. Any demographic data shared with CDC will also be stripped of HIPPAA identifiers prior to sharing. 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.

For Phase I, study participants will be compensated $25 for visit 1 and $125 for visit 2. Participants who enter into Phase II will be compensated $25 for visit 1, $50 for visit 2, and $125 for visit 3. Participants in Phase III will receive $25 for visit 1 and $25 for visit 2, $50 for visit 3, and $125 for visit 4.

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. However, participants may be provided with a MARTA card if available.

INCENTIVES
In Phase II, there will be a 6 hr. time span (+/- 2 hrs.) between participant receiving drug and participant providing specimens (urine, penile, and urethral). As a retention method, study staff will provide participant with a $15 gift card to Walmart or Starbucks while they wait.

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. Subjects who completed a previous phase will not be consented again at the start of the new phase.

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 and TGW, cisgender 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. Subjects who are interested in starting PrEP will be linked to care with a community provider.

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 Serious adverse events (SAE) Unanticipated problems (UP) during each study visit. Any SAE that is judge related to study product or UP will be reported to the IRB within 5 days of the event. The standard Emory IRB reporting guidelines for AE and SAE reporting, as documented at http://www.emory.edu/IRB/guidelines_adverse_event.php, will be followed.

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

1. Death.
2. Life-threatening situation - The subject was at risk of death at the time of the adverse event/experience. It does not refer to the hypothetical risk of death if the AE were more severe or were to progress.
3. Inpatient hospitalization or prolongation of existing hospitalization.
4. Persistent or significant disability/incapacity - Any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life

functions, including the ability to work. This is not intended to include transient interruption of daily activities.

5. Congenital anomaly/birth defects - Any structural abnormality in subject's offspring that occurs after intrauterine exposure to treatment.
6. Important medical events/experiences that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above, i.e., death, a life-threatening adverse event/experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Examples of such medical events/experiences include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
7. Spontaneous and elective abortions will be reported to the Emory IRB as serious adverse events.
8. Severity of AEs will be rated according to the following definitions:

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

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

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

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

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

Possibly Related:	An adverse event has a strong temporal relationship to the study drug, and an alternative etiology is equally or less likely compared to the potential relationship to study drug.
Probably Not Related:	An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
Not Related:	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has much more likely alternative etiology).

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

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

All AEs and laboratory abnormalities will be graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004, which can be found on the DAIDS RCC Web site: http://rcc.tech-res.com/tox_tables.htm.

DATA SAFETY MONITORING

Summaries of adverse events (Grades 3 or 4), and targeted AEs across study groups as well as study conduct will be reviewed regularly (in real time and summarized quarterly) by study investigators. Any SAE that is judge related to study product or UP will be reported to the IRB within 5 days of the event. The standard Emory IRB reporting guidelines for AE and SAE reporting, as documented at http://www.emory.edu/IRB/guidelines_adverse_event.php, will be followed. 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

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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