PROTOCOL

Bioequivalence of tenofovir and emtricitabine following overencapsulation
(A-TEAM)

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1. BACKGROUND AND SIGNIFICANCE

1.1. The need for PrEP in YMSM

Pre-exposure HIV prophylaxis (PrEP) with daily oral tenofovir-disoproxil fumarate plus emtricitabine (TDF-FTC) is highly effective in reducing HIV acquisition in numerous populations. One population in great need of PrEP is young men who have sex with men, who are experiencing accelerating HIV infections in the United States [6]. National HIV incidence data highlight the crisis of HIV among YMSM; from 2008-2011 HIV incidence for YMSM aged 13-24 years increased 26% [9]. CDC has estimated that 80% of YMSM in 15 cities surveyed had not been accessed by HIV-prevention intervention services [10]. In this context, PrEP has been identified as a high impact intervention for HIV prevention specifically for YMSM.

1.2. The need for real-time adherence measures

However, inadequate adherence, and the lack of tools that can reliably and rapidly ascertain non-adherence, is a significant problem for the PrEP domain [17-20]. PrEP studies show that younger age is associated with poorer adherence including particular adherence challenges for YMSM. Current adherence monitoring approaches include self-report, pharmacy refill records, pill counts, MEMS/Wisepills, and plasma, PBMC or hair concentration measurement [21-25]. Many of these approaches have been available for decades, but have not made a substantial impact on the adherence field because of various weaknesses including lack of precision, inability to detect adherence dose ingestion behaviors (inferring rather than biologically confirming ingestion, "white-coat" adherence with doses taken just before a visit), incompatibility with pill boxes, dependence upon patient participation/engagement, expense, and difficulty implementing into routine practice [21,23,26]. The critical importance of adherence, and the vital need for better approaches to measure it was highlighted by the FDA as part of their review of FTC/TDF for PrEP [28].

The current proposal addresses the need for new approaches to rapidly and accurately assess PrEP adherence by evaluating a novel sensor system for adherence monitoring. This new approach uses a tiny sensor that is co-formulated with the drug of interest (in our case FTC/TDF) that electronically confirms ingestion of the drug of interest. Ultimately, such a system would monitor adherence both in real-time and longitudinally, and provide real-time and periodic feedback mechanisms to promote enhanced adherence behaviors, which is a great need for the YMSM population. This protocol is a first step in testing this novel sensor. The goal of this study is to show that co-formulation of the novel sensor with FTC/TDF, in an overencapsulation, does not significantly alter the rate and extent of absorption for the drugs of interest. This protocol is a necessary first step in studying this sensor system for PrEP in YMSM.

1.3. The Proteus Sensor System

The Proteus Sensor System is the first FDA-approved application of an integrated circuit sensor designed to directly measure drug ingestion events. The Proteus Sensor System consists of three interacting components: the ingestible sensor tablet, the adhesive personal monitor (ie a patch), and the wireless communication network (ie a smartphone). Once the sensor tablet is swallowed, it interacts with gastric fluids and a signal is generated which is transmitted to the patch, and ultimately the smartphone device. Figure 1 shows the components of the system.

The present study will only include the sensor tablet, and will not include the patch or wireless communication unit. The ingestible tablet consists of three functional components: 1) the active layers, 2) the integrated circuit, and 3) the insulating skirt disk. The integrated circuit and insulting skirt are shown individually in Figure 1 (although they are attached as the sensor tablet). The integrated circuit is a tiny sized 1 mm x 1 mm x 0.3 mm chip. The active layers are thin films of magnesium and cuprous chloride. The gold under-layer acts as a current collector underneath the cuprous chloride. Upon contact with electrolytes in gastric fluid, these layers create a battery that ultimately sends a signal to the patch worn by the patient [76]. The function of the skirt is to shape and amplify the electric field generated by the sensor. The skirt is made of standard edible pharmaceutical excipients (ethyl cellulose, hydoxypropyl cellulose, and triethyl citrate).

Fig 1. The Proteus Sensor System. The sensor tablet is made of a skirt and integrated circuit (separated here for visualization).
From: http://mobihealthnews.com/39612/proteus-oracle-launch-integrated-software-ingestible-sensors-for-clinical-trials. Accessed 01-10-16

The quantities of various materials released to the body by the sensor tablet are extremely low compared to the levels commonly present in the GI tract or ingested as part of a typical diet. The flow of current produced by electrochemical reactions is similar in nature to the electrophysiological signals generated by the brain, heart, and gastrointestinal tract. The Proteus Sensor System has demonstrated acceptable safety in clinical trials involving healthy volunteers or patients in specific therapeutic areas, including those with hypertension, heart failure, diabetes mellitus, tuberculosis, bipolar affective disorder, and schizophrenia. The safety of the ingested components has also been evaluated relative to established ingestion guidelines, and the extractable amount of copper and magnesium that can be absorbed from the intestine from a single sensor is below the recommended daily intake for human consumption at 0.3% (7.7 ng) and 0.003% (9.8 ng), respectively, of daily allowable amounts. The FDA evaluated the Proteus Sensor System and approved it in 2012.

The goal of this protocol is to overencapsulate the sensor with FTC/TDF to show that co-formulation does not significantly alter the rate and extent of absorption for these drugs.

2. HYPOTHESIS AND AIMS

2.1. Hypothesis

The rate and extent of tenofovir and FTC absorption when overencapsulated with the sensor will be similar to that of native FTC/TDF tablets without the sensor.

2.2. Primary Objectives

1) Compare the plasma AUC and Cmax of tenofovir and emtricitabine with the overencapsulation of the sensor tablet versus that of the native FTC/TDF tablet.

2.3. Secondary Objectives

1) Examine relationships among drug and anabolite concentrations in dried blood spots (DBS), red blood cells (RBC), PBMC.
2) For those who consent to collection of DNA, examine the relationship between genetic variability and pharmacology.
3) Examine relationships between baseline endogenous compounds such as deoxyribonucleotides with pharmacology.

3. STUDY DESIGN

Twenty-four HIV negative healthy adult volunteers with creatinine clearance >60 ml/min (MDRD), and no contraindicated medical conditions or medications will be recruited from CU/Denver. Recruitment will attempt to target the inclusion of African American participants and biological males under the age of 24, but enrollment will be according to the demographics in the Denver area. Participants will be randomized 1:1 to overencapsulated FTC/TDF versus native form FTC/TDF. A general overview of the encapsulation procedure is shown in Fig 2. A single dose of medication will be administered with 250 mL of water after a ≥ 10 hour (overnight) fast. A pre-dose blood collection will be obtained followed by blood at approximately 0.25, 0.5, 1, 2, 4, 6, 10, 24, 48, and 72 hours after the dose. A meal will be administered 4 hours after the dose. The rationale for the sampling is to collect baseline blood and samples near the Cmax and to continue collecting samples for at least 3 half-lives (one half-life is approximately 15 hours). Participants will then undergo a 14 day washout (> 7 half-lives) and the study procedures will be repeated for the other FTC/TDF dose form.

Fig 2. A general overview of the encapsulation procedure.

Upon bioequivalence confirmation, The Ruth M. Rothestein CORE Center PrEP Clinic (Chicago, Illinois) will conduct a pilot study under separate IRB approval using the overencapsulated Truvada and PSS system. The specimens from this pilot study will be tested in our Colorado Antiviral Pharmacology Laboratory.

4. STUDY POPULATION

4.1. Selection of the Study Population

Subjects will be recruited from the Anschutz Medical Campus and surrounding areas. Recruiting strategies will include website advertising, flyer postings, and email notices (subsequent to IRB approvals). Additionally, we have accumulated a database of over 100 HIV negative subjects who consented in previous studies to be contacted for future research (COMIRB protocol 16-1163) [53-56].

4.2. Inclusion/Exclusion Criteria

4.2.1. Inclusion Criteria

1. Ambulatory 18-45 year old adults.
2. Ability to comply with study procedures.

4.2.2. Exclusion Criteria

1. Inability to give informed consent
2. Pregnancy or planning to become pregnant within 3 months of study completion
3. Currently breastfeeding
4. High risk of HIV-1 infection (for example: sexually active with an HIV infected partner; men who have sex with men who may engage in condomless intercourse with HIV-infected partners or partner of unknown status during the study; males or females who exchange sex for money, shelter, or gifts; active injection drug use or during the last 12 months; newly diagnosed sexually transmitted infections in last 6 months)
5. Positive HIV+ ELISA or suspected acute HIV infection in the opinion of the clinician. (example signs and symptoms of acute HIV infection include combinations of fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy cervical or inguinal)
6. Positive HBV surface antigen test
7. Uncontrolled or symptomatic bone disease or history of non-traumatic bone fractures
8. Active psychiatric illness or alcohol/drug abuse that, in the opinion of the investigators, would interfere with study requirements
9. Creatinine clearance < 60 ml/min, or history of serious renal disease
10. Urine dipstick protein ≥ 2+
11. Total bilirubin and/or hepatic transaminases (ALT and AST) ≥ 2.5x upper limit of normal
12. Absolute neutrophil count ≤ 1,500/mm3, platelets count ≤ 100,000/mm3, or hemoglobin ≤ 10 g/dL.
13. Any laboratory value or uncontrolled medical conditions that, in the opinion of investigators, would interfere with the study conditions or increase risk to the participant
14. > Grade I abnormalities in screening laboratory tests (CBC, CMP, Lipase, Phosphorus) per DAIDS Grading Table

15. Contraindicated concomitant medications based upon product information or that, in the opinion of the investigators, would interact with the study medications or increase risk to participant such as: investigational agents (within 30 days of enrollment), aminoglycosides, ganciclovir/valganciclovir, chronic high-dose acyclovir/valacyclovir (>800mg acyclovir or > 500mg valacyclovir for > 7 days), cyclosporine, amphotericin B, foscarnet, and cidofovir, and products with same or similar active ingredients as the study medications including TRUVADA®, ATRIPLA®, COMPLERA®, EMTRIVA®, VIREAD®; or drugs containing lamivudine or adefovir, which are close analogs of FTC and tenofovir.
16. Current participation in other interventional research studies

5. STUDY PRODUCT INTERVENTION(S)

5.1. Regimen

Participants will be randomized 1:1 to a single dose of overencapsulated FTC/TDF versus a single dose of non-encapsulated FTC/TDF. There will be two pharmacokinetic (PK) visits separated by a 14 day washout period.

5.2. Study Product Formulation and Preparation

The study drug is Truvada®, manufactured by Gilead Sciences. Each Truvada® tablet contains a co-formulation of TDF 300mg/FTC 200mg. An authorized study clinician will prescribe Truvada® as part of this study, as described in this protocol.

The Truvada® tablet will be overencapsulated with the Proteus Discover™ sensor by research pharmacists at UCH-IDS. The Proteus Pill contains the inactive sensor that contains no medication, as described earlier. The Ingestible Sensor is made of biodegradable ingredients. The study drug and the Proteus sensor will be overencapsulated in gelatin capsule shells from a vendor such as Capsugel[57].

5.2.1. Study Product Storage

Prior to dispensing, FTC/TDF tablets must be stored in the original container with the provided silica gel desiccant to protect the product from humidity. Store at 68°F to 77°F (20°C to 25°C). Excursions permitted between 15° to 30°C. The Proteus sensor system will be stored in similar conditions.

5.3. Study Product Supply and Accountability

Gilead Sciences will donate the study drug and Proteus Digital Health, Inc. will donate the Proteus sensor tablets. Study drug will be shipped to the investigational pharmacies and dispensed through the investigational pharmacies according to the research pharmacy policies and procedures. The pharmacist of record will receive and inventory the study medications, will dispense and track prescriptions, and will provide directions for returning unused medications for destruction according to local policy. They will track the accountability of the study medications according to established procedures developed by the investigational pharmacies.

5.3.1. Study Product Dispensation
The investigational pharmacy will dispense the study drugs for each participant prior to the study visit. The investigational pharmacist and study staff will record the date that a FTC/TDF bottle is opened and will ensure that opened bottles are used within 6 weeks.

5.3.2. Return and Destruction of Study Product
The investigational pharmacies will account for and destroy the medications in accordance with their policies and procedures.

5.4. Concomitant Medications
Concomitant medications will be evaluated at the screening visit for interactions with the study medications. Certain medications are permitted and other medications are prohibited as described in the sections that follow. Medications not listed in these sections will be evaluated for potential interactions with the study medications or procedures and a decision to enroll the subject will be made accordingly. Additionally, should a new concomitant medication be started during the study, the same evaluation will take place.

5.5. Permitted Medications
These medications are allowed: acetaminophen, anti-emetics, anti-diarrhea medications, ibuprofen or similar non-steroidal anti-inflammatory medications, vitamins, and contraception.

5.6. Prohibited Medications
Prohibited concomitant medications were listed in the exclusion criteria.

5.7. Precautionary Medications
Any medication or herbal supplement not listed above will be evaluated at the screening visit for interactions with the study medications. Should there be potential for serious interaction, based on the opinion of the investigators, the subject will not be invited to participate. Additionally, should a new concomitant medication be started during the study, the same evaluation will take place.

6. STUDY PROCEDURES/EVALUATIONS

6.1. Clinical Evaluations and Procedures
The study consists of three visits: Screening, first PK visit, and second PK visit.

Blood will be collected from an arm vein for all visits for pharmacology and/or safety laboratories. All study visits and a summary of the study evaluations are provided below.

Visit #1: Screening visit (must be ≤ 30 days before first PK visit):

- Informed consent
- Urine sample for UA
- Blood draw for CBC, CMP, Lipase, Phosphorus, HBV surface antigen
- HIV antibody (rapid test or blood)

- Pregnancy test (urine or blood)
- Medical history and physical exam
- Medication/vaccination history

Note: a screening test(s) may be repeated at the discretion of the investigators within the 30-day screening window. A participant who is unable to schedule the first PK visit within the 30 day screening window must be re-screened prior to entry into the study. An HBV Antibody test may be ordered for participants who are unsure of their vaccination history. An HBV vaccine will be offered, if indicated, as this is standard of care.

The randomization assignments will be made between the screening and the first PK visits if the participant is eligible and agrees to enroll. Randomization is 1:1 to overencapsulated FTC/TDF versus non-encapsulated FTC/TDF and will be administered by the study statistician. This will be communicated by email to the study investigator. The first PK Visit indicates enrollment into the study.

Visit #2.1: First PK visit (must be ≤ 30 days after screening visit):

- Preceded by an overnight fast (≥10 hours)
- Medication history
- Adverse effect questionnaire
- HIV Ab, Pregnancy test, or other safety labs, if clinically warranted
- Single dose administered with 250 mL water
- Meal administered 4 hours after dose
- Blood draw for PK before the dose and at approximately 0.25, 0.5, 1, 2, 4, 6, 10 hours post dose (pharmacology)
- Blood for DNA

Visit #2.2: 24 Hour PK Blood Draw

- Blood draw for PK

Visit #2.3: 36 Hour PK Blood Draw

- Blood draw for PK

Visit #2.4: 72 Hour PK Blood Draw

- Blood draw for PK
- Process Stipend

Participants will undergo a 14 day (-1/+7 days) washout period.

Visit #3: PK Visit 2 (can be 13 to 21 days after the first PK Visit):

- Following an overnight fast (≥10 hours)
- Medication history

- Adverse effect questionnaire
- HIV Ab, pregnancy test, or other safety labs, if clinically warranted
- Single dose administered with 250 mL water
- Meal administered 4 hours after dose
- Blood draw for PK before the dose and approximately 0.25, 0.5, 1, 2, 4, 6, 10 post dose (pharmacology)

Visit #3.2: 24 Hour PK Blood Draw

- Blood draw for PK

Visit #3.3: 36 Hour PK Blood Draw

- Blood draw for PK

Visit #3.4: 72 Hour PK Blood Draw

- Blood draw for PK
- Process Stipend

6.1.1 Medical History and Physical Exam

At the screening visit a qualified study clinician will perform a history and physical for each participant. A complete medication history will be obtained including all drug allergies, immunization history, prescription, over the counter, and herbal treatments. Routine vital signs will be collected such as height, weight, blood pressure, pulse, respiratory rate and temperature.

6.1.2 Blood collections

Approximately 120 mL of blood will be collected from each subject over the study. The blood will be collected from an arm vein by trained professionals according to CTRC policies and procedures.

6.1.3 Urine Testing

A urine sample will be obtained at the screening visit (and other visits as warranted) to assess protein in urine. The participant will be asked to void a small amount of urine into a sterile specimen container per standard CTRC procedures. This sample will be transported to the hospital laboratory for analyses.

6.1.4 Adverse Events Questionnaire

Subjects will undergo adverse event assessment at each PK visit.

6.2. Laboratory Evaluations

6.2.1 Laboratory Evaluations and Specimen Collection

The following safety and monitoring laboratories will be collected at the screening visit (and other visits as warranted): Urine for protein, complete metabolic panels (chemistries with liver and renal function tests), complete hematology panels, pregnancy tests (urine or blood), and HIV (rapid or blood) and HBV surface Ag test. The tests are provided according to established laboratory procedures at the University of Colorado Hospital clinical laboratory. The clinical

laboratory conforms to CAP and/or CLIA-regulations, and the results will be posted to the medical record.

Study-related evaluations include blood for pharmacology. Both PK visits will include 11 blood collections; one before the dose and approximately 0.25, 0.5, 1, 2, 4, 6, 10, 24, 48, 72 hours post dose. Participants will undergo the 24, 48, and 72 hour draws by returning to the CTRC for single blood draws. There is a 14 day washout period in between the two PK visits.

6.2.2 Specimen Preparation, Handling and Shipping

Specimens will be collected in the CTRC Outpatient clinic by skilled medical professionals or study personnel in accordance with University Hospital policies and procedures. All specimen collections are described in the protocol, physician orders (as required), and nursing flow sheets (if applicable). Initial sample processing such as harvesting plasma from blood may be provided by the CTRC core laboratory, or will be transported to the pharmacology laboratory for processing. Samples will be transported to various laboratories and tracked according to local hospital/study site policies and study-specific SOPs.

Inpatient and Outpatient CTRC clinic use will be dependent on the type of visit and availability. Typically, screening visits will take place in outpatient where initial PK visits (2.1 and 3.1) will occur in the inpatient CTRC. Inpatient CTRC clinic use is preferable for the initial PK visits due to the length and frequent blood draws. Follow up PK visits where only a blood draw is completed could occur in either the Outpatient or Inpatient CTRC.

At this time, samples will not be shipped to outside entities, as all the samples will be processed and analyzed at the University of Colorado. Should outside shipping become necessary, the outbound shipment of biological, chemical, or radioactive materials is regulated by the International Air Transportation Association. Such training and certification of pharmacology laboratory employees is handled through the University of Colorado Denver Environmental Health and Safety Division.

6.3. Biohazard Containment

All study personnel will follow universal precautions, as recommended by the Center for Disease Control and the NIH including the appropriate disposal of needles (etc.) and human wastes to prevent the accidental transmission of blood borne pathogens. Training as such will be documented in study personnel's records. Study specific SOPs will outline procedures for safe procurement and handling of study specimens. The Colorado Antiviral Pharmacology Laboratory has biosafety authorization from the University of Colorado.

6.4. Schedule of Events

Procedure	**Screen**	**PK Visit 1**				**PK Visit 2**			
Visits	**1**	**2.1**	**2.2**	**2.3**	**2.4**	**3.1**	**3.2**	**3.3**	**3.4**
Time Post Dose (hour)	**-**	**0**	**24**	**48**	**72**	**0**	**24**	**48**	**72**
Informed Consent	X								
Concomitant Medication Review	X	X				X			
Medical History	X								

Physical Exam	X								
Adverse Event Assessment		X	X	X	X	X	X	X	X
Safety Labs: CBC, CMP, Lipase, Phosphorus [a]	X								
Urine Dipstick [a]	X								
Pregnancy Test (women)[a]	X								
HBSAg	X								
HIV-1 rapid test [a]	X								
Blood for PK		X [b]	X	X	X	X [b]	X	X	X
DNA for pharmacogenetics		X							

a. Any safety labs can be performed as needed at any time at the discretion of the study physician
b. Multiple Blood Draws: 8 Time Points: 0, 0.25, .5, 1, 2, 4, 6, 10

Stipends are $125 for visits 2.1 and 3.1 and $25 for visits 2.2, 2.3, 2.4, 3.2, 3.3, and 3.4. Subject payments will be made by check and requested from the UCD Procurement Service Center following Visits 2.4 and 3.4

A washout period of approximately 14 days will occur between the two PK visits. The first day of the PK visits (visit 2.1 and visit 3.1) will be 10 hours long. The remaining days of the PK visits (visits 2.2, 2.3, 2.4, 3.2, 3.3, 3.4) are single blood draws at hours 24, 48, and 72.

7. ASSESSMENT OF SAFETY

7.1. Adverse Event Definition

From the DAIDS Expedited Adverse Event Reporting policy No.:DWD-POL-SR-02.00:

> **Adverse Event (AE)** – Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. In addition, if an untoward medical occurrence occurs as a result of study participation or study-related interventions, it is considered to be an adverse event.

Clinical adverse events will be collected with standardized questionnaires and laboratory adverse events will be collected and posted to the medical record during the course of the study. Subjects will have contact information for study personnel in the event of adverse events, and can contact personnel any time during the study. The following adverse events information (grade II and above) will be recorded by study personnel: date of onset, assessment of severity, relationship to study medication, date of resolution/stabilization of event. The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November, 2014 will be used and is available on the DAIDS RSC Web site: http://rsc.tech-res.com/safetyandpharmacovigilance/ [58].

7.2. Adverse Events Procedures and Reporting Requirements

The adverse events (AEs) that must be reported in an expedited fashion to DAIDS Regulatory Support Center (RSC) Safety Office include all serious adverse events (SAEs) as defined by ICH guidelines regardless of relationship to the study agent(s):

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above must also be reported in an expedited timeframe to DAIDS. Such determination may be made through medical or scientific judgment. Examples include the following: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; development of drug dependency or drug abuse; etc.

*The following types of hospitalization do not require expedited reporting to DAIDS:

- *Any admission unrelated to an AE (e.g. for labor/delivery, cosmetic surgery, administrative or social admission for temporary placement for lack of a place to sleep)*
- *Protocol-specified admission (e.g. for procedure required by protocol, or)*
- *Admission for diagnosis or therapy of a condition that existed before receipt of study agent(s) (and has not increased in severity or frequency as judged by the clinical investigator, Note: a new AIDS-defining event in a subject already known to be HIV-infected would be considered an increase in severity of a pre-existing condition (HIV infection) and would therefore be reportable.)*

7.3. Expedited Adverse Events

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/ .

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.

The study agents for which expedited reporting are required are:

- TDF/FTC (tenofovir disoproxil fumarate/emtricitabine)
- Proteus Sensor System

7.4. Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table, Version 2.0, November, 2014 will be used for the duration of the study even in the event that a new version is released. This will be done for study consistency. The DAIDS AE Grading Table is available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/.

7.5. Expedited AE Reporting Period

The expedited AE reporting period for this study 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).

After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

8. CLINICAL MANAGEMENT

8.1. Safety Officer

A Safety Officer will be used to discuss safety issues that arise during the study as outlined in this section. The safety officer will be a physician. Email communications or calls will be held as needed to discuss safety concerns as described below.

8.2. Adverse Event Management

Grade I or II adverse event will be managed in consultation with a clinician on the protocol. The clinician may add follow up testing and evaluations, as medically indicated. The study can be continued at the discretion of the study physician.

Grade III adverse events will be communicated to the Safety officer and managed under the direction of a study physician. Follow up testing and evaluations will be added, as medically indicated. The adverse event will be evaluated for subject safety and relatedness to the study. If the adverse event may put the subject at increased risk, or jeopardizes the study's intent, even if not related with study drug, the subject will discontinue the study. If the adverse event is deemed not to be a significant health risk, the Safety Officer and study physician may recommend continuing the study with close monitoring.

Grade IV adverse events will be communicated to the Safety officer and managed under the direction of a study physician. If a grade IV event is related to the study drug, the participant will permanently discontinue the study and will be followed as medically indicated. If the grade IV is not related to the study, the Safety Officer and study physician will determine whether study can be continued with close monitoring, or permanently/temporarily discontinued.

8.3. Other Disease Events

Certain disease states are prohibited at screening and would result in ineligibility as described in section 4. Should these diseases arise during the course of this study, the study team and safety officer will evaluate continued study involvement. Other relevant clinical events and treatment complications not mentioned previously will be managed on a case by case basis by qualified study team members, and safety officer, if applicable.

8.4. Pregnancy

Tenofovir and emtricitabine are pregnancy category B drugs. To our knowledge, the Proteus Sensor System has not been evaluated in pregnancy. Thus, women will be tested for pregnancy before taking part in this study and a woman cannot be in the study if found to be pregnant, or if planning to become pregnant during the timeframe of the study. Likewise, men who are attempting to father a child during the study timeframe will also be excluded. If a woman is found to be pregnant during the study, they will discontinue the study.

Hormonal contraception such as birth control pills, injections or implants are allowed in this study but barrier contraception should be used as well. We advise the following birth control methods for male and female subjects (as gender appropriate) during the study and for at least 12 weeks after medication is stopped

- Double barrier method (i.e., use a male or female condom with either a diaphragm or cervical cap)
- Hormonal-based contraceptive in combination with a barrier method (i.e., female or male condom, diaphragm, cervical cap).
- IUD (intrauterine device) in combination with a barrier method (i.e., female or male condom, diaphragm, cervical cap).
- Practice abstinence
- Sterilization (e.g. vasectomy, tubal ligation) of partner, subject, or both with confirmed sterilization.

Double coverage that includes barriers also helps to minimize the risk of acquiring and/or transmitting sexually transmitted diseases including HIV.

Women who become pregnant during the study will be discontinued, but followed to determine the pregnancy outcome, if they are willing. The outcome will be shared with the pregnancy registry. For male subjects, it is recommended to use a barrier method like condoms or have your partner use hormonal contraception if engaging in sexual activity that could lead to pregnancy while exposed to the agents, and for 12 weeks after the study to allow for the drug to wash out. This will also help minimize the risk of acquiring and/or transmitting sexually transmitted diseases including HIV.

8.5. Breastfeeding

Breastfeeding is an exclusionary criterion for this study.

8.6. Criteria for Study Discontinuation

If three persons experience a grade IV adverse event and/or serious unexpected social harms related with the study or study drug, the study will be stopped (no new enrollment) and

reassessed for safety by the study team, Safety Officer, DAIDS representative, and study physician.

8.7. Criteria for Study Discontinuation for an Individual Participant

Subjects may withdraw from the study at any time. Subjects who become pregnant, acquire HIV infection, or become incarcerated will be discontinued from the study. Subjects who are deemed to be non-compliant with the study medications and/or procedures – for example as evidenced by consecutive missed study visits – may be discontinued from the study, at the discretion of the PI. Subjects who require an exclusionary medication during the study will be discontinued unless it is only during the washout period in which continuation will be considered by the PI on a case-by-case basis. Subjects with a gradable adverse event will be managed and discontinued as outlined in section 8.2. The study investigators or study physician can remove a subject at any time if they deem that the study is no longer in the subject's best interest or the subject is not adhering to the protocol. Subjects who discontinue treatment will be replaced such that approximately 24 complete both PK visits. The IRB, DAIDS/NIAID, OHRP and the FDA may discontinue the study at any time.

8.8. Replacement of Study Participants

Study participants who permanently discontinue treatment will be replaced so that approximately 24 participants complete the study. Data from people who discontinue will be used in analyses.

9. STATISTICAL CONSIDERATIONS

9.1. Primary Outcomes

The primary outcome is tenofovir and emtricitabine AUC and C_{max} following FTC/TDF in the overencapsulated versus non-encapsulated form. Drug concentrations will be assayed with validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methodology. We will analyze AUC and Cmax using non-compartmental methods for AUC. The C_{max} and time to C_{max} (T_{max}) will be determined directly from the concentration – time data. For each formulation, AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$ will be calculated. Logarithmic transformation will be applied to all measures used for demonstration of bioequivalence due to expected skewness in the distribution of the arithmetic means. Analysis of variance (ANOVA) with participant, period, and treatment factors will be used to establish 90% confidence intervals for the geometric mean ratio of the encapsulated to conventional formulations. Formulations will be determined to be bioequivalent when the 90% confidence intervals around AUC_{∞} and C_{max} fall between 0.8 and 1.25[59].

Hektoen Institute for Medical Research may complete analysis as outlined above.

9.2. Sample Size Considerations

The sample size is estimated to provide ≥80% power to establish bioequivalence of the overencapsulated sensor versus non-encapsulated FTC/TDF using a 2x2 cross-over design. Power is estimated to establish 90% confidence intervals around the geometric mean ratio of the overencapsulated to non-encapsulated formulation within 0.80-1.25. A sample size of 24 per sequence would yield ≥80% power to establish bioequivalence for geometric mean ratios

between 0.95 and 1.0 when the intra-subject coefficient of variation (CV) is 23% or lower, which is consistent with previously published literature [60].

9.3. Enrollment/Stratification/Randomization/Blinding Procedures

This is a randomized, open label, cross-over study. Subjects will be enrolled with the attempt to target the inclusion of African Americans and biological males under the age of 24. This will be achieved by tracking race and sex distributions during enrollment. Note that 24 subjects are sought to complete the study, as shown in the table, but COMIRB-approval will be for 48 subjects to allow for screen-disqualifications and drop-outs.

9.4. Participant Enrollment Follow-Up

Enrollment will be discussed at bi-weekly meetings among investigators.

9.5. Planned Interim Analyses and Stopping Guidelines

Because the study is non-therapeutic and relatively small (N=24) the study team will not monitor efficacy. Safety will be monitored as described above.

10. DATA HANDLING AND RECORDKEEPING

10.1. Data Management Responsibilities

Data will be managed by study personnel. Data will be accessed and centralized on the School of Pharmacy, password protected server. System maintenance is performed on a daily basis by the University of Colorado IT Department. All relevant personnel will go through data collection training. Data will be stored both in hard copy and electronic format (RedCap). Hard copies are kept in a locked cabinet to ensure privacy, confidentiality and security. A quality control database checklist for data entry will be used providing a system to ensure uniformity and accuracy.

10.2. Source Documents and Access to Source Data/Documents

Source documents will be kept in subject study records (binders). Documentation will be sufficient such that study data can be reconstructed, evaluated, and validated for all clinical activities during the trial. The goals are to ensure that protocol, hospital, IRBs, and DAIDS requirements and standards are adhered to and that all data will be verifiable from the written source document and will create an audit trail to verify that data is present, complete and accurate. Source data consists of all information in original records and certified copies of original records. The “ALCOA” method is used to achieve and maintain data quality: Attributable, Legible, Contemporaneous, Original and Accurate.

10.3. Quality Control and Quality Assurance

A program for quality assurance and quality control has been developed as a system of self-monitoring to promote the integrity and quality of the study. The program is detailed in SOP.

11. CLINICAL SITE MONITORING

The study site will be monitored continuously by study personnel as outlined in section 10. Additionally, an external site monitoring program may be implemented, at the discretion of

DAIDS to ensure consistency, completeness, and validity of research data, safety of the participants, and compliance with the protocol and all regulatory laws and requirements.

12. HUMAN SUBJECTS PROTECTION

12.1. Potential Risks and Benefits

The risks associated with this study include the following: study medications in HIV-uninfected volunteers (although the drug is FDA-approved in HIV-uninfected persons for HIV prophylaxis); use of Proteus Discover™ (although the Proteus Pill and Patch are FDA-approved); blood draws; and privacy issues. Each of these will be detailed below.

Participants will receive compensation for their time.

12.2.1 Study Medication Risks

This study includes only two doses of TDF/FTC; most use of TDF/FTC has been chronic daily dosing. TDF/FTC was FDA-approved in 2012 for HIV-negative persons for PrEP demonstrating a generally favorable adverse event profile in this population. The most common side effects for both TDF/FTC are gastrointestinal complaints and headache (> or = 10%), which are generally mild and reversible, and slight reductions in bone mineral density. New or worsening cases of renal insufficiency and renal failure have been reported for TDF in certain patients (<1% in PrEP studies). The following may be risk factors for renal complications: advanced HIV; low bodyweight, pre-existing renal dysfunction; and concomitant nephrotoxic drugs (e.g. aminoglycosides, amphotericin B, cidofovir) or certain antiretroviral drugs (e.g. atazanavir, didanosine, lopinavir/ritonavir) [61].

Hepatitis flares have been reported in patients co-infected with hepatitis B virus (HBV) when TDF/FTC therapy has been withdrawn, as both agents are active against HBV (<1%). Bone mineral loss leading to pathologic bone fractures with TDF has been reported rarely in patients and the same side effects were evident in animal studies (<1%). Metabolic acidosis with hepatomegaly and steatosis has been reported rarely with all NRTIs (<1%). Changes in body fat (subcutaneous lipoatrophy and abdominal hypertrophy) and metabolic derangements (elevations in lipids and hyperglycemia) have been reported for many antiretroviral drugs especially after prolonged use (>10% depending on agent). TDF/FTC are less likely to cause body fat changes and metabolic derangements compared with other antiretroviral agents. Immune reconstitution syndrome, and subsequent autoimmune disorders, is a risk in HIV-infected patients starting therapy. Finally, as patients take these drugs for longer courses and as patient's age, there may be new risks or long-term complications that arise. A summary of the side effect profile of TDF/FTC is provided below. These were obtained from the product information.

The following side effects have been reported most commonly with TDF-FTC in HIV-uninfected individuals (>2%).

- Abdominal pain
- Headache
- Weight decrease

In addition, the following side effects have been reported in HIV-uninfected individuals for PrEP (incidence ≥2%).

- Diarrhea,
- Pharyngitis, urethritis, urinary tract infection, syphilis, secondary syphilis, anogenital warts,
- Back pain,
- Depression,
- Anxiety,
- Genital ulceration,
- Abnormal lab values (increased creatinine, decreased phosphorous, increased LFTs, decreased hemoglobin and neutrophils)

The following additional side effects have been reported with TDF-FTC in HIV-infected individuals when combined with efavirenz (incidence ≥5%).

- Nausea,
- Fatigue,
- Sinusitis, nasopharyngitis, or upper respiratory infection
- Dizziness,
- Insomnia,
- Abnormal dreams,
- Rash,
- Hyperpigmentation of soles/palms, and
- Abnormal lab values (proteinuria, elevated cholesterol, amylase, creatine kinase, phosphorous).

Other adverse events reported in clinical trials or after marketing include (dyspnea, hepatitis, arthralgia, increased cough, dyspepsia, fever, myalgia, back pain, paresthesia, peripheral neuropathy, pneumonia, myopathy, rhabdomyolysis, muscle weakness, diabetes insipidus, rhinitis, and renal failure).

Other laboratory abnormalities reported include (increased lipase, neutropenia, LFTs, glucose, bilirubin, hematuria, glycosuria, triglycerides, hypokalemia, hypophosphatemia).

The following are rare but potentially serious side effects:

- Lactic acidosis and hepatomegaly with steatosis,
- New or worsening renal insufficiency/failure,
- Severe hypophosphatemia,
- Osteomalacia – pathologic bone fractures,
- Pancreatitis,
- Hepatitis (especially hepatitis B flares after stopping therapy),
- Immune reconstitution syndrome (HIV-infected patients with opportunistic infections such as TB), and
- Allergic reaction

12.2.2 Proteus Discover™ Risks

Participants will only take the sensor pill portion of the Protease Sensor System, so this section will include potential side effects specific to the sensor pill portion of the Protease Sensor system. This system was FDA-approved to help an individual schedule their medicines, remind them to take them, and show when they have been taken. There is a small chance (2% or less) that an individual may experience nausea, vomiting, constipation, or abdominal cramping related to the Proteus sensor pill.

Testing has shown that the signals from the sensor are smaller than those created from a heartbeat, and are too small to affect the body. To date, injury from these signals has not occurred during animal or human testing, or been reported during commercial use. The capsule and Ingestible Sensor are made from inactive ingredients meaning that they do not affect the function of your body or the medications that they are combined with. The ingredients of the Ingestible Sensors are normally found in small amounts in the body or a person's diet, and the amounts in Sensor that are swallowed are far below acceptable daily intake limits. Additionally, the ingestible sensors are about the size of a grain of sand and thus are too small to affect the walls of the gut. Most of the material will dissolve in the gut; some will not. The part that does not dissolve will pass through the stool.

It is possible that an individual may experience side effects or discomforts that are not known. In other studies, 412 volunteers swallowed more than 20,000 Proteus Sensor pills. Some of these volunteers ingested co-encapsulated medicines. In these studies, no serious health problems have occurred to date.

12.2.3 Privacy Risks

This study will test apparently HIV-negative volunteers for HIV and HBV infection. Some questions related with assessments of HIV risk may be embarrassing to the participant (for example, relate with their sexual practices). A positive HIV or HBV result would render the subject ineligible for the study and may require reporting to the State Department of Health. This study will also collect DNA to evaluate potential relationships between genetic variability and pharmacology. There is a very remote risk that a third party could access DNA information and use it to discriminate against subjects.

12.2.4 Risks from other study interventions

Approximately 120 mL of blood will be collected from each subject over the course of the study. Blood will be collected from an arm vein. Risks of blood draws include pain, bruising, infection, clotting, or fainting. The blood volumes are below the maximal volumes set for blood donations and clinical research of 450 to 550 mL in 8 weeks.

12.2. Approaches to minimize risks

12.2.1 Informed Consent

The study will be reviewed and approved by the IRB prior to initiation of enrollment. Before enrollment begins, all IRB requirements will be met and all monitoring procedures will be in place. IRB annual reviews will be filed according to IRB requirements. A DAIDS-assigned monitor may audit the study regularly, at the discretion of DAIDS. Enrollment, subject accrual

and retention, protocol adherence, data quality and completeness, adverse events and participant safety and confidentiality will be reviewed by study personnel as outlined in this document.

In obtaining and documenting informed consent, the investigators will comply with all applicable local and/or domestic regulatory requirements. Written documentation of informed consent approval will be present prior to initiation of any study related procedures (although a waiver of consent will be needed for telephone screening). A consent form will be emailed or mailed to participants who request it. Ample time will be allotted for the consenting process, which will take place in a private room. Subjects will be encouraged to ask questions and take as much time as needed to reach a decision. Subjects will be given a copy of the signed consent document. At study visits, study personnel and the subject will reaffirm the subject's understanding of the research and their desire to continue.

12.2.2. Reducing drug and Proteus Discover™ risks

This study is taking several precautions to minimize drug and Proteus sensor pill risks in these HIV-uninfected volunteers. First, we are recruiting HIV-negative volunteers who are at low risk of HIV infection. HIV risk will be assessed by a study clinician and may include whether participants have an HIV-infected partner; engage in unprotected sex in a network of high risk (e.g. men who have sex with men); exchange sex for shelter, money, or food; use of injection drugs; or were recently diagnosed with other sexually acquired infections. Participants must have a HIV-negative test at screening, and must not have signs or symptoms of recent HIV infection, in the opinion of the investigator, including fever, headache, fatigue, arthralgia, vomiting, myalgia, diarrhea, pharyngitis, rash, night sweats, and adenopathy (cervical or inguinal), in the last month. Participants will be reminded during the study to inform study personnel if they were potentially exposed to HIV. Participants may be tested for HIV infection at any point during the study, at the discretion of the investigators. Second, we are testing volunteers for pregnancy and HBV-infection to protect subjects from drug exposure during pregnancy and HBV-associated hepatitis flares when the drugs are withdrawn. Breastfeeding will not be allowed to prevent risks to nursing infants. We are excluding subjects who have serious underlying illnesses such as cancer and heart disease. We are screening subjects for hepatic and renal dysfunction, and comprehensive metabolic and hematologic panels to rule out serious pre-existing abnormalities. Participants must have an estimated creatinine clearance, by the MDRD equation of >60 ml/min. Other concomitant nephrotoxic drugs will be exclusionary.

In summary, the most likely risks associated with TDF/FTC in HIV-negative persons and the use of Proteus Discover™ appear to be reversible gastrointestinal complaints, headache, and/or weight decrease. These side effects are probably less likely with two doses. There is a remote risk of serious or fatal side effects including renal failure, lactic acidosis with hepatomegaly and steatosis, bone pathology, hypophosphatemia, hepatitis, pancreatitis, and there are possible side effects not listed here, or possible unforeseen long-term complications. We believe the risk of these serious side effects is remote given the rarity of the events during long-term treatment and PrEP in previous studies, as well as the length of this study. We have designed the inclusion and exclusion criteria to exclude subjects who might be at higher risk of these toxicities.

12.2.3 Reducing Privacy Risks

Every effort will be made to protect the privacy of participants. Study records will not be released to insurance companies or any other unauthorized parties without the subject's written

consent. The IRB, DAIDS/NIAID (and affiliated monitoring services), OHRP, Gilead Sciences (supplier of study drug), Proteus Digital Health, Inc (supplier of Proteus sensor system), and the FDA are entities that may also review participants' records. The data management plan for this protocol will separate all of the 18 HIPAA protected health identifiers from the electronic research database, which will identify subjects with only their participant ID. The electronic research database will be password protected and backed-up on secure servers. Recovery and restoration of data is covered under the terms of the University of Colorado Information Services Department. Paper study records, which include the protected health identifiers, will be kept in binders in a locked cabinet in a locked office.

Should a participant test positive for HIV or HBV, a qualified study clinician from the protocol will counsel the subject about confirmatory tests, as needed, and will refer the subject to appropriate follow up care.

12.2.4 Reducing risks from other study interventions

The blood will be collected from an arm vein by trained staff at the CTRC outpatient clinic according to standard medical procedures. Hematology will be monitored.

12.3. Institutional Review Board/Ethics Committee

The University of Colorado holds current U.S. Federal-Wide Assurances issued by the Office for Human Research Protections (OHRP), and both are accredited by the Association for the Accreditation of Human Research Protection Programs. The University is responsible for assuring that this protocol and the associated informed consent documents and study-related documents are reviewed prior to implementation of the protocol. All amendments to the protocol, informed consent and other study related documents are approved by the IRB prior to implementation. Continuing review will be determined by the IRB and the study may not continue without this continuing review approval.

12.4. Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, the site may, at the discretion of DAIDS, have the protocol and the protocol informed consent form approved, and submitted with all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. A copy of the Initial Registration Notification should be retained in the site's regulatory files. In such circumstance, Protocol registration will occur before any subjects are enrolled into the study.

13. PUBLICATION POLICY

The Principal Investigator will have oversight of publications and presentations emanating from this study. The Principal Investigator will ensure that authorship and authorship order is equitable with respect to the effort contributed to the work. Contributing effort that justifies authorship includes participation in the design of the study and assays used in the study; participation in carrying out the study; participation in analyzing the data; and participation in writing the manuscript or presentation. Trainees or students who contribute work will be equally eligible for authorship. First authorship will reflect the individual who contributes the most effort

and writing to the manuscript. First authorship may be split if two individuals contributed to the effort equally. Senior authorship will reflect the individual who provided the scientific oversight and direction for the manuscript or presentation.

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