STUDY PROTOCOL

Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

The Women TAF-FTC Benchmark Study

SPONSOR:
University of Washington

FUNDING SUPPORT:
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Study Drug Donated by Gilead Sciences

PRINCIPAL INVESTIGATORS:

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ClinicalTrials.gov: NCT05140954

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LIST OF ACRONYMS

AE	Adverse Event
ART	Anti-Retroviral Therapy
BMI	Body Mass Index
CAB	Community Advisory Board
CBC	Complete Blood Count
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CrCl	Creatinine Clearance
CRFs	Case Report Forms
Css	Drug concentration at steady state
CV	Coefficient of Variation (SD/Mean)
DAIDS	Division of Acquired Immunodeficiency Syndrome
DBS	Dried Blood Spots
DNA	Deoxyribonucleic acid
DOT	Directly Observed Therapy
EAE	Expedited Adverse Event
FDA	Food and Drug Administration
FTC	Emtricitabine
FTC-DP	Emtricitabine-diphosphate
GCP	Good Clinical Practices
GEMS	Global Evaluation of Microbicide Sensitivity
GFR	Glomerular Filtration Rate
GT	Gonorrhea Trichomoniasis
HBAg	Hepatitis B Antigen
HBV	Hepatitis B Virus
HCT	Hematocrit
hDNA	Human Deoxyribonucleic acid
HIV	Human Immunodeficiency Virus
IEC	Information, Education and Communication
IoR	Investigator of Record
IRB	Institution Review Board

KEMRI	Kenya Medical Research Institute
MEMS	Medication Event Monitoring System
MOH	Ministry of Health
MSM	Men Who have Sex with Men
NASCOP	National AIDS & STI Control Programme
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PBMCs	Peripheral Blood Mononuclear Cells
PI	Principal Investigator
PK	Pharmacokinetics
PMTCT	Prevention of mother-to-child transmission
PPB	Pharmacy and Poisons Board
PrEP	Pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
RBC	Red Blood Cells
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SSP	Study Specific Procedures
STI	Sexually Transmitted Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	Tenofovir Alafenamide Fumarate
TDF	Tenofovir Disoproxil Fumarate
TDF/FTC	Truvada® or Tenofovir Disoproxil Fumarate/Emtricitabine
TFV	Tenofovir
TFV-DP	Tenofovir-diphosphate
TP	Triphosphate
UC	University of Colorado
UW	University of Washington
WB	Whole blood
WHO	World Health Organization
βHCG	Beta-Human chorionic gonadotropin

Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

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The Women TAF-FTC Benchmark Study

Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

Version 1.0 **August 15, 2021**

ClinicalTrials.gov: NCT05140954

PROTOCOL SIGNATURE PAGE

Funding Support by:
Gilead Sciences

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all the stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. Federal regulations and International Conference on Harmonisation guidelines.

_____

Name of Site Investigator of Record

_____ _____

Signature of Site Investigator of Record Date

Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

PROTOCOL SCHEMA

Full Title: **Safety and Pharmacokinetics** of TAF-FTC Pre-exposure Prophylaxis in African Cisgender women

Short Title: The Women TAF-FTC Benchmark Study

Clinical Phase: IIb

Principal Investigators: Kenneth K. Mugwanya, MBChB, PhD**,** Peter L. Anderson, Pharm.D.

Purpose: To assess the safety and define blood and tissue benchmark concentrations of Tenofovir (TFV) and Tenofovir diphosphate (TFV-DP) in cisgender women using directly observed tenofovir alafenamide (TAF)-emtricitabine (TAF-FTC) PrEP. These data will help guide accurate interpretation of efficacy results obtained in HIV prevention trials and programs in cisgender women.

Study design: An open-label, randomized, three-arm, directly observed therapy, pharmacokinetics study. HIV-uninfected non-pregnant cisgender women will be randomly assigned 1:1:1 to 1 of 3 dosing frequencies of DOT TAF-FTC PrEP: 2, 4, or 7 doses/week to help differentiate poor and modest adherence from perfect adherence. Drug concentrations in blood, cervico-vaginal fluid, and tissue will be measured during the study. The frequency of adverse events will be described.

Study population: The study will enroll 18-30 years old HIV uninfected, non-pregnant Kenyan cisgender women at low risk of HIV.

Study site: The Kenya Medical Research Institute-Thika Research Site, Thika, Kenya

Study regimen: Volunteers will receive 25 mg TAF/ 200mg FTC according to the dosing regimens outlined in the study design.

Study duration: The study will last for up to approximately 18 weeks for each participant. Recruitment, enrollment, and follow up will continue for approximately 2 years.

Hypothesis: TFV and TFV-DP dose-response thresholds from DOT TAF-FTC PrEP dosing for cisgender women will be defined but will differ from thresholds defined for TDF-FTC PrEP

Primary objectives:

1. To describe the safety of TAF-FTC-based PrEP in HIV-uninfected cisgender women.
2. To define cisgender women-specific expected blood concentrations and dose-proportionality for TFV-DP in DBS and PBMCs using directly observed TAF-FTC therapy at 2, 4, 7 doses per week.
3. To establish a model to predict adherence rate to TAF-FTC by level of TFV-DP in DBS for cisgender women.

Secondary objectives:

1. To define the expected concentrations and dose-proportionally for TFV-DP in PBMCs and vaginal tissue

2. To examine relationships among drug concentrations in plasma, WB, DBS, and PBMCs.
3. To determine the influence of biological variables (e.g. mean corpuscular volume and HCT, age, weight, sex) on drug concentrations.
4. To compare drug concentrations in DBS from fingerstick versus drug concentrations in DBS transferred from blood tubes.

Primary outcomes: Benchmark concentrations of TFV-DP from TAF in DBS and PBMCs, and the dosing frequency (i.e., doses per week) required to generate them.

Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

STUDY SUMMARY

PROTOCOL ABSTRACT/SUMMARY

Pre-exposure prophylaxis (PrEP) using co-formulated emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) is a potent HIV prevention method for cis- and transgender men and gender women. Efficacy is highly dependent on adherence. Pivotal studies that combined clinical epidemiology and pharmacology defined thresholds for PrEP protection in cisgender men who have sex with men (MSM) that have been key to PrEP promotion and development of new PrEP agents. For African cisgender women at risk for HIV, a priority group due to disproportionately high incident HIV infections, variable adherence in PrEP clinical trials and limited pharmacokinetics data have resulted in lack of clarity about levels of PrEP use required for HIV protection. A new form of tenofovir, tenofovir alafenamide fumarate, co-formulated with emtricitabine (TAF-FTC) or Descovy® has recently been approved by the U.S. Food and Drug Administration for PrEP use in cisgender men and transgender women. However, Descovy® is not indicated in at risk cisgender women because its safety and effectiveness in this population has not been evaluated. Studies are now planned or ongoing in African cisgender women to evaluate TAF-FTC for PrEP. Tenofovir-diphospate (TFV-DP) in dried blood spots was critical for interpreting Descovy® study outcomes in the DISCOVER trial, and will again be essential for the planned studies to evaluate the effectiveness of Descovy® for PrEP in cisgender women. Thus, clear knowledge of African cisgender women-specific adherence-concentration benchmark for TAF-FTC relationship is essential to define success of these studies. To date, no study has evaluated safety and directly observed expected TAF-FTC PrEP concentrations in African cisgender women with varying frequency of PrEP adherence. TAF efficiently achieves higher concentrations within lymphoid cells while attaining lower TFV concentration in plasma compared to TDF. This creates potential advantages of TAF for PrEP, as the higher TFV-DP in lymphoid cells may confer high activity, whereas the lower plasma TFV concentrations may improve markers of bone and renal changes compared with TDF. Although the clinical significance of these marker changes is unknown, it is thought that TAF may exhibit improved long-term safety compared with TDF. We will conduct an open-label, randomized, three-arm, directly observed dosing pharmacokinetics study of TAF-FTC PrEP in African cisgender women. The primary objectives are: **1) To assess the safety of TAF-FTC PrEP in cisgender women. 2) To define the cisgender women-specific expected blood concentrations and dose-proportionality for TFV-DP in DBS and PBMCs using directly observed TAF-FTC therapy at 2, 4, 7 doses per week. 3) To establish a model to predict adherence rate to TAF-FTC by level of TFV-DP in DBS for cisgender women.** HIV-uninfected non-pregnant cisgender women will be randomly assigned to 1 of 3 dosing frequencies of directly observed therapy (DOT) TAF-FTC PrEP: 2, 4, or 7 doses/week, to represent poor, modest, and perfect adherence, respectively. The study will enroll up to 54 18-30 years old HIV uninfected cisgender women at low risk of HIV at Thika site in Kenya. The proposed study will be the first to define TAF-PrEP adherence-blood concentration thresholds for African cisgender women, a priority population for HIV prevention. The findings will guide accurate interpretation of safety, adherence, and efficacy of planned or ongoing HIV prevention trials in African cisgender women.

Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenya Cisgender women

LAY SUMMARY

Title: Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

Lay title: A project to assess the safety and define the expected blood levels of PrEP medications in cisgender women derived from varying number of PrEP doses taken per week.

Background:
African cisgender women are disproportionately affected by HIV. Pre-exposure prophylaxis (PrEP) is an effective HIV prevention strategy, but variable adherence in PrEP clinical trials among African cisgender women and limited pharmacokinetics data have resulted in a lack of clarity about the degree of PrEP use required for HIV protection in cisgender women. For cisgender men who have sex with men, the STRAND and DOT-DBS studies defined the adherence levels to PrEP medication and expected drug concentrations arising from varying directly observed therapy (DOT) doses per week. Those thresholds are today being applied to studies of African cisgender women taking PrEP, and cisgender women-specific levels associated with HIV prevention have never been defined. However, recent data from large PrEP studies we have done among African cisgender women ─ including the Partners PrEP Study and Partners Demonstration Projects conducted at Thika site ─ suggest those these levels may not reflect the pharmacology of cisgender women in African settings. In these studies in African populations, however, PrEP dosing was not directly observed therapy; no study has established expected PrEP concentrations in African cisgender women with varying frequency of PrEP adherence. Thus, there is an urgent need to define the frequency of adverse events, adherence and expected blood concentrations of PrEP medications in cisgender women.

What questions are we trying to answer?
We seek to assess the safety and define the expected blood levels of PrEP medications (tenofovir) for cisgender women taking directly observed oral PrEP therapy to understand the frequency of PrEP dosing associated with HIV protection in cisgender women. Cisgender women will be randomly assigned to receive varying frequency of weekly PrEP doses and followed for up to 18 weeks.

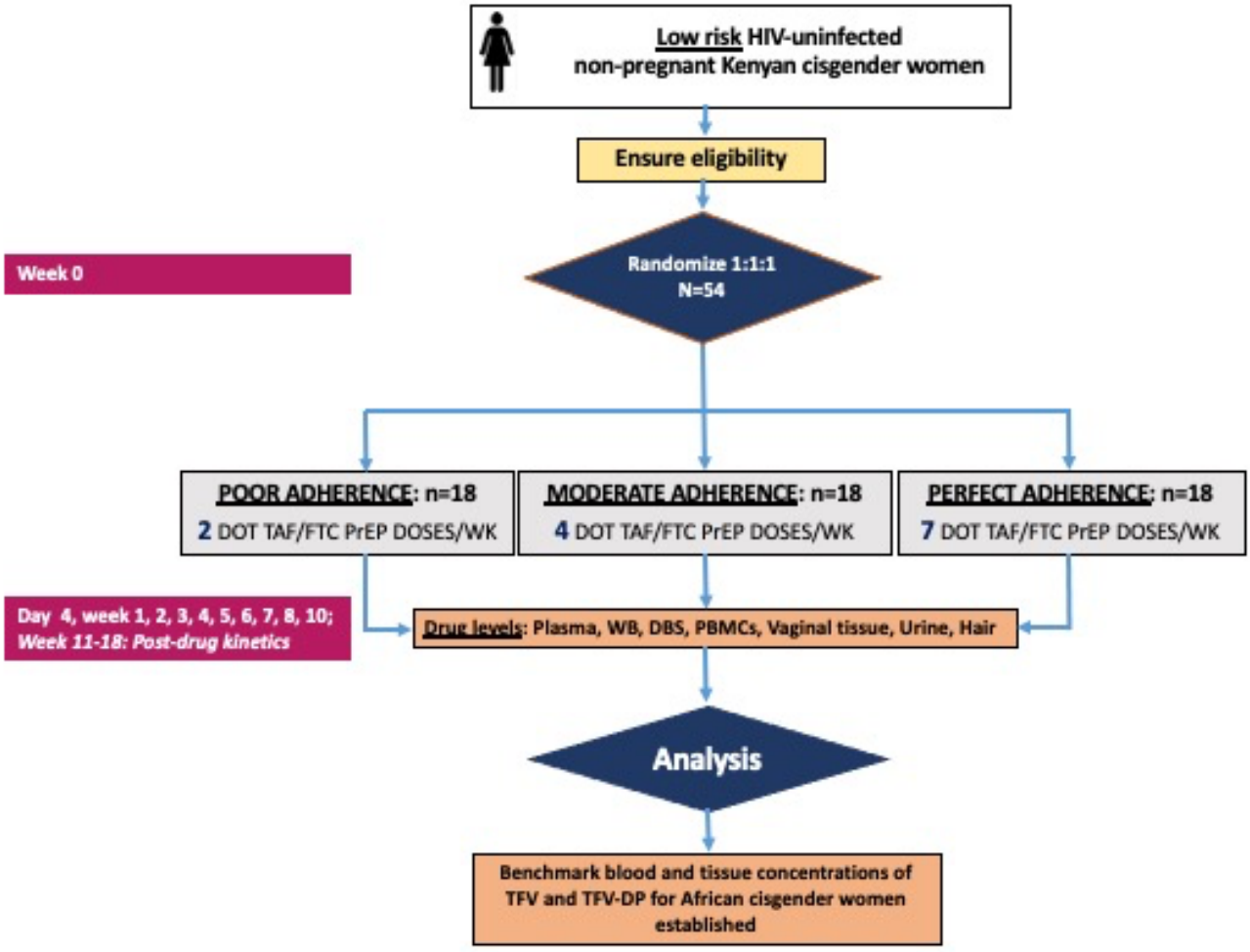
Where is the project taking place?
The study will take place in Thika, Kenya.

How will the project benefit society?

We propose to conduct the first study of oral PrEP adherence-concentration thresholds in Kenyan cisgender women, a population facing significant burden of incident HIV infection. Knowledge gained from the proposed study will include the frequency of adverse events, key blood concentrations of PrEP medications, and the frequency of pill taking required to achieve those concentrations in cisgender women. The results of this work will have immediate implications for PrEP programs, HIV prevention, and the global HIV prevention field.

Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

CONSORT DIAGRAM



1 INTRODUCTION

1.1 Background and prior studies

Adherence is critical to therapeutic success for HIV treatment and pre-exposure prophylaxis of new HIV infections (PrEP). This section describes HIV risk in African cisgender women, TDF/FTC effectiveness and the importance of adherence, the lack of progress in quantifying adherence clinically, the high promise of TFV-DP in DBS as a novel adherence measure, and considerations for implementing adherence monitoring into clinical care.

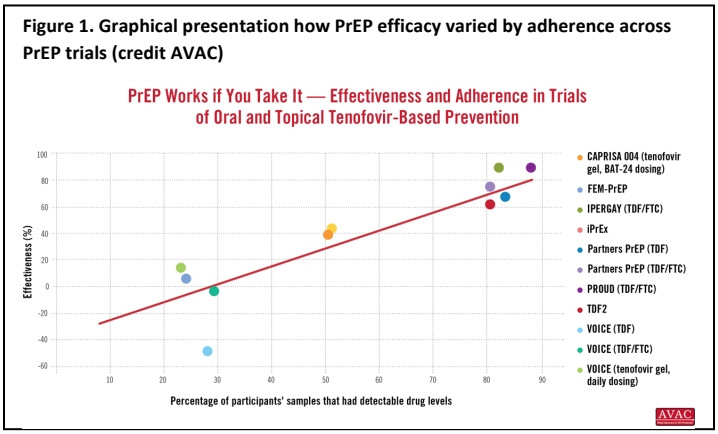
1.1.1 Disproportionate risk for HIV among African cisgender women

More than 600 000 new HIV infections occur annually among young African cisgender women[1], with incidence rates often double or more than those among their cisgender male age-mates[2-4]. A recent clinical trial in eastern and southern Africa (the ECHO Study)[5] that evaluated the risk of HIV acquisition in HIV-negative cisgender women who used three common contraceptive methods found that HIV incidence among sexually active cisgender women was alarmingly high — on average nearly 4% — with higher rates of HIV infection for cisgender women <25 years irrespective of the contraceptive method. These recent results emphasize that HIV remains a significant personal risk and public health challenge for many cisgender women in African countries.

1.1.2 Evidence of TDF/FTC PrEP efficacy and relationship to adherence

FTC/TDF PrEP is a highly efficacious and safe strategy for reducing HIV risk among cisgender men and transgender women who have sex with men [6], heterosexual cis- and transgender men and women[7, 8], and injection drug users[9], and is now recommended as a prevention option for all persons at high risk for acquiring HIV[10-12]. There was variation in HIV protection across first generation FTC/TDF PrEP trials (**Figure 1**)[13], and pharmacokinetics measurements as markers of adherence have transformed our understanding of FTC/TDF PrEP adherence and efficacy. In the Partners PrEP Study, which included 1,785 East African cisgender women with a mutually disclosed HIV-infected partner, PrEP efficacy among cisgender women was 66% for TDF and 71% for FTC/TDF PrEP vs placebo[7], and the protective effect was consistent in subgroups of cisgender women at high risk for HIV acquisition[14]. In the TDF2 study in Botswana, PrEP efficacy among cisgender women was 49%, but interpretation was limited by the small sample size[8]. However, the enthusiasm for PrEP use in cisgender women faltered after the FEM PrEP and VOICE trials failed to demonstrate efficacy[15, 16]. While there were initially several potential explanations for the failure of PrEP in these two trials, including behavior and biologic factors, the consensus settled on poor adherence[17].

Figure 1. Graphical presentation how PrEP efficacy varied by adherence across PrEP trials (credit AVAC)



1.1.3 A new form of tenofovir for PrEP

The DISCOVER trial evaluated the safety and efficacy tenofovir alafenamide fumarate co-formulated with emtricitabine (F-TAF) (Descovy®) for PrEP use in cisgender men and transgender women[18]. This randomized, double-blind multinational trial, enrolled 5,387 HIV-negative cisgender men and transgender women who have sex with men and were at risk of HIV-1 infection to compare once daily Descovy® to Truvada (emtricitabine, tenofovir disoproxil fumarate, 200 mg/300 mg)[19]. Following the trial, Descovy® was approved by the U.S. Food and Drug Administration for PrEP use in cisgender men and transgender women[18]. However, Descovy® is not yet indicated in at risk cisgender women because the effectiveness in this population has not been evaluated. Studies are now ongoing in African cisgender women to

evaluate F-TAF (TAF-FTC) for PrEP. For persons with HIV, Descovy® has been approved for FDA for treatment of HIV in combination with other antiretroviral drugs since 2016[20].

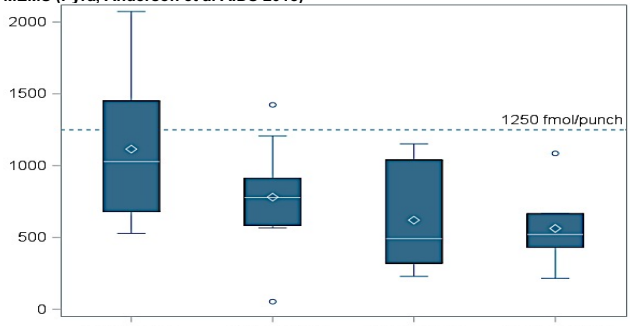
In the original TDF prodrug form, tenofovir was liberated during hepatic first pass by esterases and phosphodiasterases leading to high tenofovir concentrations in the plasma compartment[21]. TAF, on the other hand, largely survives first pass intact allowing it circulate in blood from which it efficiently enters lymphoid cells where it liberates TFV through cathepsin A[21]. This creates potential advantages of TAF for PrEP, as the higher TFV-DP in lymphoid cells may confer high activity, whereas the lower plasma TFV concentrations may improve markers of bone and renal changes compared with TDF. Although, the clinical significance of these marker changes is unknown, it is thought that TAF may exhibit improved long-term safety compared with TDF[22].

DISCOVER used tenofovir diphosphate concentrations (TFV-DP) in DBS to determine adherence to FTC/TDF and TAF-FTC. To interpret adherence, adherence benchmarks were determined in cisgender men and cisgender women in the USA through the DOT-DBS and TAF-DBS studies using directly-observed therapy (DOT)**.** These benchmarks were determined using 2, 4, and 7 DOT doses/ week, has and have proven to be critical for understanding PrEP adherence and efficacy in cisgender men and transgender women. Taken together, TAF is a promising new pro-drug for treatment and as PrEP for prevention of HIV infection, but studies are needed in cisgender women to determine if TFV-DP in DBS will provide the same adherence assessments for TAF as it did for TDF. This due to differing cell pharmacology between TDF and TAF, meaning that TFV-DP in DBS described above from TDF cannot be extrapolated to TAF. Ultimately, we believe that TFV-DP in DBS will have a similar half-life and accumulation as TDF, and will thus provide similar "dose-response" information for TAF-based PrEP, but studies are needed to define TFV-DP in DBS following F-TAF dosing. This protocol is designed to fill that need. The results from this protocol will be used to interpret drug levels and DBS testing that has been incorporated into planned or ongoing TAF-FTC PrEP studies in African cisgender women, where adherence monitoring is a key outcome.

1.1.4 Pharmacology of TFV and TFV-DP in African cisgender women

For African cisgender women at risk for HIV, variable adherence in PrEP clinical trials and limited data for TFV-DP in DBS have resulted in lack of clarity about levels of PrEP use required for HIV protection. Indeed, the absence of robust pharmacokinetics data for cisgender women, particularly studies that link adherence to expected concentrations, helped prevent the TAF-FTC indication for HIV prevention to be extended to cisgender women. Recent data from large FTC/TDF PrEP studies we have done among cisgender women[23, 24], including the *IMPAACT 2009 Study* [25]*,* indicate that the pharmacology of FTC/TDF in DBS in cisgender women in African settings may be different from that in USA settings, in general and particularly in pregnancy where TFV-DP concentrations may be reduced by 30-40%[23, 24]. With NIH funding, we will define adherence benchmarks and dose-proportionality for TFV-DP in DBS (and PBMCs) among Kenyan cisgender women using directly observed F-TDF therapy at 2, 4, 7 doses per week.

Figure 2: Concentrations among Cisgender women with 100% Adherence by MEMS (Pyra, Anderson et al AIDS 2018)



1250 fmol/punch: US male–derived TFV-DP concentration threshold for 100% adherence (7 doses/week)

TFV-DP in DBS was critical for interpreting Descovy® study outcomes in the DISCOVER trial, and will again be essential for the planned studies to evaluate the effectiveness of Descovy® for PrEP in cisgender women. Interpretation of reductions in HIV infection rates attributable to TAF-FTC and defining success of these studies will greatly depend, in great part, on accurate understanding of the degree of adherence/non-adherence to TAF-FTC and FTC/TDF

in the study population. Thus, clear knowledge of African cisgender women-specific adherence-concentration benchmark relationship is essential to define success of these studies, and this study will directly address this need. Using our combined complementary expertise in HIV prevention research in African women and antiretroviral pharmacology, we will define specific adherence-concentration benchmarks for TAF-FTC in African cisgender women that will help interpretation of ongoing F/TAF (Descovy®) PrEP studies in cisgender women.

1.2 Problem statement

TAF-FTC (Descovy®) is a promising new pro-drug for treatment and prevention of HIV infection and is approved by the U.S[18]. Food and Drug Administration as HIV PrEP to reduce the risk of HIV infection from sex in at-risk adult and adolescent cisgender MSM and transgender women weighing at least 35kg[18]. However, the absence of robust pharmacokinetics data for cisgender women, in particular studies that link adherence to expected drug concentrations, prevented the extension of the TAF-FTC indication for HIV prevention to cisgender women. Thus, studies are needed in cisgender women to determine if TFV-DP levels in blood will provide the same adherence assessments for TAF as it did for TDF. This study will address this issue, and the study results from this will be used to interpret safety and drug levels and DBS testing that has been incorporated into ongoing TAF-FTC PrEP studies in African cisgender women, where adherence monitoring is a key outcome.

1.3 Justification

TFV-DP in DBS was critical for interpreting Descovy® study outcomes in the DISCOVER trial, and was critical for understanding PrEP efficacy for Truvada in cisgender men and transgender women. As described above, TAF may improve upon TDF for HIV prevention in both efficacy and safety, and there is a need to define cisgender women-specific adherence benchmarks. To interpret adherence, adherence benchmarks were determined in cisgender men and cisgender women in the USA through the DOT-DBS and TAF-DBS studies using DOT which has proven to be critical for understanding PrEP adherence and efficacy in cisgender men and transgender women. Because the cell pharmacology for TDF and TAF differs, and TFV-DP benchmarks defined TDF in cisgender men and transgender women cannot be extrapolated to TAF, cisgender women-specific benchmark concentration thus need to be defined. Ultimately, we believe that TFV-DP in DBS will have a similar half-life and accumulation as TDF thus providing similar “dose-response” information for TAF-based PrEP, but studies in cisgender African women ─ who are disproportionately affected by HIV and thus a priority target for PrEP ─ are needed to define safety and TFV-DP in DBS following TAF-FTC dosing in cisgender women.

2 STUDY OBJECTIVE AND DESIGN

2.1 Overall Hypothesis

Safety and TAF-FTC dose-response thresholds from DOT dosing for cisgender women will be defined but will differ from TDF-FTC thresholds defined for cisgender women. The comparator thresholds from TDF-FTC PrEP will be obtained from an ongoing contepreneous DOT dosing study for cisgender women at same site.

2.2 Overall Objective

The central objective of this proposal is to describe the safety and expected blood and tissue adherence-concentration benchmarks for DOT TAF-FTC PrEP for Kenyan cisgender women.

2.3 Primary Objectives

1) To describe the safety of TAF-FTC-based PrEP in HIV-unifected cisgender women.

2) To define the cisgender women-specific expected blood concentrations and dose-proportionality for TFV-DP in DBS and PBMCs in cisgender women using directly observed TAF-FTC therapy at 2, 4, 7 doses per week.

3) To establish a model to predict adherence rate to TAF-FTC by level of TFV-DP in DBS for cisgender women.

2.4 Secondary Objectives

1) To define the expected concentrations and dose-proportionally for TFV-DP in PBMC and vaginal tissue

2) To examine relationships among drug concentrations in plasma, WB, DBS, and PBMC.

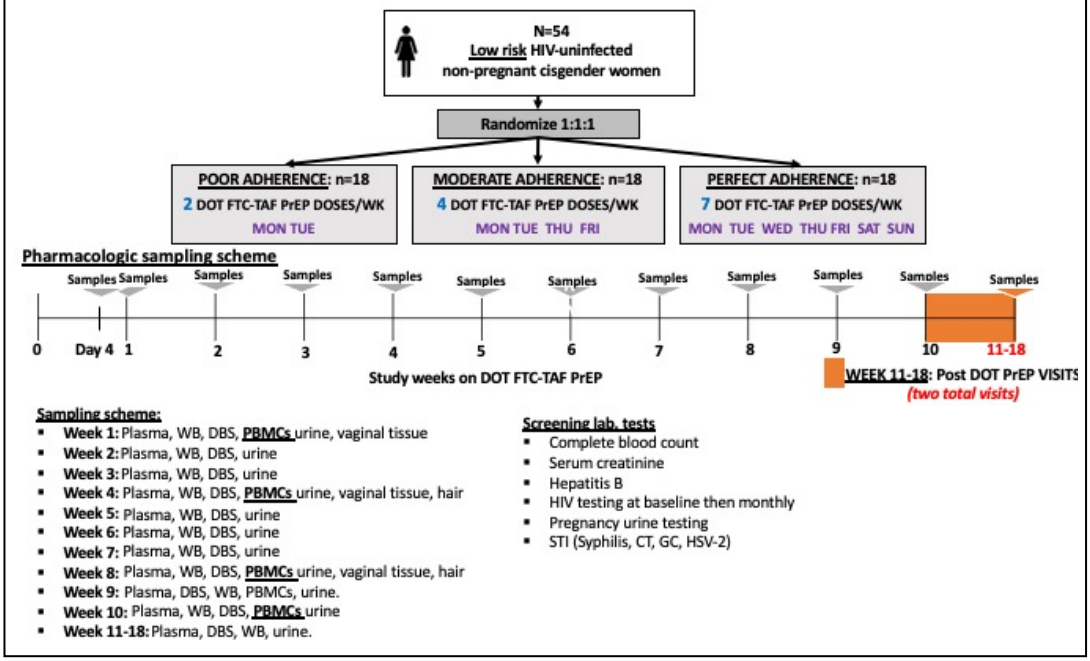
3) To determine the influence of biological variables (e.g., HCT, age, weight, sex, metabolites from metabolomics, and genetic variability in drug transporter/clearance proteins) on drug concentrations.

4) To compare drug concentrations in DBS from fingerstick versus drug concentrations in DBS transferred from blood tubes.

2.5 Study Design

This is an open-label, randomized, three-arm, directly observed therapy, pharmacokinetic study of TAF-FTC PrEP among low-risk HIV-uninfected non-pregnant cisgender women. HIV-uninfected non-pregnant cisgender women at low risk for HIV will be randomly assigned to 1 of 3 dosing frequencies of DOT TAF-FTC PrEP **(Figure 3)**: **2, 4, or 7** doses per week to help differentiate poor and modest from perfect adherence (**Figure 3**).

Figure 3 : Schema for directly observed TAF-FTC PrEP dosing and pharmacokinetics sampling



Enrollment will continue until 54 non-pregnant evaluable participants (i.e., participant with completed data on dosing and PK samples) are enrolled.

- **Group #1**: "7 doses per week or Perfect Adherence arm"— cisgender women will receive a single tablet of co-formulated 25 mg TAF/ 200mg FTC once daily (7 doses per week).
- **Group #2**: "4 doses per week or Moderate Adherence arm" — cisgender women will receive a single tablet of co-formulated 25 mg TAF/ 200mg FTC tablet on Monday, Tuesday, Thursday, Friday.
- **Group #3**: **"**2 doses per week or Poor Adherence arm" — cisgender women will receive a single tablet of co-formulated 25 mg TAF/ 200mg FTC tablet on Monday and Tuesday

Justification for non-daily dosing of PrEP groups:

In this study we propose to randomize cisgender women to non-daily dosing of PrEP (2, or 4 doses per week). The non-daily dosing is needed to investigate and demonstrate dose proportionality of TFV and TFV-DP concentrations. The adherence-concentration thresholds derived from this dosing frequency will help guide appropriate interpretation of adherence to TAF-based PrEP in clinical studies and implementation programs of PrEP. To minimize the risk of HIV infection in the non-daily dosing groups, as detailed in the eligibility section, only non-pregnant cisgender women at low HIV risk based on Kenya

guidelines will be enrolled and participants will receive a full package of HIV prevention, including risk reduction counseling, condoms and STI treatment at each visit. We will also perform monthly HIV testing. We will closely monitor the frequency of adverse events, including emergent HIV serocoversion (expected to be very rare) between groups.

2.6 Enrollment Targets

A cohort of up to 54 cisgender women who meet the inclusion and exclusion criteria described in Section 3 below will be enrolled at the KEMRI Thika Research Site, in Thika, Kenya. Enrollment will continue until 54 evaluable cisgender women are enrolled who agree to use PrEP at the Enrollment visit. Cisgender women who accept PrEP will be randomized 1:1:1: **2, 4, or 7** DOT doses per week to help differentiate poor and modest from perfect adherence.

3 STUDY POPULATION

We will enroll a novel cohort of up to 54 healthy, HIV-uninfected non-pregnant Kenyan cisgender women volunteers 18-30 years to establish benchmark adherence-concentration thresholds for TAF-based PrEP. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. They will be recruited, screened, and enrolled as described in Section 3.4.

3.1 Inclusion Criteria

This study will enroll young Kenyan cisgender women (aged 18-30 years old). Cisgender women bear the greatest burden for HIV infection; thus, the study will focus solely on cisgender women. HIV incidence is greatest in younger cisgender women ages 15-24, as is interest in accumulating PrEP data from Kenya. Thehe age limitation on enrollees into the study reflects that clinical and epidemiologic need. Enrollment criteria will be finalized at the time of protocol development to account for any updates to Kenyan national guidelines, but the central clinical criteria are as follows:

For all cisgender women

- Age ≥18 and ≤30 years old.
- Willing to undergo urine pregnancy tests.
- Has understood the information provided and has provided written informed consent before any study-related procedures are performed.
- HIV uninfected based on negative HIV rapid tests, according to Kenyan national algorithm.
- Normal renal function (estimated glomerular filtration rate >60 mL/min).
- Hepatitis B surface antigen negative.
- No active, clinically significant medical or psychiatric conditions that, in the opinion of the investigators, would interfere with study participation .
- Lack of severe anemia (Hemoglobin >10 g/dL).
- Willing to use DOT and come to clinic frequently for DOT PrEP for at least 10 weeks.
- Willing to have home visits for follow up.
- Has access to an active smartphone to allow off-site observation of dosing if unable to come to the clinic, or, as determined by the study staff, the participant resides in a close enough location to the clinic to permit a home visit if unable to come to the clinic. That is, potential participants without a smatphone may be enrolled in the study if investigator determines that the participant resides within reasonable distance from the clinic for a home visit in the case of a missed clinic visit.
- Intention to stay within the study site's catchment area for at least 10 weeks.
- Resides or works in catchment area with high speed internet coverage to permit video streaming.
- Not pregnant or breast feeding.
- Willing to use effective contraception during the study period.
- At low risk for HIV. *In Kenya, national guidelines define substantial risk for HIV and recommend PrEP be an option for individuals reporting: partner of HIV-infected person not on*

ART or on ART for <6 months, >1 partner of unknown status, transactional sex, recent STI, recurrent PEP use, inconsistent condom use, or injection drug use. So, non-pregnant cisgender women reporting any of these factors will not be eligible for the study but will be linked for PrEP at clinic of choice including at Thika Site itself.

- Willing to be randomized to non-daily PrEP and to come to the clinic frequently for DOT PrEP.
- Willingness and ability to be abstinent for at least 7 days after each vaginal biopsy visit.

3.2 Exclusion Criteria

For all cisgender women

- Inability to give informed consent
- Positive screening HIV+ as determined by standard rapid serologic assays 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 cervical or inguinal adenopathy.)
- Positive HBV surface antigen test at screening.
- Calculated creatinine clearance <60 ml/min.
- Any laboratory value or uncontrolled medical conditions that, in the opinion of the investigators, would interfere with the study conditions such as, heart disease and/or cancer.
- Prohibited concomitant medications are: 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 TAF®, TRUVADA®, ATRIPLA®, COMPLERA®, EMTRIVA®, VIREAD®; or drugs containing lamivudine or adefovir, which are close analogs of FTC and tenofovir, respectively.
- Current or past use of PrEP (pre-exposure prophylaxis).
- Not willing to have home visits.
- Pregnant or plan to become pregnant in the next 6 months or unwillingness to use birth control .
- Currently breastfeeding.
- High risk of HIV infection (for example: sexually active with an HIV infected partner; engages in condomless intercourse with HIV-infected partners or partner of unknown status during the study; exchanges 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.

3.3 Study Setting

The proposed work will take place in Thika, Kenya. The site has extensive experience conducting large biomedical and PK studies[7, 26-35] and has a long-standing relationship with local public health authorities, HIV prevention advocates, and community leaders. Over the past decade, the Thika site has established a multi-disciplinary team focused on HIV prevention research (more than a dozen projects currently) and on provision of clinical care, including clinical studies involving follow up of pregnant cisgender women**.** The Thika site is a center of excellence for PrEP in Kenya and leads PrEP technical assistance to other clinics as part of Kenya national PrEP scale-up. As stated in the background section, the Thika site conducted the DOT PrEP PK study in breastfeeding cisgender women (**see Figure 3**)[26], achieving 100% retention.

3.4 Recruitment and Prescreening Process

We will enroll a novel cohort of up to 54 evaluable non-pregnant, healthy, HIV-uninfected adult cisgender women volunteers. The experienced community outreach team at the study site in Thika employs community-based mobilization strategies, including working with the neighboring Thika District Hospital to identify pregnant cisgender women, engaging community health volunteers, gate keepers, peer to peer mobilization, youth peer providers and ambassador models, use of printed and electronica IEC materials, social media (WhatsApp and Facebook), radio talk shows in English and Kiswahili, active participation in local social events for information sharing, and partnering with learning institutions to give health talks and to provide study related information. The methods for recruitment proposed in this study are similar to those that were successfully used to conduct the pharmacokinetic study of PrEP in Breastfeeding cisgender women at the Thika site. From these strategies, we will identify those that are highest yielding and shift focus to primarily rely on them. The outreach team at PHRD is well-suited to develop innovative recruitment methods and collaborate with local partners to ensure that we achieve the accrual rate needed and enroll cisgender women who are highly dedicated to research procedures. The Thika team has >10 years of experience of conducting clinical trials, including in populations of cisgender women (**Table 1**). In many of the studies we have conducted, the Thika site has achieved the highest recruitment and data quality site compared to others in multisite/multinational studies – for example, in the Partners PrEP Study clinical trial of PrEP, and the MPYA Study. We will replicate and extend all of those previously proven recruitment strategies for this study.

Table 1: Studies involving pregnant cisgender women at Thika

Study and funding	***Number of cisgender women enrolled***
Partners PrEP *(BMGF)*	*112*
Partner Demo Project *(R01MH0559907)*	*332*
SCIP *(R00HD076679)*	*74*
MPYA *(R01MH109309)*	*175*
NuvaRing (*R01HD077872)*	*122*
GHS *(CDC U48DP005013)*	*400*

3.5 Co-Enrollment Guidelines

Participants in this study should not take part in any concurrent research studies that use drugs or medical devices while on follow up. Co-enrollment in observational or other studies may be allowable with approval of the site IoR or designee. Previous participation in the placebo arm of an HIV vaccine trial may be allowable with approval of Co-Chairs.

3.6 Retention of Study Participants

For this DOT pharmacokinetics study, high retention begins with the exclusion of participants who indicate a high likelihood of travel outside of the study area, who appear to lack dedication to the research process, or who may experience personal challenges with compliance with study visits. We will follow usual Kenyan clinical practices for notifying participants of their study follow-up visits, which include sending participants reminders via SMS messaging and telephone calls. In addition, an extensive tracing record at the time of study entry will be completed by a trained research staff member and will be used to trace participants who miss visits; the experienced community outreach team has established methods for successful participant tracing. As detailed in the Introduction Section, the Thika Site successfully recruited lactating cisgender women (and their infants, half <13 weeks of age) into a similar DOT PrEP PK study previously, achieving 100% retention for breastfeeding-month infant pairs and sample collection. The following approaches will be used to promote compliance and to achiev planned evaluable enrollment with pharmacokinetic sample collection.

> **Medication calendar**: At study enrollment, subjects will be given a calendar for study visit appointments, dosing schedules, and to record unsolicited adverse events. For those interested and willing, visit schedule and reminders will be added to the calendar on their smartphones.

Video streaming and phone reminders: Flexible clinic scheduling will be available to promote high rates of follow-up and compliance and to minimize participant's burden. Video live streaming services via social media (e.g., WhatsApp, Skype, etc.) will be employed; only cisgender women with an active smart phone will be enrolled into the study to permit offsite observation of required DOT PrEP doses if needed. Use of live streaming will be supported with provision of weekly data/internet bundles consistent with the local IRB regulation. Remote DOT via video streaming is intended to increase compliance as well as minimize participant burden. Enrolled participants will receive a reminder message (sent via text message or phone call) the morning of every scheduled study visit. A one-month supply of back-up medication will be provided to participants at study enrollment to be used if the participant is unable to complete a visit at the clinic; all doses taken offsite will be directly observed by study staff via live video streaming on smart cell phone or computer via WhatsApp. For DOT doses taken via video streaming, participants will be asked to open their mouth afterwards to confirm swallowing.and

Home visits: We will conduct home visits for patients unable to attend their scheduled clinic visits or procedures in order to promote compliance with study procedures. During home visits, study staff may conduct study procedures e.g., observing of dose taking or collection of study samples (blood, urine, hair) where applicable. Any offsite collection of study sample will follow the same safety standards followed at the clinic. **For this short-term intensive pharmacokinetics study where complete DOT compliance is pivotal for primary outcome measurement, only cisgender women who consent for home visits will be enrolled**.

3.7 Participant Withdrawal

Regardless of the participant retention methods used, participants may voluntarily withdraw from the study for any reason at any time. The Site Investigator of Record or designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures. Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site IRBs/ECs terminates the study overall or at a specific site prior to 18 weeks.

Every reasonable effort will be made to complete final evaluations for participants who terminate from the study prior to the last study assessment or visit; study staff will record the reason(s) for all withdrawals from the study in participants' study records.

3.8 Replacement of Study Participants

Data from participants who permanently discontinue study treatment will be used in analyses. Study participants who miss two consecutive scheduled doses, miss any pharmacokinetic samples, or permanently discontinue DOT PrEP will be replaced so that approximately 54 evaluable participants complete the study. No more than 20% of the target population (n=54) will be replaced. Data from subjects who discontinue prematurely will be used in analyses. Cisgender women who become pregnant will be replaced but will continue to be followed up to the end of their scheduled protocol study follow up. Seroconversions (unlikely, though possible) will not be replaced.

4 STUDY PRODUCT

The study product is Descovy® formulated as tenofovir alafenamide (TAF) 25 mg/ emtricitabine 200 mg (FTC).

4.1 Study Product Formulation

Each TAF-FTC tablet contains a co-formulation of TAF 25mg / FTC 200mg. An authorized study clinician will prescribe TAF-FTC as part of this study, with dosing instructions as described in this protocol.

4.1.1 Study product storage

Prior to dispensing, TAF-FTC tablets will be stored in the pharmacy in the original container. Each bottle contains a desiccant to protect the product from humidity. Study drug is to be stored at 68 °F to 77 °F (20 °C to 25 °C), with temperature excursions permitted between 15° to 30°C.

4.2 Source of Study Product and Accountability

Gilead Sciences will donate the study drug for this study. Study drug will be shipped to the investigational pharmacy and dispensed through the Thika Research Site pharmacy according to the research pharmacy policies and procedures of Kenya Pharmacy and poison board. The pharmacist of record will receive and inventory study medication, will dispense and track prescriptions, and will provide directions for returning unused medications for destruction according to local policy. The pharmacist of record will track the accountability of the study medications according to established procedures developed by the investigational pharmacy.

4.2.1 Study product dispensation

Two supplies of study drug will be dispensed for each participant. Both supplies will be dispensed in the original containers. Study personnel will be in possession of the main medication supply, which will be stored in a locked cabinet except during transportation to and from the directly observed dosing visits. This main supply will be enough for the entire 10-week DOT dosing period (enough medication to cover 10 weeks will be dispensed for the 70-84 day dosing window). Study personnel will record on the bottle the date that it is opened, and will ensure that opened bottles are used within 8 weeks. The locked cabinet will be in a temperature-controlled building, which is maintained at approximately 21°C. A second medication supply, a take-home supply, will be given to participants for non in-person dosing (video-streaming). Participants will be reminded to keep the medication in the original container with the desiccant, and to store it in a dry place with the cap tightly sealed. This take-home supply will be a maximum of one bottle of medication, with additional bottles given to participants when the current bottle is exhausted.

4.2.2 Return and Destruction of Study Product

Unused medications will be returned to the site study pharmacy at the end of the dosing periods or after a participant permanently discontinues study drug. The site pharmacy will account for and manage the returned medications in accordance with the local policies and procedures.

4.3 Assessment of Participant Adherence with Study Product/Intervention

Adherence will be assessed with directly observed dosing. All doses will be observed in person, when possible, at an agreed-upon private room at the research clinic or other predetermined location to maximize convenience for the participant. In circumstances where doses cannot be witnessed in person, doses will be witnessed by live audio-video communication or time-stamped videos . If video confirmation fails, this will be recorded as non-DOT dose.

4.4 Concomitant Medications

Concomitant medications will be evaluated on a case-by-case basis 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.

4.5 Prohibited Medications

Prohibited concomitant medications are: investigational agents, aminoglycosides, ganciclovir/valganciclovir, chronic high-dose acyclovir/valacyclovir, 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, respectively.

4.6 Precautionary Medications

Any medication or herbal supplement not listed under sections prohibited medication section will be evaluated on a case-by-case basis 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.

4.7 Toxicity Management

Safety related laboratory testing will be performed at study entry and at week 8 and or as indicated by clinician during follow up. If enrollment occurs more 30 days after screening, entry safety labs will be repeated. These include HIV rapid testing, complete blood count, HBV surface antigen, serum creatinine, and urine pregnancy test. Toxicity will be managed in consultation with a clinician on the protocol. The clinician may discontinue the study drug at any time if he/she feels that continued use would be harmful to the participant. The PSRT should be consulted when possible. The PSRT will be consulted when considering further holding or recommencing study medication.

4.8 HIV Seroconversion

Frequent testing for HIV acquisition during the study period will allow prompt cessation of study drug in an HIV-infected participant, minimizing the risk that resistant virus will emerge. Therefore, HIV testing will be performed at all monthly study visits. HIV rapid testing and specimen collection will be completed prior to administration of study medication. Participants who have any reactive or positive HIV test result after initiating PrEP will be instructed to discontinue study drug immediately and will have further testing to clarify their HIV infection status, as described in Section 5.3. Any enrolled participant who is confirmed to have acquired HIV infection during the study will permanently discontinue study product and will be transitioned to a local HIV care clinic for appropriate follow-up and clinical management. Procedures for participants who acquire HIV infection are described in Section 5.3.

4.9 Dose Modification

Study personnel will record all events of participants who vomit immediately after dosing. Participants will not be asked to re-dose, unless they are confident that a recurrence of vomiting can be avoided. Additionally, re-dosing will only be allowed if an intact tablet is visible in the emesis. The same directly observed dosing rules will apply if re-dosing is attempted. Dose modifications of up to 3 sequential missed doses will be allowed if a participant has, for example, an acute gastrointestinal illness. Further dose modifications or other dose modification issues will be discussed with the PSRT. The PSRT may decide on further missed doses, or participant withdrawal from the study.

5 STUDY PROCEDURES

An overview of the study visits and procedures schedule is presented in Table 5. Presented below is additional information on visit-specific study procedures.

5.1 Screening Procedures

Screening for COVID-19 symptoms and protection measures: We will follow the standard of care of the Kenya Ministry of Health, KEMRI, and WHO guidelines on the COVID-19 virus. Participants will be informed about practicing good hand hygiene, masking, good respiratory hygiene, and maintaining social distancing. Staff will adhere to social procedures including maintaining a six foot distance and wearing masks. Unvaccinated participants and staff will be screened for COVID-19-related symptoms when they arrive at the clinic using a checklist to check for risk of COVID-19 exposure based on symptoms or contacts. Any person that comes to the clinic with symptoms consistent with COVID-19 that include 1 or more of fever, cough (dry or productive), dyspnea, or myalgias will be isolated. Participants will be educated about the Ministry of Health specified measures for seeking healthcare during this time. Referral

mechanisms to local public health facilities are in place. Finally, the clinical site will maintain a register of all visitors and participants who enter the study site, to support usual care contact tracing efforts where necessary.

At the screening visit a qualified study clinician will perform a history and physical exam for each participant. A complete medication history will be obtained including all drug allergies, immunization history, prescription, over the counter, and herbal treatments. Vital signs will include height, weight, blood pressure, pulse, respiratory rate and temperature. The following procedures will be conducted:

- Informed consent
- Safety Labs: Complete blood count (CBC, specifically hematocrit and hemoglobin), HBV surface antigen, serum creatinine)
- HIV antibody (rapid test or blood)
- Urine pregnancy test
- Medical, medication, vaccine history
- Physical exam

A screening test(s) may be repeated within the 30-day screening window. A participant who is unable to schedule a study entry visit within the 30-day screening window must be re-screened prior to entry into the study. Participants who have not been immunized for HBV will be offered vaccination, as per standard of care. An HBV Antibody test may be ordered for participants who are unsure of their vaccination history.

5.2 Enrollment and Follow up Procedures

Up to 54 evaluable HIV uninfected participants will be enrolled and followed up for 18 weeks: 10 weeks with DOT PrEP and up to 8 weeks for post drug kinetics sampling, with one visit at one week following dose cessation and an additional visit to occur between weeks 12 to 18. Enrollment must occur within 30 days of screening. An eligible participant who is unable to schedule a study entry visit within the 30-day screening window must be re-screened prior to entry into the study. All enrolments will be scheduled on specific days to avoid confusion in implementing the proposed dosing and sampling scheme. An adverse event questionnaire and medical and medication review will be conducted at each visit from study entry (enrollment) through week 10. Safety labs and vitals can be ordered as needed at any visit.

5.2.1 Dosing schedule and assessment of compliance

The design of the study is guided by the ~17-day half-life of TFV-DP in DBS, and includes 10 weeks of dosing to achieve approximately 90% of steady-state, weekly sampling at convenience times (i.e., rather than troughs), and three dosing groups (2, 4, and 7 doses per week) to demonstrate dose-proportionality. All cisgender women will have 10 weeks of DOT PrEP to establish steady state in DBS and WB. We have chosen a dosing frequency scheme for non-daily doses to directly replicate the STRAND DOT study schedule based on the ~17-day half-life of TFV-DP in DBS: The 2 doses per week will be taken on Monday and Tuesday, and the 4 doses per week on Monday, Tuesday, Thursday, and Friday. This schedule will permit simultaneous evaluation of concentrations derived from intermittent and day-by-day dosing. The operationalization of specific days for dose taking can be adjusted prior to study start while maintaining the randomized adherence patterns (frequency of dosing taking) to permit efficient study operations and to minimize the burden on study participants. This is possible due to the long half-life of TFV-DP and planned sampling at steady state. Therefore, any chosen days would be appropriate.

All doses will be witnessed, as described above, in person by a study personnel in either a private room at the Thika clinic or at another predetermined location to maximize convenience for the participant. On dosing visits, the participant will take the dose by mouth and study personnel will ensure the tablet is swallowed by asking the participant to show that their mouth is empty. Flexible clinic scheduling will be available to promote high rates of follow-up and compliance and to minimize participants' burden. Where dosing cannot be witnessed in person, dosing will be witnessed over video via WhatsApp, Zoom, FaceTime, Skype, or other video-streaming device that is agreed upon by the participant and study

personnel. Only cisgender women with an active smart phone will be enrolled in this pharmacokinetics study to permit offsite observation of dose taking for the required DOT PrEP, and participants will be supported with commensurate data/internet bundles. A one-month supply of back-up medication will be provided to participants at study enrollment to be used if the participant is unable to attend their visit at the clinic. All doses taken offsite will be directly observed by study staff by live video streaming and participants will be asked to open their mouth afterwards to confirm swallowing. Dosing may occur at variable times within the assigned dosing day. All doses will be taken without regard to food, but meal information will be collected with each dosing event.

Study personnel will use a dosing log to document directly observed doses. Participants will be given a detailed calendar that shows scheduled dosing days. This schedule will also be reinforced when study personnel interact with participants.

5.2.2 Protocol pharmacology sampling visit schedule

During protocol-specified clinic visits (described below and in Table 2), a blood sample will be collected from an arm vein for plasma/WB/RBC/DBS/PBMC isolation and safety laboratories. Hair will be cut from the scalp for comparison with other drug measures. Adverse events will be assessed. All protocol-specified clinic visits are detailed below. Each protocol-specified clinic visit will have a window of up to 10 days for sample collection.

Clinic visit 1: Study entry visit (must be within 30 days after screening visit)

- Medical, sexual, contraception, antenatal and vaccine history review
- Study blood work: WB, DBS, PBMC, plasma, (pre-drug for endogenous molecules such as nucleosides)
- Urine pregnancy test (urine β HCG)
- Study urine: (baseline endogenous molecules such as nucleosides)
- STI tests (CT, GC, syphilis, HSV-2)
- Blood work: hDNA for those who consent to drug transport gene testing
- Vaginal swab
- Dispense back up PrEP medication: subject home supply
- Dispense study dosing calendar
- DOT: Witness first PrEP dose

Clinic visit 2: Week 1 Day/Dose 4 visit (for 2 doses per week group this will be 4 days since first dose:

- Study Bloodwork: WB, DBS, PBMC, plasma
- Study urine
- Finger stick for DBS
- Cervicovaginal biopsy: **Random subset (50%) of cohort. These participants will not have a biopsy collected at the Week 1, Day 7 visit.**
- Vaginal swab
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 3: Week 1 (Dose 7) visit:

- Study bloodwork: WB, DBS, PBMC, plasma
- Study urine
- Finger stick for DBS

- Vaginal biopsy: **Random subset (50%) of cohort, comprising participants who did not have a biopsy collected at the Week 1, Day 4 visit**
- Vaginal swab
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 4: Week 2 (Dose 14) visit:

- Study bloodwork: WB, DBS, PBMC, plasma
- Study urine
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 5: Week 3 (Dose 21) visit:

- Study bloodwork: WB, DBS, plasma
- Study urine
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 6: Week 4 (Dose 28) visit:

- HIV rapid test
- Study bloodwork: WB, DBS, PBMC, plasma
- Study urine
- Finger stick for DBS
- Vaginal biopsy (all participants)
- Vaginal swab
- Hair collection
- Urine pregnancy test (urine β HCG)
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 7: Week 5 (Dose 35) visit:

- Study bloodwork: WB, DBS, PBMC, plasma
- Study urine
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 8: Week 6 (Dose 42) visit:

- Study bloodwork: WB, DBS, PBMC, plasma

- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT
- Study urine

Clinic visit 9: Week 7 (Dose 49) visit:

- Study bloodwork: WB, DBS, PBMC, plasma
- Study urine
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 10: Week 8 (Dose 56) visit:

- HIV rapid test
- Urine pregnancy test (urine βHCG)
- Study bloodwork: WB, DBS, PBMC, plasma
- Finger stick for DBS
- Study urine
- Vaginal biopsy (all participants)
- Vaginal swab
- Hair collection
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 11: Week 9 (Dose 63) visit:

- Study bloodwork: WB, DBS, PBMC, plasma
- Study urine
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 12: Week 10 Dose 70) visit:

- HIV rapid test
- Study bloodwork: WB, DBS, PBMC, plasma
- Finger stick for DBS
- Study urine
- Safety Labs: Creatinine
- STI testing
- Medical, sexual, contraception, antenatal and vaccine history review
- AE assessment
- Concomitant Medication Review
- DOT

Clinic visit 13: Post DOT PrEP visits (one week following dose cessation): One visit at least 48 hours after the last DOT PrEP dose.

- Study bloodwork: WB, DBS, PBMC, plasma
- Study urine

Clinic visit 14: Post DOT PrEP visits (Week 12-18): One visit at least 14 days after visit above (i.e., the visit can occur any time between 2-8 weeks after the last DOT F/TAF PrEP which is between about week 12 and week 18 since enrollment)

- Study bloodwork: WB, DBS, PBMC, plasma
- Study urine
- Hair collection

5.2.3 Clinical Evaluations/Procedures

Scheduled protocol visits and procedures are outlined in Table 5. 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, herbal treatments, contraception use history. Vital signs will include height, weight, blood pressure, pulse, respiratory rate and temperature.

5.2.3.1 Specimen collection

All pharmacokinetic samples must be collected as per the protocol-specified schedule. Each protocol-specified pharmacokinetic sampling visit will have a window of up to 10 days for sample collection. The pharmacokinetic samples will be collected as follows:

Blood

A blood sample will be obtained at protocol specified visits to process plasma, whole blood, DBS, and PBMCs. On a given study day blood collection, up to 21mL of blood for study bloodwork will be drawn with no planned timing relationship with dosing. The blood will be collected from an arm vein by trained clinic staff according to study site policies and procedures.

The schedule of protocol visits and procedures are outlined in Table 2.

Table 2: Schedule of protocol visit schedule and procedures.

	Screening	Entry	DOT PrEP Period (weeks)											Post DOT Period	
Timeline (weeks)			W1		W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12-18
			Day 4	Day 7											
Clinic Visits #		1	2	3	4	5	6	7	8	9	10	11	12	13	14
Procedure															
Informed consent	x														
Medical, sexual, contraception, antenatal history review, vaccine history	x	x	x	x	x	x	x	x	x	x	x	x			
Physical exam [a]	x														
Dispense back up PrEP medication[e]		x													
Issue medical calendar		x													
AE assessment		x	x	x	x	x	x	x	x	x	x	x			
Safety Labs [a,c]	x	[x]									x				
Urine βHCG [a]	x	[x]					x				x				
HBS Ag	x														
HIV-1 rapid test [a]	x	[x]					x				x				
Hair collection							x				x				x
hDNA		x		x											
Study Bloodwork [d] (WB, plasma, DBS, PBMC)*PBMC is collected bi-weekly		x	x	x	x	x	x	x	x	x	x	x		x	x
Vaginal tissue[f]			x	x			x				x				
Vaginal swab		x	x	x			x				x				
DBS by fingerstick			x	x			x				x				
Study Urine [d]		x	x	x	x	x	x	x	x	x	x	x		x	x
Concomitant Medication Review	x	x	x	x	x	x	x	x	x	x	x	x			
STI testing (CT,GC, syphilis, HSV-2)		x											x		
DOT[b]		x	x	x	x	x	x	x	x	x	x	x			

[x] Indicated if screening occurred more 30 days before planned enrollment. *The screen and entry visits must be ≤ 30 days apart.*

a. Safety labs or vitals can be performed as needed at any time

b. DOT performed if applicable per randomization schedule

c. Protocol-specified safety labs include: CBC, HBAg, Creatinine clearance, in addition to monthly HIV testing and urine pregnancy tests.

d. Study Bloodwork: WB, DBS, PBMC, plasma and all available blood cell types; Study Urine: endogenous molecules such as nucleosides.

*PBMC is collected bi-weekly (baseline, week 2, 4, 6, 8, 10)

e. Study medications will be dispensed as described

f. Random subset (50%) on day 4 and the remaining subset (50%) on day 7. All participants will have week 4 and week 8 sample.

Vaginal swab and tissue

Vaginal swabs and a vaginal tissue sample will be collected. Vaginal biopsies will be taken with 2.3 x 4.2-mm Tischler gold-plated gynecological forceps.

Justification for vaginal tissue sampling: Vaginal mucosa is a tissue of great relevance to the acquisition of HIV infection for cisgender women. The planned sampling schedule will help to define early drug kinetics and how soon drugs accumulate in vaginal tissue following PrEP initiation the week until steady state is reached. To minimize risk associated with this procedure and the burden on study participants, we will ensure each participant will have only one biopsy in a 4 week-period by sampling separate participants at days 4 and 7 of Week 1. Thus, in week 1, half of the participants will be biopsied on day 4, and half will be biopsied on day 7. All participants will provide tissue samples at week 4 and 8.

Urine testing

A urine samples will be obtained at each visit for future testing to help refine models of prediction of PrEP adherence in cisgender women based on urine. The participant will be asked to void a small amount of urine into a sterile specimen container per standard procedures.

Hair collection

A small amount of hair (about 50-100 strands) will be collected from the occipital portion of the scalp in order to refine models for prediction of long-term PrEP adherence in cisgender women based on hair. The hair will be cut from as close to the scalp as possible with scissors. The hair that is cut will be taken from underneath the top layer of hair to minimize visibility of the removed hair. Measuring TFV/FTC exposure in small hair samples is feasible and acceptable in Kenya PrEP trials[36].

Blood for DNA

Blood for DNA will be obtained during Week 1 visit from participants who consent to sample storage for future testing. Genomic DNA will be isolated using a commercially available kit, according to standard manufacturer protocol. The DNA will be analyzed pharmacogenetic studies of protein drug transporters, and will not be used for whole genome sequencing. Only gene DNA analysis related to antiretroviral drug disposition or treatment response (drug transporters) will be evaluated. An addendum consent will be used to obtain informed consent for future testing.

5.3 Procedures for participants identified as HIV infected and/or pregnant

While it is expected to be very rare, this study may identify persons who become infected with HIV-1 during follow-up. Study staff will provide participants with their HIV test results in the context of post-test counseling. In the case of a positive test, a blood sample will be obtained for HIV drug resistance testing conducted through the standard national GEMS protocol for drug resistance surveillance. These results will be communicated to participants as soon as they are available. Persons identified as HIV infected during the study will be initiated on free HIV treatment and will also be referred to nearby HIV care services for follow up at completion of this trial. For participants who are pregnant and become infected with HIV during study follow-up, every effort will be made to facilitate immediate access to programs for preventing mother-to-child HIV transmission for appropriate antiretroviral treatment to reduce the probability of HIV transmission from mother to child.

6 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

A Protocol Safety Review Team (PSRT) discuss and regularly monitor safety issues that arise during the study, as outlined in this section. The PSRT will consist of the Principal Investigators, a study coordinator, a Gilead representative, and a Study Safety medical Officer. Email communications or calls will be held approximately every month, or as needed to discuss safety or study-related concerns, as described below. Conference calls will be held approximately every 6 months to summarize cumulative safety reports and enrollment. These reports will include all clinical and laboratory adverse events; social harms; enrollment including gender/ethnicity; and disqualified/excluded individuals. The Seattle-based Study safety monitor will review all safety data, and will prepare routine study conduct and safety reports for the PSRT, which will meet by conference call approximately every 6 months or as needed. The study site Investigators are responsible for continuous close monitoring and management of AEs in conjunction with IoRs. Sites are required to have detailed SOPs describing methods for AE reporting and toxicity management to ensure that AEs are reported and managed in accordance with the protocol and for alerting the PSRT if unexpected concerns arise

6.2 Clinical Data Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the PSRT if unexpected concerns arise.

Participant safety data will also be monitored by the Seattle-based Study safety monitor, who will review incoming safety data for completeness and consistency on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification.

The Seattle-based Study safety monitor will prepare routine study conduct and safety reports for the PSRT, which will meet by conference call approximately every 6 months and will review accrual and retention data, as well as safety data. More frequent or ad hoc reviews of safety data may be conducted by the PSRT as needed. A recommendation to stop the trial may be made by the PSRT at any such time that the team agrees an unacceptable type and/or frequency of AEs has been observed. If at any time a decision is made to discontinue the study product in all participants, the protocol chair will notify appropriate regulatory agencies, as well as the site IoRs, who will notify the responsible IRBs expeditiously

6.3 Adverse Event Definition and Reporting

An adverse event (AE) is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the study product (TAF/FTC). As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

Study participants will be provided a 24-hour telephone number and contact information and instructed to contact the study clinician to report any AEs they may experience. For life-threatening events, they will also be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based, and to request that the clinician be contacted upon their arrival. With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study CRFs. All participants reporting an AE will be followed clinically, until the AE resolves (i.e., returns to baseline) or stabilizes.

Study site staff will document AEs in source documents and the appropriate e-CRF. Grade 1 and higher clinical AEs, Grade 2 and higher laboratory AEs, and any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) that are reported by or observed in enrolled (defined as after randomization has occurred) study participants will be captured on AE e-CRFs regardless of their severity and presumed relationship to the study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.1 corrected, July 2017.

6.4 Relationship to Study Product

Relatedness is an assessment made by a study clinician of whether or not an adverse event is related to the study product. The relationship of all AEs to the study product will be assessed per the clinical judgment of the investigator based on the package insert and investigator's brochure.

6.5 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, will be used for determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

6.6 Serious Adverse Event (SAE)

All SAEs as defined by ICH guidelines will be reported regardless of relationship to the study agent(s), and are as follows:

- 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. 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.

6.7 Discontinuation of Study Medication

Subjects may withdraw from the study at any time. Any participant who prematurely discontinues study medication (for toxicity or pregnancy) should be followed for study duration. Subjects who become pregnant or who acquire HIV infection will have study drug discontinued but will be followed to determine the pregnancy outcome.

6.8 Discontinuation of study drug with toxicity

Grade I or II toxicity will be managed in consultation with a clinician on the protocol. The clinician may add follow up testing and evaluations, as medically indicated. Study drug can be continued except as noted below.

Grade III toxicities will be communicated to the PSRT and managed under the direction of a study physician. Follow up testing and evaluations will be added, as medically indicated. The toxicity will be evaluated for subject safety. 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 study drug. The PSRT will decide whether study drug can be restarted. If the adverse event is deemed not to be a significant health risk, the PSRT may recommend continuing study drug with close monitoring.

Grade IV toxicities will be communicated to the PSRT 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 drug and will be followed as medically indicated. If the grade IV is not related to the study drug, the PSRT will recommend whether study drug can be continued with close monitoring, or permanently/temporarily discontinued.

Participants who discontinue drug permanently due to a study drug-related AE will be followed until AE resolves or stabilizes and then the subject will be discontinued from the study.

6.8.1 AE Grades 1 or 2

Grade I or II toxicity will be managed in consultation with a clinician on the protocol. The clinician may add follow up testing and evaluations, as medically indicated. Study drug can be continued except as noted below.

6.8.2 AE Grade 3

TAF-FTC may be continued as directed by the site investigator if a Grade 3 toxicity is considered to be unrelated to the study medication. Study medication will be temporarily withheld if Grade 3 toxicity is considered to be related to the study medication. After a Grade 3 toxicity returns to Grade 1, the participant can be reintroduced to medication after consultation with the site investigator and other members of the PSRT. If a Grade 3 toxicity recurs and is considered to be related to study medication, TAF-FTC will be permanently discontinued.

6.8.3 Grade 4

For all Grade 4 laboratory-identified or clinical toxicities, TAF-FTC will be withheld unless it is determined to be not related. If a Grade 4 laboratory toxicity is not confirmed by repeat testing, it should be managed per algorithm for the new toxicity grade. Participants with Grade 4 AEs will be followed until the event resolves to baseline or stabilizes. Study drug may be restarted in the event of the resolution of a Grade 4 AE back to Grade 1, after consultation with the site investigator and other members of the PSRT. If the toxicity recurs to Grade 3 or higher after TAF-FTC is restarted and is considered to be related to TAF-FTC, the study medication will be permanently discontinued.

6.8.4 Creatinine Clearance

Participants who enroll with a Grade 2 CrCl will discontinue study drug only if there is an increase in severity (to Grade 3 or 4). If the calculated creatinine clearance is <60mL/min, it should be confirmed ideally within approximately one week of the receipt of the results. Study drug should be halted temporarily awaiting confirmatory testing. The PSRT should be consulted for further guidance about restarting study drug for participants who fail to have a confirmed test within two weeks of receiving the initial result.If the calculated creatinine clearance is confirmed to be <60 mL/min, the study drug must be temporarily discontinued. The participant will be monitored as deemed clinically necessary in consultation with the PSRT until level returns to baseline (screening value) or stabilizes.

6.9 Reporting Requirements for this Study

For each study participant, the SAE/EAE reporting period begins at Enrollment (Day 0) and ends when the participant's follow-up in the study ends. All reportable SAEs occurring during the study reporting period will be reported to the principal investigator

6.10 Social Impact Reporting

It is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as being HIV-infected or at risk or "high risk" for HIV infection). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. A social impact that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs at least annually, or according to their individual requirements. Social impacts will be collected and reported on CRFs during regular visits. In the event that a participant reports a social impact, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. The study site will provide such care and counseling in accordance with standardized guidance in the SSP Manual. While maintaining participant confidentiality, study site may engage their CAB in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

7 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

An open-label, randomized, three-arm, directly observed therapy, pharmacokinetic study. HIV-uninfected non-pregnant cisgender women will be randomly assigned 1:1:1 to 1 of 3 dosing frequencies of DOT TAF-FTC: 2, 4, or 7 doses/week to help differentiate poor and modest from perfect adherence. Drug concentrations in blood, cervico-vaginal fluid, and tissue will be measured during the study.

7.2 Study endpoints

- **Aim 1**: Mean, variance, and dose proportionality for TFV-DP or TFV in plasma, DBS, and PBMC for 2, 4, 7of DOT TAF-FTC dosing per week.
- **Aim 2**: Prediction model of adherence rate by level of TFV-DP in DBS.

7.3 Data Analysis

7.3.1 Primary outcomes

Primary outcome 1: The goal is to describe the frequency of adverse events, including emergent HIV infection during the study period. We will conduct a descriptive analysis for meeting PrEP157 eligibility among participants. The distribution of demographics and graded adverse events will characteristics by overall and study arms and proportions will compared between study arms using chi-square statistics.
Primary outcome 2: The goal is to quantify the effect of dose on steady state TFV-DP in DBS and PBMC based on an incomplete block design. Css (drug concentration at steady state) will likely require a normalizing log transform, such that geometric means and CIs will be reported. Dose proportionality will be assessed using the power model (on the natural log scale) $\ln(Y_{ijk}) = \mu + S_i + P_j + \beta\log(Dk) + \varepsilon_{ijk}$ (Eqn. 1).[37] Where Y_{ijk} is the response, Css, for the kth dose (k=2, 4, 7 doses/week), jth period (j=1,2), ith subject(i=1,…45); μ is the overall mean, Si is a random subject effect, Pj is the period effect and ε_{ijk} is random error. Dose proportionality dictates that $\beta=1$ for dose-dependent parameters and we will assume dose proportionality if the 90% CI is contained within the limits (0.8, 1.25). The SAS mixed procedure will be utilized for model (Eqn 1), again assuming a random subject effect. Although we do not anticipate a period effect, our design allows us to test this effect. For the primary analysis, we assume no effect of 'non-daily dosing' regimens; although this will be examined in a secondary analysis. If dose proportionality is not shown, we will examine proportionality separately for each of the ''non-daily dosing' dosing regimens. If dose proportionality is still not demonstrated when adherence regimens are examined separately we will consider dose as a categorical predictor.

In addition to the power model, we will utilize nonlinear mixed effects models using PK software (NONMEN and/or ADAPT-5) to model drug concentration over time on drug.[38-42] For this analysis, all available drug concentration samples will be utilized, thereby accounting for missed doses due to protocol deviations. Change in objective function and/or AIC will be used to compare models. This approach will be used to further probe dose proportionality and the final model(s) will be used as a basis for simulation studies.

Primary outcome 3: The goal is to identify TFV-DP cut points associated with adherence levels. For the primary analyses, we will attempt to discriminate adherence for 2, 4 and 7 dosing based upon TFV-DP. As above, we will combine the "non-daily dosing'" regimens. Linear mixed models with random intercepts, 25th percentiles, and receiver operating characteristics curves will be used to generate predicted concentration thresholds for varying dosing frequency (ranging from 1 to 7 doses/week) for each matrix-analyte pair. Analyses will be adjusted for age, contraception use, study arm, BMI, eGFR, and hematocrit.

7.3.2 Secondary outcomes

1. Examine models to predict non-daily adherence based on TFV/FTC and FTC-TP/TFV-DP in DBS.

   We assume the modeling approaches of Aim-1. We will first consider a saturated model allowing a separate mean for each dose/adherence group. The results will then be compared to a reduced model with a class variable indicating non-daily dosing groups" or 100% dosing (that is, the effect of "non-daily dosing" adherence does not differ by dose groups). Drug concentration predictors of "non-daily dosing" will focus on TFV-DP in relationship to other drug moieties such as FTC-TP and FTC and TFV. For instance, the ratio of TFV-DP to FTC-TP may be used as a predictor of "2" versus "4 dosing per week. A proportional odds logistic approach which allows for an ordinal outcome and extensions which control for correlations between repeated measurements on a subject will be utilized in SAS or R statistical software. In addition, we will employ PK models (see Aim-1) to simulate TFV-DP to FTC-TP ratios for other dose regimens and estimate cut points for predicting non-daily dosing patterns.

2. Examine relationships among drug concentrations in plasma, RBC, DBS, and PBMC.

We will use mixed and non-linear mixed effects models to determine if concentrations in various matrices are related.

3. Evaluate the influence of demographics, biological on drug concentrations.

   Kruskal-Wallis parametric test will be used to compare demographics and key study variables (e.g., age, pregnancy, HCT, contraception use, study arm, BMI, eGFR). Non-linear mixed effects models also will be used to probe covariate effects on PK. Secondary analyses are considered hypothesis generating and will not correct for multiple comparisons.

4. Compare drug concentrations in DBS from fingerstick versus transferring blood from blood tubes.

   Since these are paired DBS samples, we will compute the ratio of TFV-DP in the two samples and a mixed model on the natural log of the ratio will be utilized to determine if CI is within 0.8 and 1.25, indicating equivalence. Bland-Altman analyses will also be evaluated.

7.4 Sample Size Considerations

The overall sample size was chosen to have up to 18 cisgender women in each relevant group (overall, n=54 non-pregnant cisgender women) sufficient to provide precise information on drug concentrations and to balance feasibility, efficiency, and provide robust TAF/FTC data in DBS for cisgender women. The sample size for drug concentration parameters is based on ensuring precision in the estimates to accurately describe the concentration kinetics of TAF/FTC in non-pregnant cisgender women and is consistent with multiple DOT PrEP studies done in US populations[43, 44]. The precision desired is a mean TFV-DP in DBS at steady state within ±15% of the true population mean. The mean (± standard deviation) TFV-DP at steady-state in HIV-uninfected US cisgender men and cisgender women following directly observed doses of 25 mg TAF/200mg FTC once daily for 12 weeks was 2381 ± 601 fmol/punches [coefficient of variation (CV) of 25%] (*Anderson et al*)[43]. Based on this variability and assuming average TFV-DP results are normally distributed, to be 90% confident that the DBS TFV-DP sample mean is within 15% of the true mean, a sample size of 15 participants is required for non-pregnant cisgender women with conservative assumptions. With the planned enrollment of 18 cisgender women per group for this study, even a 10% non-completion rate at 8 weeks of DOT therapy, we provide ample data to estimate steady-state means to within 10% in cisgender women.

7.5 Randomization and Blinding Procedures

The study design will be an open-label, randomized study with three arms. The randomization assignment will be made at enrollment if the participant is eligible and agrees to enroll. Randomization will be according to the PrEP dosing frequency and vaginal tissue collection plan (either sampling day 4 or day 7) 1:1:1 fashion programmed by the study statistician and generated from REDcap.

The allocation of participants for the 3 study arms will be the following:

	2 doses per week	4 doses per week	7 doses per week	Total
Total	**18**	**18**	**18**	**54**

8 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will be reviewed and approved by the University of Washington Human Subjects Ethical Committee and the Scientific and Ethics Review (SERU) Committee of the Kenya Medical Research Institute responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

8.2 Informed Consent

In obtaining and documenting informed consent, the investigators will comply with all applicable local and/or domestic regulatory requirements and will adhere to Good Clinical Practices and to all ethical principles from the Declaration of Helsinki. A trained research staff person will conduct the informed consent process. Written informed consent will be obtained individually from each participant. Staff will explain the study, read the consent form, and answer any questions the participant may have. Consent information will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. We will translate the forms into the local language (Kiswahili) and verify the accuracy of the translation by performing an independent back-translation. The consent process will occur either in English or the local language (Kiswahili) depending on the participant's preference. We will perform paper-based and/or electronic-based consenting of participants. For the electronic version, we will program the complete consent form with signature pages onto tablets and participants will read along on the tablet during the consenting process. The study team member conducting consent will allow the participant time to ask any questions that they may have before signing the consent form. After we have ensured that participants have read and understood the consent forms, we will ask them to append their signature on the tablet. The signature will be stored electronically. In addition, any participant who wants their consent form to take home will have a paper copy printed and given to them. At each visit after enrollment, participants will have the opportunity to ask questions and the study staff will remind them their participation is voluntary. Participants will be informed that they may withdraw from any of the research procedures at any time, without it affecting the care they receive at the clinic.

8.3 Voluntary Participation

The consenting process will emphasize and give information that study participation is voluntary and that the participant can withdraw from the study at any time without losing the care they would otherwise receive.

8.4 Potential Risks to Human Subjects

Safety assessment will be measured in all participants: serious adverse events (SAEs), related Grade 3 and 4 AEs and discontinuations, and side effects. The medical risks of blood collection and vaginal tissue collection are small, with some anticipated mild discomfort from vaginal speculum insertion, and venipuncture. Participants may become embarrassed, worried, or anxious while undergoing pelvic exams for collection of samples.

Risks related to non-daily TAF-FTC PrEP dosing

Descovy® is approved by the U.S. Food and Drug Administration for PrEP use in cisgender men and transgender women[18]. However, Descovy® is not yet indicated in at risk cisgender women because the effectiveness in cisgender women has not been evaluated. Only daily FTC/TDF PrEP is currently approved for PrEP in cisgender women but large studies of Descovy® (F/TAF) PrEP for cisgender women are currently planned or ongoing in African cisgender women. We have carefully considered the risk for TAF-FTC PrEP and non-daily dosing (i.e., 2 or 4 doses per week) in cisgender women, including the potential for risk of HIV infection. The non-daily dosing is needed to help investigate and demonstrate dose proportionality of TFV and TFV-DP concentrations. For people living with HIV, Descovy® has been approved by the FDA for treatment of HIV in combination with other antiretroviral drugs since 2016[20], with very favorable safety profile compared to FTC/TDF. As detailed in the eligibility section, to minimize risks

only cisgender women at low risk of HIV based on the Kenya guidelines for PrEP will be enrolled and cisgender women will receive a full package of HIV prevention, including risk reduction counseling, condoms and STI treatment at each visit. We will also perform monthly HIV testing. We will use Kenya national PrEP guidelines to guide identification of cisgender women at elevated risk of HIV to guide recruitment into this study. Cisgender women found to be at risk for HIV through the screening process will be given PrEP at the clinic if interested or referred at their clinic of choice. Each visit will include risk-reduction counseling for all cisgender women. All participants in this study will have HIV test at baseline and then every 4 weeks and study drug will be immediately discontinue in case of seroconversion.

Risks related to TAF-FTC PrEP

Study medication risks and side effects related to TAF-based PrEP include: occurring in a minority of individuals taking PrEP - gastrointestinal intolerance, such as nausea, diarrhea or vomiting, flatulence typically during the first month after PrEP initiation; rare but serious side effects of lactic acidosis/ severe hepatomegaly with steatosis, renal impairment, including cases of acute renal failure and Fanconi's syndrome (renal tubular injury with severe hypophosphatemia), increase in bone metabolism leading to osteopenia, and hypersensitivity reaction. Because TAF achieves lower blood concentrations but higher concentrations in tissue after dosing, these risks are hypothesized to be lower compared FTC/TDF PrEP, the currently approved oral PrEP regimen.

Risks from vaginal biopsy

Vaginal tissue biopsy is an in invasive procedure and we have carefully considered the risk involved including some discomfort, pain and potential for bleeding and burden on cisgender women. Sampling vaginal tissue is important to fully characterize HIV protection in cisgender women since it is a tissue of relevance to the acquisition of HIV infection for cisgender women and will help to define early drug kinetics and how soon drugs accumulate in vaginal tissue from PrEP initiation until steady state. To minimize risks, we have carefully considered sampling schedule to minimize risk associated with this procedure and burden on cisgender women: Each participant will provide only one biopsy in a 4-week period by sampling unique cisgender women (i.e., for each planned tissue sampling visit different cisgender women will be sampled at day 4 and day 7). All participants will provide a vaginal tissue sample for week 4 and 8.

Social harm and stigma risks

We have considered the risk of social harm related to both DOT study medication use and frequent clinic visits, including risks of depression/anxiety and disclosure and stigma. Our extensive experience with successful and safe longitudinal follow-up of cisgender women at risk mitigates some of this risk, and we will measure social harms and provide/refer services when harms are reported. Participants also may become embarrassed, worried, or anxious while completing surveys or interviews regarding sexual behavior and acceptability. Counseling will be provided by clinical study staff who have been trained in specific issues related to STI/HIV risk, PrEP, STI/HIV acquisition, and care of HIV infected cisgender women, including stigma, blame, methods to avoid transmission, and available support services.

Behavior disinhibition risks

The potential for behavior disinhibition may exist as a result of PrEP and is an important outcome, especially given the potential for some participant to receive less than daily dosing of PrEP. This study is specifically recruiting cisgender women at low risk of HIV, which reduces this risk. Nevertheless, we will use brief standardized questionnaires, which we have used for prior studies in cisgender women to explore partner number, sexual frequency, and condom use over time.

Privacy and confidentiality risks

Although study site will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others. For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families

and/or communities. We have extensive experience with the strategies to minimize the potential for social harms in populations participating in HIV prevention studies.

Risks from other study procedures

Blood for safety labs and study pharmacokinetic samples will be collected from each subject during the study period. Blood will be collected from an arm vein and by fingerstick. Risks of blood draws include pain when the needle or lancet pierces the skin, bruising, and/or infection. The blood volumes are well below the maximal volumes set for blood donations and clinical research in 18 weeks. Approximately 100 strands of hair will be cut from the back portion of the scalp on multiple occasions. This could leave a noticeable spot from where the hair was cut.

8.5 Approaches to Minimize Risks

Protection of risks related to non-daily PrEP dosing

We have carefully considered the risk associated with using non-daily dosing for PrEP (i.e., 2 or 4 doses per week) in non-pregnant cisgender women and the potential for behavior disinhibition as a result of PrEP is an important outcome. We will make all efforts to enroll only healthy cisgender women volunteers deemed at low risk for HIV. We will rely on Kenya national guidelines as well as published HIV risk scores (Voice risk) to guide identification of cisgender women who may be at elevated risk of HIV to guide recruitment into this study ─those found to be at elevated risk for HIV will be immediately linked for PrEP and other prevention services here at the Thika site or at the participants' clinic of choice. Each visit will include risk-reduction counseling for all cisgender women. All participants in this study will have an HIV test at baseline and then every 4 weeks, with immediate discontinuation of PrEP in case of HIV seroconversion.

Protection against risks related to TAF-FTC PrEP

All participants will have HIV testing, creatinine testing, hepatitis B, and urine pregnancy testing at baseline. Only cisgender women with creatinine clearance >60 mL/min and uninfected with hepatitis B will be enrolled. Testing of volunteers for HBV-infection is conducted to protect subjects from HBV-associated hepatitis flares when study drugs are withdrawn. Breastfeeding will not be allowed to prevent risks to nursing infants. We will exclude subjects who have serious underlying illnesses such as cancer and heart disease. All participants will be counseled about potential side effects at enrollment and at each follow up visit, and they will be reminded that the side effects are self-limiting within 1-2 weeks. Subjects will be followed with clinical laboratories at entry and 10 weeks (serum creatinine, complete hematology, monthly pregnancy urine test) and more frequently with interviews to assess tolerability and safety over the course of the study, including during directly observed dosing. Participants will be tested for HIV infection at any point during the study as needed, and prior to and at the final visits of the dosing periods.

The most likely risks associated with TAF-FTC in HIV-negative persons appear to be reversible gastrointestinal complaints, headache, and/or weight decrease. These side effects are most likely mild and reversible.[45] There is a remote risk of serious side effects including renal injury, 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. We have designed the inclusion and exclusion criteria to exclude subjects who might be at higher risk of these toxicities. We have also designed a monitoring strategy for early detection of side effects and for quick study drug discontinuation, if needed, to protect subjects.

Protection of risk related to vaginal tissue biopsy

We have also carefully considered our sampling schedule to minimize risk associated with vaginal tissue biopsy and burden on cisgender women and will take the following measures: 1) Only low HIV risk non-pregnant cisgender women will provide vaginal tissue samples 2) Each participant will provide only one

biopsy in a 4-week period. We will sample cisgender women as two separate groups during the first week, i.e. half of participants on day 1 and the other half on day 7. This will ensure sufficient time between the week 1 and week 4 sample. All participants will provide vaginal tissues samples during weeks 4 and 8. Participants will be counseled to avoid sex in ~7 days after biopsy.

Reducing social harm risks
In addition to protecting the privacy of participants, as described above, we will monitor for social harms. Social harms will be recorded on separate case report forms. Severe unexpected social harms will be considered unexpected problems and reported to the IRB according to local regulations. Social harms will be included on summary reports for the PSRT, as described in this protocol.

Reducing risks behavior disinhibition
We will use brief standardized questionnaires, which we have used for prior studies in cisgender women to explore partner number, sexual frequency, and condom use over time. Each visit will include risk-reduction counseling for all cisgender women and cisgender women will be provided with condoms.

Reducing risks from other study procedures
Blood will be collected from an arm vein, and/or by finger stick, by trained staff at the study site according to standard medical procedures. Hematology will be monitored. The hair that is cut will be taken from underneath the top layer of hair to minimize the ability to see where the hair was cut from and to avoid sun-bleached hair.

All participants in this study will have an HIV test at baseline and then every 4 weeks. All data received at the University of Washington will be labeled only with participant ID number and no identifying information will be transmitted. The study team has extensive experience with counseling about HIV risk, PrEP (and ART), and strategies for HIV prevention in general. In addition to PrEP and STI treatments, condoms will be provided to all participants by the study site and will follow Kenya clinical guidelines. Counseling about safe sex and medication adherence for prevention will include messaging describing the benefits of all strategies, based on evolving available data and national policies for HIV prevention.

For data collection, standardized questionnaires will be used that will include questions on sensitive topics, including sexual behavior, and stigma. We have extensive experience with these questionnaires from our prior studies and the expertise and counseling resources required to attend to study participants. We have extensive experience with management of potential social harms, through our prevention studies. The risks from the anticipated activities will be no greater than in our previous studies; in fact, given the proven prevention benefits of PrEP and now normalized national roll-out in Kenya, risks are anticipated to be less than in some of our prior studies.

8.6 Benefits.
Participants will benefit from ongoing access to standard clinical care as part of this study. Additionally, participants or others may benefit in the future from information learned in this study, including its contribution to our understanding of HIV prevention and effective PrEP use in cisgender women in Africa. While enrolled in the study participants will have access to all services available to those not in the study, including access to counseling for reducing risk of getting HIV from their sexual partner, and provision of free condoms. For care and treatment that is not available at the clinic, study staff will inform and refer participants to other health facilities where care and treatment may be available.

8.7 Treatment for Injury
Participants will be asked to inform the clinic staff if they feel they have been injured because of taking part in the study. Injuries may also be identified during laboratory testing, medical histories, and physical examinations. Treatment for adverse events related to study participation will be provided by the treatment clinic. If treatment is required that is beyond the capacity of the clinic, the clinic staff will refer

the participant to appropriate services or organizations that can provide care for the injury.

8.8 Study Records

Study investigators will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. Study records include administrative documentation and regulatory documentation as well as documentation related to each participant enrolled in the cohort, including informed consent forms, data forms, documentations of all contacts with the participant, and all other source documents.

8.9 Confidentiality

Every effort will be made to protect participant privacy and confidentiality to the extent possible. At the pharmacy, clients will perform HIV self-testing in a private space within the pharmacy area to encourage privacy during the self-testing process. Records pertaining to clinical and programmatic provision of PrEP (i.e. not related to research) will remain at the public health clinic and maintained by MOH staff at clinic as per standard of care practices.

All research-related information will be stored securely at the research clinic in Thika. Research data collection, administrative forms, laboratory specimens, and other reports will be identified only by a coded number to maintain participant confidentiality. All research records that contain names or other personal identifiers, such as informed consent forms, will be stored separately in locked cabinets at the research clinic in Thika away from study records identified by code number. All local databases will be secured with password-protected access systems and only project staff with permission will have access to them. Data collected or abstracted from clinical forms during the course of this project will be entered electronically on tablets via REDCap collection software and transmitted to in aggregate to a web server via encrypted secure socket layer (SSL) and only accessible by authenticated users. All computers, tablets (used for data collection), and individual study databases will be encrypted, and password protected.

Participants' study information will not be released without their written permission, except as necessary for oversight by:

- Kenya Ministry of Health
- Kenya Medical Research Institute
- University of Washington
- University of Colorado
- Gilead Sciences
- U.S., local, and international regulatory entities

8.10 Reimbursement

Participants will receive reimbursement for their transport for visiting the clinic, and 400 KSh for their time and effort at each scheduled study visit. All visits that include collection of vaginal biopsies will be reimbursed 2000 KSh and visits that include collection of vaginal swabs only will be reimbursed 1000 KSh.

8.11 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

8.12 Reports of Sexual Abuse

Reporting requirements and confidentiality of minor's information should be detailed in site specific consents/assents and SOPs.

8.13 Study Discontinuation

The study also may be discontinued at any time by government or regulatory authorities, or site IRBs/ECs.

Subjects may withdraw from the study at any time. Depending on the time point and circumstances of a subject's withdrawal they will be asked to complete/offer an "Early Discontinuation/Exit Visit" to confirm safety and health status as the time of withdrawal. The study investigators 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. Discontinuation of a subject by the PI/Co-I(s) could be a result of but is not limited to the following:

- Subjects who become incarcerated while on the study.
- Subjects who acquire other infectious diseases (i.e. not HIV) while in the study will be reviewed by the PI/PSRT to confirm subject is still considered low-risk for HIV infection (See Exclusion criterion) This determination will be done by the PI/study physician.
- Subjects who are deemed to be non-compliant with the study medication(s) and/or procedures (e.g. 2 consecutive missed study visits or medication doses) may be discontinued from the study by the PI.
- Permanent study drug discontinuations for toxicity were described above. These participants will be followed until the completion of scheduled protocol study duration.
- Subjects who require an exclusionary medication during the study will be discussed among the PSRT. Participant's continued study involvement will be determined the PSRT and PI's.

The PSRT will be consulted if and when these circumstances arise.

9 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Laboratory evaluations and specimen collections

The following safety and monitoring laboratories will be collected at regular intervals during the study as described above: complete hematology panels, pregnancy tests (urine), HIV tests (rapid or regular), serum creatinine (estimated creatinine clearance), and HBV surface antigen test. The HIV and HBV tests will be used to screen HIV-negative volunteers for inclusion in the study. The tests are provided according to established laboratory procedures at site. These clinical laboratories/sites conform to CAP and/or CLIA-regulations, and the results will be posted to the participant's medical record as positive or negative.

All pharmacokinetics samples will be collected, processed, and stored according to standard operating procedures developed by the Colorado Antiviral Pharmacology Laboratory. On each pharmacokinetics sample visit day, samples will be collected without regard to the dosing time within each day (i.e., sampling is at convenience times rather than troughs). The only exception will be at the entry visit, where samples are to be obtained pre-dose. We will take a comprehensive approach to establish benchmark adherence-concentration thresholds for cisgender women using daily DOT TAF/FTC PrEP by collecting samples for pharmacokinetic measurements in multiple biologic matrices: plasma, whole blood, DBS, PBMCs, vaginal swabs, and vaginal tissue and by archiving urine and hair samples. All cisgender women will contribute to this comprehensive assessment during the study participation duration of up to 18 weeks (10 weeks of DOT PrEP and 8 weeks post DOT PrEP for post drug kinetics). Within each group, we will collect pharmacokinetic samples (plasma, whole blood, DBS, PBMCs) to measure the respective concentrations of TAF/FTC moieties at day 4 and weekly up to 8 weeks with daily DOT PrEP dosing and vaginal tissue at day 4, week 1, 4, and 8.

9.2 Specimen preparation, handling, and shipping

All pharmacokinetic samples will be collected, processed, stored, and shipped according to standard operating procedures developed by the Colorado Antiviral Pharmacology Laboratory. Specimens will be collected by skilled study personnel in accordance with local study site policies and procedures. All specimen collections are described in this protocol.

Samples that are shipped to outside entities are regulated by the International Air Transportation Association. Such training and certification of study personnel is handled through the University of Colorado Denver Environmental Health and Safety Division. This training is required on a biannual basis. This protocol follows IATA Guidance 48-DGR when air transport is required.

9.3 Specimen Storage and Possible Future Research Testing

We will store blood, urine, hair, and genital specimens collected in this study for future testing. Study participants will be asked to provide written informed consent for their specimens to be stored after the end of the study for possible future testing related to the study objectives. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed after all protocol-related testing has been completed; sample destruction must be coordinated with the protocol leadership and PSRT.

9.4 Quantification of drug concentrations

Drug concentrations will be determined using analytical methodologies (such as liquid chromatography tandem mass spectrometry (LC/MS) methods) described previously [6, 46] and validated for each biological matrix of origin (plasma, whole blood, DBS, PBMCs) by the Colorado Antiviral Pharmacology Laboratory (CLIA 06D1094710; PI: Dr. Anderson)[47-50]. The CLIA laboratory participates in the NIH-supported Clinical Pharmacology Quality Assurance program of assay method external review and approval and periodic proficiency testing[51]. All assays were validated based on the FDA recommendations for Industry, Bioanalytical Method Validation and met all acceptability criteria. Validation metrics include precision, accuracy, stability, and matrix effects. The laboratory has a long history of innovative and lasting contributions to antiviral clinical-translational research including development and validation of methodology for intracellular TVF-DP and FTC-DP in various cell types from human subjects. Data from this assay was used to support the pharmacology measurements for the iPrEx[6] and DISCOVER studies that helped lead to the FDA-indication of daily TDF/FTC and TAF/FTC PrEP for MSM and the pharmacokinetic study that developed an estimate of protective concentrations of tenofovir as a surrogate of HIV protection in MSM. We will use the same methods to support the current proposal. These assays have been implemented in a number of preclinical, clinical, and registration trials.

9.5 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 waste products 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. All dangerous goods materials, including diagnostic specimens and infectious substances, will be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

10 ADMINISTRATIVE PROCEDURES

10.1 Study activation

Pending successful protocol registration and submission of all required documents, the protocol chair will "activate" a site. Study implementation (screening and enrollment) may not be initiated until a study activation notice is provided to the site by the protocol chair. In addition, if study "activation" is determined to be necessary for any subsequent amendments, study implementation may not be initiated until a study activation notice is provided to the site by the protocol chair.

10.2 Study coordination

Study implementation will be directed by this protocol. Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the protocol team. The Protocol Co-Chairs and Protocol Biostatistician will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

10.2.1 Data storage and management responsibilities

Data will be managed by study personnel at the site and University of Washington. Clinical and baseline data collected during the course of this study will be collected electronically via REDCap data collection software. Quantitative survey data, clinic and pharmacy records will be abstracted in real time to tablet-based case report forms and entered into an electronic database in REDCap. Automated legal range checks will be programmed to reduce data entry errors and internal quality control reports will be run monthly. Our team has experience using this data capture method in other studies of HIV prevention. Data will be uploaded daily via REDCap Survey and will be transported via secure socket layer (SSL) and only accessible by authenticated users. Weekly reports will be generated to monitor study progress and troubleshoot problems. All computers, tablets (used for primary data collection), and individual study databases will be encrypted, and password protected. Participants will be assigned a non-identifiable study code upon enrollment. Study analysts will receive only coded data. The links to patient identifiers will be retained in a password protected file on an encrypted computer.

10.2.2 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, IRBs, and funder 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.

10.2.3 Data monitoring

The study team will review project progress in the weekly operational meeting and monthly for an all-team meeting; teleconference or internet-based mechanisms (Skype, Zoom) will be used for these meetings. The Seattle-based data manager will conduct data monitoring weekly via routine operational reports to track participant accrual, retention, completion of study procedures, and a check of eligibility criteria for all enrolled participants. Data quality checks will be conducted monthly to identify missing values, inconsistent information, and unacceptable lags between the timing of study visits and data updates to the web-based data entry platform. Twice per year, the PI and a Seattle-based research manager will travel to study site in Kenya to conduct an on-site assessment of data and laboratory quality; site Co-Investigators will perform day-to-day oversight of quality for the project.

The study and updated information will be registered on ClinicalTrials.gov according to UW Office of Sponsored Program and NIH policies.

10.2.4 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 an SOP.

10.3 Study monitoring

Study monitors will visit the site to:

- Verify compliance with human subjects and other research regulations and guidelines;

- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- Confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., ICFs, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the UW, NIAID, site IRBs/ECs, US regulatory authorities (OHRP), Kenya MOH, PPB, and other U.S., local, and international regulatory entities. A site visit log will be maintained at each study site to document all visits.

The International Clinical Research Center (ICRC) at the University of Washington will provide regular study monitoring for the Thika site. The Study Monitor will be a Senior Research Manager at ICRC. The Research Manager will have a graduate degree and will be experienced in site monitoring activities. The site monitor will conduct on site reviews of source documents, participant records, regulatory files, facilities, laboratories and the dispensing pharmacy. The signed informed consent documents will be made available for review for compliance with GCP requirements. Original source documents will be made available to verify all inclusion/exclusion criteria. Individual participant's source documents will also be available for review and comparison to protocol requirements and the completed case report forms (CRFs). Through this detailed review, monitoring will focus on the following key processes of the study:

- Informed consent process
- Study eligibility criteria met for all participants
- Timely completion of study CRFs
- Sample collection and handling in accordance to Protocol and SOP(s)
- Review of data management procedure
- Reporting of adverse events and protocols violations according to SOP(s)
- Follow up assessments and procedures
- Product accountability
- Regulatory documents on file

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by the UW or funder. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity[52]. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 compliant may be utilized.

10.4 Investigator's Records

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g. when all subjects are off study);
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;
- All analysis of identifiable private information described in the IRB/EC-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including ICFs, locator forms, CRFs, notations of all contacts with the participant, and all other source documents.

10.5 Use of Information and Publications

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.

10.6 Resource sharing and dissemination plan

10.6.1 Resource Sharing:

For all data generated during the course of this project, we will follow the prevailing standards and guidelines in documenting and depositing datasets. We will make quality-controlled raw data as well as processed data used in publications available. As described in the grant application, protocols and workflows will be implemented exactly as described and documented such that other groups will be able to precisely reproduce results from the raw data.

The study personnel assigned to the project, including KEMRI-based and University of Washington-based investigators, will disseminate results from this research through presentations at public lectures, scientific institutions and meetings, and/or publication in major journals.

10.6.2 Data Sharing Plan

Intellectual property, data and materials generated under the project will be disseminated in accordance with KEMRI, University of Washington, University of Colorado, and Gilead policies. Depending on such policies, materials may be transferred to others under the terms of a material transfer agreement. Access to databases and associated software tools generated under the project will be available for educational, research, and non-profit purposes. Such access will be provided using web-based applications, as appropriate. Publication of data shall occur during the project, if appropriate, or at the end of the project, consistent with normal scientific practices. Research data that documents, supports, and validates research findings will be made available after the main findings from the final research data set have been accepted for publication. Such research data will be modified to prevent the disclosure of personal identifiers to remain in compliance with the Protection of Human Subjects guidelines.

10.6.3 Collaborative research

The proposed project is a collaborative effort between Gilead, UW, UC, and KEMRI. The aforementioned institutions will jointly share ownership of the data. Authorship on publications, conference presentations, abstracts and other materials generated from this program will reflect contribution to design, execution and analysis of the program data.

10.6.4 Dissemination plan

Dissemination of study results will follow principles of good participatory practice. Study results will be disseminated through presentations to stakeholders and policymakers and published in conference abstracts and peer-reviewed journals. We will disseminate the results from this research as broadly as possible. First, we will publish our results in Open Access journals, if appropriate. Second, we will post

author PDFs of our manuscripts on our respective websites in accordance with the copyright rules of the journals.

10.6.5 Presentations

We expect that all the research personnel will attend national conferences periodically and present the results from this research to the scientific community. Because of the multidisciplinary nature of the work, different group members will present at various conferences, such as the Conference on Retrovirus and Opportunistic Infections, International AIDS Society, and Kenya-based conferences, which focus on the appropriate aspects of our research.

The study team for this project is committed to the public dissemination of clinical trial results to trial participants, local stakeholders in Kenya, the global scientific community, and US, Kenyan, and global policymakers. Dissemination of study results will follow principles of good participatory practice. The clinical trial will be registered with ClinicalTrials.gov prior to initiation and results will be updated there in a timely fashion. Results will be published in conference abstracts and peer-reviewed journals. Study results will be disseminated through presentations to local stakeholders and policymakers in Kenya, including the Ministry of Health.

11 TIMELINES

We have planned for an efficient time-sensitive two-year project, given the timely nature of the question (Table 7).

Table 7

		Project Years	Y1				Y2			
AIM	**MILESTONE**	**Quarter**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
Funding	Funding Announced									
Protocol Planning	Protocol Development									
	IRB Submission, SOP development									
Protocol Execution	Enrollment, follow up in DOT study, pharmacokinetics sample collection									
	Regulatory application from MOH and IRB to ship samples									
	Ship DOT pharmacokinetic samples									
	Test DOT study samples									
	Statistical analyses and compilation of full spectrum of results									
Dissemination	Writing and results dissemination									

12 EXPECTED APPLICATION OF RESULTS

The study will be the first to define TAF-PrEP adherence-concentration thresholds in Africa cisgender women, a population facing significant burden of incident HIV infection. Knowledge gained from the proposed study will include key concentrations of TAF-PrEP medications associated with HIV protection and the required adherence to achieve those concentrations for cisgender women. In addition, data from this work will help to estimate the quantitative concentrations of PrEP medication associated with protection against HIV in cisgender women and adherence required to generate those concentrations. The results of this work will have immediate implications for the global TAF-PrEP programs among cisgender women.

13 STUDY LIMITATIONS

The study team recognizes potential limitation of the proposed work which may include: 1) Part of preliminary data are not from DOT studies and that observed effects might be due to correlation between MEMS and blood levels and not related to pharmacokinetic differences between US male and African cisgender women blood levels. However, we take confidence in fact that our pregnancy data from the same population have been replicated by the IMPAACT 2009 study; 2) Intensive sampling for individual PK parameters is not planned as that is well defined. DBS exhibits a long half-life and is not suited for intensive PK. Nevertheless, while plasma steady-state levels do not pinpoint the mechanism for PK differences, they will indicate whether or not recent PK exposure differs and by how much. Furthermore, population PK models will be developed to determine individual-level PK in plasma.

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15 APPENDIXES— STUDY CONSENT FORM TEMPLATES

Study Title: Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

Study Screening Informed Consent Form

Version 1.1, August 15, 2022

INVESTIGATORS

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Elizabeth Irungu	MBChB, MPH, PhD	Kenya Medical Research Institute	067 2222561
Catherine Kiptinness	B. Pharm, MPH	Kenya Medical Research Institute	067 2222561

STUDY LOCATION: The study will be conducted at Thika.

You are being asked to take part in a research study. The box below tells you important things you should think about before deciding to join the study. We will provide more detailed information below the box. Please ask questions about any of the information before you decide whether to participate. You may also wish to talk to others (for example, your family, friends, or your doctor) about this study, before agreeing to join.

Key Information for You to Consider

- **Voluntary Consent**. You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There are no penalties and you will not lose anything if you decide not to joint or if after you join, you decide to quit.
- **Purpose**. We are doing this research to find out more about the medication called Tenofovir alafenamide /Emtricitabine (TAF/FTC Descovy®). Descovy® has been shown to lower the chances of getting HIV in men.This is also called preexposure prophylaxis or PrEP. Research studies are ongoing to understand how Descovy® PrEP works to prevent in women. We want to learn more about the levels of PrEP in blood and other body parts when used by women.
- **Duration.** Your part of the study will last for up to about up to 4 ½ months; up to 2 and half months when taking medication and 2 months after you stop.
- **Procedures and Activities.** We will ask you questions about yourself including your medical and sexual history, and some blood samples will be collected. Should you be eligible and agree to participate, we will collect additional samples including blood, hair and fluids from your genital area.
- **Risks.** Most studies have some possible harms that could happen to you if you join. In this study, we expect that the primary risks will be some discomfort from sample collection, stress or discomfort from answering survey questions.
- **Benefits**. We expect some benefits from this study, as well. For you, we don't think that you may get direct benefit from being in this study. However, we will inform you about any test results that are done that could be useful to your health care.

- **Alternatives.** Participation is voluntary and the only alternative is to not participate.

INFORMED CONSENT

We are asking you to volunteer to have screening tests to find out if you are eligible for a research study. This study is open to women who do not have HIV. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, and what would be expected of you if you agree to be in the study. This study is being coordinated through the Kenya Medical Research Institute in Kenya and the University of Washington located in Seattle, Washington, USA. The study is being funded through the pharmaceutical company, Gilead Sciences, which makes Descovy®™. If you decide to participate in the research study, you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form if you choose to have. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

PURPOSE OF THE STUDY

Medication called Tenofovir /Emtricitabine (Truvada) can lower the chances for HIV-uninfected men and women to get the HIV virus. This is called preexposure prophylaxis or PrEP. Truvada PrEP is approved by the World Health Organization and the Kenya ministry of Health as one option to prevent getting HIV. A similar medication called Tenofovir alafenamide /Emtricitabine (Descovy®) has also been shown to work as well as Truvada PrEP to lower the chances of getting HIV in men . Research studies are ongoing to understand how Descovy® PrEP works in women in Africa. Other research studies have shown that the levels of drugs in blood after taking PrEP may be different in men and women. The purpose of this study is to find out more about the levels of TAF PrEP in blood and other body samples when used by women.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that we will discuss with you. Before you learn about the study procedures, it is important that you know the following:

- You do not have to be in this study if you do not want to join.
- You may decide not to take part in the study, or to withdraw from the study at any time.
- If you decide not to take part in the study, you can still join another research study later, if one is available and you qualify.

SCREENING PROCEDURES

Screening procedures will begin today, after you read, discuss, and sign or make your mark on this form. The screening procedures will include the following:

- The study staff will check your temperature and ask you questions about COVID-19 symptoms and people you been in physical contact with, to see if you have been exposed to COVID-19. Should the staff determine that you have been exposed, they will follow the recommended Ministry of Health guidelines in referring you for healthcare. We will reschedule your visit for another time based on these guidelines.
- The study staff will ask you where you live and other questions about your sexual practices, medical history and, pregnancy and contraceptive use intentions.
- A clinician will perform a physical exam, urine pregnancy test and review your medication and COVID-19 vaccination status.

- We will counsel you about HIV and other infections passed during sex, and how to avoid these infections.
- Even if you have recently been tested for HIV, we will need to repeat the HIV test today as part of screening for the study. The study staff will talk with you about the HIV test, what it may mean to know your HIV test results. You must receive your HIV test results to be in the research study.
- If you do not have HIV infection:
  - We will ask you questions about your medical and sexual health history, and pregnancy intentions.
  - You will be asked to give us permission to obtain a blood sample for laboratory tests. No more than 21 ml (about one and quarter tablespoons) will be collected for all the screening tests, including the HIV test. Some of the blood sample will be used to test for hepatitis B infection and some will be used to test the function of your kidneys.

The study staff will fully explain the study to you and answer any questions you have. You must have at least one other visit here at the clinic to learn about the study. If you decide to take part in the research study and found to meet all the requirements for the study, you will be asked to sign another consent form at another visit.

RISKS AND/OR DISCOMFORTS

You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may have a bruise where the sterile instrument (needle) goes into your arm. On rare occasions, infection may occur at the site of blood draw or fingerstick. All efforts will be made to ensure this doesn't happen by using standard clean and sterile procedures for drawing blood. In the unlikely event that the infection occurs at the site of blood draw, trained clinicians will help you get the necessary treatment or refer you the appropriate health facility, at no cost to you.

You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against HIV and other infections passed during sex, and your test results. You may become worried or anxious while waiting for your test results. Having the screening tests, talking about HIV, and finding out your results could cause problems between you and your partner. The counseling that you will receive through the study staff will help you understand the results. Trained counselors are available through the study who will help you deal with any feelings or questions you may have.

The study staff will make every effort to protect your privacy and confidentiality while you are having the screening tests. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.

BENEFITS

You may get no direct benefit from the screening tests. However, you will get counseling and testing for HIV. You will get information on how to protect against HIV and other infections passed during sex. You will get free condoms. For other health problems that cannot be treated at this clinic, the study staff will tell you about other places you can go for treatment. The study staff will also tell you about other places that provide HIV prevention and care services. You may also contribute to understanding HIV prevention in women in Africa, which will help others in the future.

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you by the study will be

free of charge.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY
You may be removed from the study without your consent for the following reasons:

- The research study is stopped or canceled.
- You are not willing to find out your HIV test result.
- You are put in prison
- You are not able to attend clinic visits or complete the screening tests.
- The researchers may determine that this study may not be a good fit for you
- The study staff feels that having the screening tests would be harmful to you.

ALTERNATIVES TO PARTICIPATION
There may be other studies going on here or in the community that you or your partner may be eligible for. You may also be able to access PrEP through other research studies going on here or in other clinics in the community. If you wish, the study staff will tell you about other studies or healthcare facilities which offer PrEP that we know about. There also may be other places you can go for HIV counseling and testing. We will tell you about those places if you wish.

REIMBURSEMENT
You will receive reimbursement for your transport for visiting the clinic, and 400 KSh for your time and effort at each scheduled study screening visit.

CONFIDENTIALITY
All study staff will make every effort to protect the privacy of your personal information but cannot completely guarantee this. Any sample from you or information about you will be identified only by code and not by name. The link between your name and code will be kept in a secure location at the clinic only. The U.S. Food and Drug Administration (FDA) reserves the right to review study data that may contain identifying information. Any publication of this study will not use your name or identify you personally. Certain people and organizations will need to see, copy, and use your health data so that they can do their part in the study. They are called 'authorized users'. The records of your tests may be reviewed by study staff and representatives of the following authorized users:

- Kenya Medical Research Institute (KEMRI) Scientific and Ethics Review Unit (SERU)
- Kenya Pharmacy and Poisons Board
- University of Washington, including study monitors
- Gilead Sciences
- Kenya Ministry of Health
- University of Colorado
- Other local, U.S. and international regulatory entities

The review of records may be done on-site or remotely through secured authorized computer programs. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity.

FUTURE USE OF DATA
The information that we obtain from you for this study might be used for future studies. We may remove anything that might identify you from the information. If we do so, that information may

then be used for future research studies or given to another investigator without getting additional permission from you. It is also possible that in the future we may want to use or share study information that might identify you. If we do, the Scientific and Ethics Review Unit (SERU) and the researchers' appropriate ethical committee or institutional review board will decide whether or not we need to get additional permission from you.

RETURN OF RESEARCH RESULTS

You will be made aware of the results of rapid HIV, hepatitis B, creatinine, blood count, and urine pregnancy tests done as part of screening procedures for research study. If any results are abnormality and you will be referred to health facility where can get it the treatment or to a health facility of your choice.

RESEARCH-RELATED INJURY

We do not anticipate any research related injury. However, if you feel you are injured from participating in this study, you will be offered care at the study clinic, free of charge. For research related injury, please call the 24-hour emergency number: 0736464299.There is not a program of monetary compensation through this institution. If you need medical care that we cannot provide, we will refer you to the appropriate services or organizations that can provide care for the injury. You do not give up any legal rights by signing this consent form. You do not waive any right to seek payment or give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, or if you have a research-related injury, you should contact Catherine Kiptinness at the Thika Partners in Prevention Study clinic at Tel. 067 2222561/0725 641110. For research related injury, please call the 24-hour emergency number: 0736464299. If you have questions about your rights as a research participant, you should contact: The Head, Scientific and Ethics Review Unit (SERU) Kenya Medical Research Institute (KEMRI), P.O Box 54840-00202 Nairobi Phone No. 0717719477, Email address: seru@kemri.org. A description of this study will also be available on https://www.clinicaltrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

STATEMENT OF CONSENT AND SIGNATURES

I have read the study enrollment consent for this study, or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the study is voluntary. I understand that if I decide to join the study I may withdraw at any time. By signing this form, I do not give up any rights that I have as a research participant.

Participant Name (print)	Participant Signature/Thumbprint	Date
Study Staff Name	Staff Signature	Date

Witness Name (print)	Witness Signature	Date

Participating in future research studies

We would like to contact you in the future to see if you would be interested in participating in future studies. Please indicate below if you are willing to be contacted about any future research studies.

☐ Yes: I agree to be contacted about future research studies

☐ No: I do not want to be contacted about future research studies

Participant Name (print)	Participant Signature/Thumbprint	Date
Study Staff Name	Staff Signature	Date
Witness Name (print)	Witness Signature	Date

Study Title: Safety and Pharmacokinetics of TAF-FTC Pre-exposure Prophylaxis in Kenyan Cisgender women

Study Enrollment Informed Consent Form

Version 1.1, August 15, 2022

INVESTIGATORS

Investigator	Title	Institution	Telephone
Kenneth Mugwanya	MBChB, MS, PhD	University of Washington	001 206-520-3886
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Elizabeth Irungu	MBChB, MPH, PhD	Kenya Medical Research Institute	067 2222561
Catherine Kiptinness	B. Pharm, MPH	Kenya Medical Research Institute	067 2222561

STUDY LOCATION: The study will be conducted at Thika.

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Key Information for You to Consider

- **Voluntary Consent**. You are being asked to volunteer for a research study. It is up to you whether you choose to participate or not. There are no penalties and you will not lose anything if you decide not to joint or if after you join, you decide to quit.
- **Purpose**. We are doing this research to find out more about the medication called Tenofovir alafenamide /Emtricitabine (TAF/FTC or Descovy®). Descovy® has been shown to lower the chances of getting HIV in HIV-uninfected men . This is also called preexposure prophylaxis or PrEP. Research studies are now ongoing to understand how Descovy® PrEP works to prevent HIV in women. We want to learn more about the levels of PrEP medication in blood and other body parts when used by women.
- **Duration.** Your part of the study will last for about up to 4 ½ months; up to 2 ½ months when taking medication and 2 months after you stop.
- **Procedures and Activities.** We will ask you questions about yourself including your medical and sexual history. At study specified visits you will take a tablet of PrEP in the presence of study staff and study specified samples including hair, blood, tissue and fluids from your genital area will be collected.
- **Risks.** Most studies have some possible harms that could happen to you if you join. In this study, we expect that the primary risks will be some pain and discomfort from sample collection, stress or discomfort from answering survey questions, and breach in confidentiality
- **Benefits**. We expect some benefits from this study, as well. For you, we don't think that you may get direct benefit from being in this study. However, we will inform you about any test results that are done that could be useful to your health care.
- **Alternatives.** Participation is voluntary and the only alternative is to not participate.

INFORMED CONSENT

We are asking you to volunteer for a research study about medication used to prevent HIV. This study is open to women who do not have HIV and are not pregnant. Before you decide whether to take part in the study, we would like to explain the purpose of the study, the risks and benefits, and what would be expected of you if you agree to be in the study. This study is being coordinated through the Kenya Medical Research Institute in Kenya and the University of Washington located in Seattle, Washington, USA. The study is being funded through the US drug company Gilead Sciences, which makes Descovy®. If you decide to participate in the research study, you will be asked to sign this consent form or make your mark in front of a witness. We will give you a copy of this form if you choose to have. This consent form might contain some words that are unfamiliar to you. Please ask us to explain anything you may not understand.

PURPOSE OF THE STUDY

Medication called Tenofovir /Emtricitabine (Truvada) can lower the chances for HIV-uninfected men and women to get the HIV virus. This is called preexposure prophylaxis or PrEP. Truvada PrEP is approved by the World Health Organization and the Kenya ministry of Health as one option to prevent getting HIV. A similar medication called Tenofovir alafenamide /Emtricitabine (Descovy®) has also been shown to lower the chances of getting HIV in men. Research studies are now ongoing to understand how Descovy® PrEP works to prevent HIV in women. Research studies have also shown that PrEP works only when taken as prescribed. Other research studies have shown that the levels of drugs in blood after taking PrEP may be different in men and women. The purpose of this study is to find out more about the levels of TAF PrEP in blood and other body samples when used by women. The results of this study will help to understand how Descovy® works in women when used as PrEP to prevent getting HIV. Overall, approximately 54 women, all from Kenya, will be in the study. The samples and data that we collect in this study may help us learn more how these medications work to prevent HIV infection in women**.** All participants who agree to be in this study will be asked to provide data and samples for up to 18 weeks.

YOUR PARTICIPATION IS VOLUNTARY

This consent form gives information about the study that we will discuss with you. Before you learn about the study procedures, it is important that you know the following:

- You do not have to be in this study if you do not want to join.
- You may decide not to take part in the study, or to withdraw from the study at any time.
- If you decide not to take part in the study, you can still join another research study later, if one is available and you qualify.

STUDY PROCEDURES

If you decide to join the study, you will have study visits up to 18 weeks. At these visits, the study staff will confirm where you live and other questions about your sexual practices, medical history and, pregnancy and birth control use intentions. A clinician will also review your medication and vaccine history. If you are eligible to participate in the study, then the study team will randomly assign you by chance (like flipping a coin) to one of three study groups. The staff do not know ahead of time which group you will fall into.

At each clinic visit, the study staff will check your temperature and ask you questions about COVID-19 symptoms and people you been in physical contact with, to see if you have been exposed to COVID-19. Should the staff determine that you have been exposed, they will follow the recommended Ministry of Health guidelines in referring you for healthcare. We will reschedule your visit for another time based on these guidelines.

At study specified visits you will take a tablet of PrEP in the presence of study staff and study specified samples will be collected.

At enrollment you:

- Will be told the number of visits and numbers of doses of PrEP you will take every week. There are three groups of dosing of PrEP you may be assigned to. You may either be in a group that will take **two doses every week** or **four doses in a week** or **seven doses every week**. Only chance will determine which group you will be in.
- If you are assigned to **two (2) doses every week**, you will come to the clinic to take your medication on **Mondays and Tuesdays**.
- If you are assigned to **four (4) doses every week**, you will be asked to come to the clinic to take your medication on **Mondays, Tuesdays, Thursdays, and Fridays** of every week.
- If you are assigned to **seven (7) doses every week**, you will come to the clinic **every day of the week Monday to Sunday** to take your medication.
- Will be given a study follow-up calendar to help you remember study visits.
- Will be provided with a month supply (a bottle) of back-up medication to be used if you are unable to complete the visit in person at the clinic.

At enrollment and each study visit you:

- Will be given PrEP tablet medication to take in their presence (called directly observed therapy) at the clinic. All doses taken away from the clinic will still be directly observed by study staff via live video streaming on a smart cell phone or computer via WhatsApp. For doses taken via video streaming, you will be asked to open your mouth afterwards to confirm swallowing. You will be supported with reasonable internet bundles consistent with the SERU recommendation.
- Will be counseled about possible drug side effects.
- Will be asked questions about your health and medical history, sexual behaviors, and your feelings about taking medication for HIV prevention.
- Will talk with study staff about ways to avoid HIV and other infections passed during sex. You will be offered condoms.
- Will get medical care or referrals for medical care and other services if you need them.
- Will be asked to give updated information on where you live and how to keep in contact with you. The study staff will use this information to remind you of scheduled visits. If you don't return to the clinic on schedule, the study staff may try to contact you by phone or by visiting your home. They may try to reach you through the contact people that you list. If they talk to these people, they will not tell them why they are trying to reach you. If a home visit is done, study staff may ask you take study drug in their presence or provide some scheduled study samples.
- Obtain blood samples [up to 21 mL / about one and quarter tablespoon] at each of these visits.
- Provide a urine sample in a container [up to 10 mL / a little more than half tablespoon] at each of these visits

At enrollment, day 4, week 1, and then weekly up to week 10 visits:
We will ask your permission to obtain study samples at these visits. Study samples may include blood, urine, hair, and vaginal tissue. The samples will be used by study researchers for tests to determine the amount of study drugs in the samples. We will ask for your permission to:

- Obtain hair samples at week 4 and week 8. The hair sample will be about 50-100 strands (which is what we need for this test) and is less than you naturally lose from your head each day. We will test for PrEP drug levels in the hair sample at the end of the study. Your hair will not be stored in any way but destroyed after testing for the PrEP drug levels
- Obtain vaginal swab and biopsy at day 4, week 1, week 4 and week 8. Women who provide vaginal biopsy at day 4 will not have another biopsy at week 1 but will provide the remaining samples at week 4 and week 8. **When you provide a vaginal biopsy, you must abstain from sex for at least seven days.**
- Obtain a blood sample by finger prick [**week 1 (days 4 and 7), week 4 and week 8**].
- Provide urine for a pregnancy test at entry, week 4 and week 8 visits. If you become pregnant, you will stop taking the study drug and we will continue to follow you till the end of your pregnancy.
- Conduct HIV-1 rapid test at week 4 and week 8 visits.
- If you become infected with HIV, you will stop taking the study drug and we will then refer you to a nearby HIV care services or at a clinic of your choice for follow up at completion of this trial.
- If you withdraw or are withdrawn before the end of the study, we may ask you to complete a separate early exit visit, so that we can check you, to make sure you are healthy before your exit.

After 10 weeks of taking PrEP medication:
We will ask you to come in for two additional visits, where we will ask for your permission to obtain the following study samples:

- Blood samples [up to 21 mL / about one and quarter tablespoon] at each of these visits.
- Urine sample in a container [up to 10 mL / a little more than half tablespoon] at each of these visits

BIOMETRIC FINGERPRINT SCAN
To help us keep track of who is enrolled in our clinic, and who is coming for follow up visits, we will ask you to put either your right or left index finger on a small machine that will scan your fingerprint. This scan will be linked to a unique identification number and will be accessible only to study staff. We will take your fingerprint at each study visit. You are free to refuse to have your fingerprint taken and this will not affect your participation in the study. The fingerprint database will be destroyed after completion of active follow up in the study.

SPECIMEN STORAGE AND USE OF SAMPLES AND DATA FOR FUTURE STUDIES. We would like to save data from this study and samples of your blood, urine, tissue, and hair at the Thika clinic and the University of Washington for future research by us and by other researchers. Some samples will be shipped to our laboratories in Mombasa and Nairobi, Kenya for testing. For specialized tests that cannot be done in Kenya, your samples will be shipped to the University of

Washington, Ninth and Jefferson Building, 908 Jefferson Street, Seattle, WA 98104 and the Galloway Lab, FHCRC, 1100 Fairview Avenue N., C1-015, Seattle, WA 98109 and University of Colorado in the USA. **You will not receive any results that come from samples that are tested in the USA.** We will use these samples only for research related to HIV, sexually transmitted infections and reproductive health. This will include studies on HIV and STI prevention, how people respond to the medications used in this study or how the drugs interact with contraception, organism in genital areas or studies of variation in gene DNA of drug transporter. Gene studies will only be for studies related to proteins which transport drugs in the body (drug transporters) not for full genome wide sequencing.
This research is experimental, and these tests are not useful for your clinical care. Before your samples leave the clinic, they will be assigned a code and your name will not be on them. Your name will be linked to the code only at this clinic. If you do not want to have your samples saved for future research, you can still be in this study and your samples will be destroyed once testing for this study is completed. If you agree to store your samples now, but change your mind before the study ends, let the study staff know and we will make sure your samples do not get stored for future research. There will be no consequences for changing your mind. However, after the link between your samples and your name is destroyed, we will not be able to identify your samples. We will not sell your data or samples. Tests done on your samples may lead to a new invention or discovery. We have no plans to share money or other benefits resulting from such invention or discovery with you.

FUTURE USE OF DATA AND SAMPLES
The information and/or specimens that we obtain from you for this study might be used for future studies. We may remove anything that might identify you from the information and specimens. If we do so, that information and specimens may then be used for future research studies or given to another investigator without getting additional permission from you. It is also possible that in the future we may want to use or share study information that might identify you. If we do, SERU and the researchers' appropriate ethical committee or institutional review board will decide whether or not we need to get additional permission from you.

RETURN OF RESEARCH RESULTS
You will be made aware of the results of rapid HIV, hepatitis B, creatinine, blood count, and urine pregnancy tests done as part of research. Trained research staff will share the results with you in person during visits or through a phone call. You will also be made aware of results from batched baseline STI testing. If any results are abnormal, you will receive standard of care treatment here at the clinic in a timely manner. For treatment not available at the clinic, you will be referred to clinics where you can get it. Testing on blood drug levels or future studies will not be shared with you. This research is experimental, and these tests are not useful for your clinical care.

RISKS
You may become embarrassed, worried, or anxious when talking about your sexual practices, ways to protect against HIV and other infections passed during sex. If you are not now infected with HIV but become infected with HIV, this could make you worried or anxious. Talking about HIV and finding out your test results could cause problems between you and your partner. Trained counselors will help you and your partner deal with any feelings or questions you may have about

these issues. If your partner finds out that you are on PrEP, this may lead to disagreements or physical/verbal abuse. It may also lead to economic risks such as loss of income or financial support. We anticipate that these risks will be rare. If threats of violence arise, avoid confrontation and consider seeking help from family, friends, your other social networks or study staff.

The study staff will make every effort to protect your privacy and confidentiality while you are having the study procedures. However, it is possible that others may learn of your participation here and, because of this, may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job, or being accepted by your family or community.
Risks related to collection of study samples: This study requires the use of your blood. There will be some pain associated with the needle stick, but this will be only for a short period of time. There may be some bruising around the needle site and, although we will sterilize the site to minimize infection, there is a very minimal risk of infection at the site. You may feel discomfort or pain when your blood is drawn. You may feel dizzy or faint. You may also have slight discomfort or pain during the prick of your finger, and there is a small risk of infection, bleeding or bruising from the fingerstick.

Some people may be embarrassed about providing urine, hair, and tissue samples. There is also some discomfort associated with taking hair or biopsy specimens. The biopsy may feel like a pinch each time a sample is taken and may cause some cramping with it. Any pain or cramping occurring during the biopsy may be helped by relaxing and taking a few slow deep breaths. Some vaginal bleeding and a small amount of dark brown discharge are normal after the sampling. Abstaining from sex for at least 7 days after the biopsy, and taking the HIV-prevention drug, TAF/FTC, will help reduce your risk of HIV infection after having biopsies collected. **If you become pregnant during the study, you will not have a vaginal biopsy**. We will still perform vaginal swab, secretion collection, which are not a risk for the pregnancy.

Risks potentially related to the TAF/FTC PrEP medication: TAF/FTC PrEP medication is similar to TDF/FTC PrEP which is approved for PrEP in Kenya. You may have symptoms or adverse effects while participating in the study. The adverse effects that can occur in a small proportion of people taking PrEP are well known because the medication has been used by many people. These adverse effects are similar to those seen with TDF/FTC PrEP but studies have also shown that they may be even fewer in TAF/FTC. TAF/FTC PrEP medication is very safe but like any medication, some mild adverse effects are expected to occur in up to 1 in 10 persons who take TAF/FTC. These include headache, stomach upset, vomiting or loss of appetite. Occasional adverse effects may include mild problems of kidney function that are only detected by laboratory tests. Small changes in the mineral density of bones were observed in studies of people who were given TAF/FTC PrEP, but the changes in the mineral density of the bones did not cause any fractures, or other problems that bothered the patients. Other potential serious but rare risks of PrEP include kidney failures such as Fanconi's syndrome and hypersensitivity reactions.

Other adverse effects which have been seen persons who have advance HIV infection and have used TAF/FTC together with other drugs for treatment include:

- Increase in body fat around the waist and stomach area, and back of the neck

- Thinning of the face, legs and arms
- Breast enlargement
- Gas, loose or watery stools
- Generalized weakness
- Dizziness
- Depression
- Rash
- Allergic reaction: symptoms may include fever, rash, upset stomach, vomiting, loose or watery stools, abdominal pain, achiness, shortness of breath, a general feeling of illness or a potentially serious swelling of the face, lips, and/or tongue
- Muscle pain and muscle weakness
- Sleeping problems
- Lactic acidosis has occurred in some HIV-infected persons taking PrEP, in combination with other drugs. Lactic acidosis is a condition that can produce shortness of breath, nausea, and liver failure. This is a serious adverse effect of some medications used for HIV infection. Hypersensitivity reactions
- serious but rare risks of kidney failures such as Fanconi's syndrome .

These adverse events are very rare and unlikely to occur in HIV uninfected persons use FTC/TAF PrEP. **If you have these symptoms, or any other symptoms that concern you, the study staff will evaluate your symptoms and determine whether you should stop your PrEP pills.** You will be given a telephone number where the study doctors will be available 24 hours a day, 7 days a week.

Risk of acquiring HIV infection:
Only daily TDF/FTC PrEP is recommended for use to prevent HIV in men and women in Kenya. Descovy® PrEP is not yet approved for use to prevent HIV in women**.** In this study you may receive non-daily dosing of Descovy® PrEP which doesn't provide sufficient protection. You may be exposed to get HIV from sexual partners you may have. It is very important to use all the known strategies to prevent getting HIV, like using condoms for all sexual relations and keeping your number of sexual partners low. Each visit you will get risk-reduction counseling for ways to protect yourself. You will have an HIV test every 4 weeks. If we find that you have HIV, PrEP will be immediately discontinued. You will be started on free HIV treatment immediately as per the Kenya national guidelines and we will then refer you to a nearby HIV care services or at a clinic of your choice for follow up at completion of this trial.

New findings
We will provide you with any new information that we learn during the study, which might affect your willingness to participate.

BENEFITS
You may get no direct benefit from being in this study. We will inform you about any test results that are done that could be useful your health care. You or others may benefit in the future from information learned in this study. You also may get some personal satisfaction from being part of research on HIV. While enrolled in the study you will get all services available to those not in the study such as access to oral PrEP (which is known to help prevent HIV infection), counseling for reducing your risk of giving HIV to or getting HIV from your sexual partner, and free condoms. For

care and treatment that is not available at the clinic, study staff will tell you about other places where care and treatment may be available. Your participation may also contribute to understanding about HIV prevention in women in Africa, which will help others in the future.

COSTS TO YOU

There is no cost to you for being in this study. Treatments available to you by the study will be free of charge.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY

You may be removed from the study without your consent for the following reasons:

- The study is stopped or canceled.
- You are put in prison.
- Your intentions about pregnancy and birth control use change.
- The study staff feel that staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.

ALTERNATIVES TO PARTICIPATION

There may be other studies going on here or in the community that you or your partner may be eligible for. You may also be able to access PrEP through other research studies going on here or in other clinics in the community. If you wish, the study staff will tell you about other studies or healthcare facilities which offer PrEP that we know about. There also may be other places you can go for HIV counseling and testing. We will tell you about those places if you wish.

REIMBURSEMENT

You will receive reimbursement for your transport for visiting the clinic, and 400 KSh for your time and effort at each scheduled study visit. All visits that include collection of biopsies will be reimbursed 2000 KSh. All visits that include collection of vaginal swabs alone will be reimbursed 1000 KSh.

CONFIDENTIALITY

Government or university staff sometimes review studies such as this one to make sure they are being done safely and legally. If a review of this study takes place, your records may be examined. The reviewers will protect your privacy. The study records will not be used to put you at risk of legal harm. All study staff will make every effort to protect the privacy of your personal information but cannot completely guarantee this. Any sample from you or information about you will be identified only by code and not by name. The link between your name and code will be kept in a secure location at the clinic only. The U.S. Food and Drug Administration (FDA) reserves the right to review study data that may contain identifying information. Any publication of this study will not use your name or identify you personally. Certain people and organizations will need to see, copy, and use your health data so that they can do their part in the study. They are called 'authorized users'. The records of your tests may be reviewed by study staff and representatives of the following authorized users:

- Kenya Medical Research Institute (KEMRI) Scientific and Ethics Review Unit (SERU)
- Kenya Pharmacy and Poisons Board
- University of Washington, including study monitors
- Gilead Sciences
- Kenya Ministry of Health
- University of Colorado
- Other local, U.S. and international regulatory entities

The review of records may be done on-site or remotely through secured authorized computer programs. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity.

RESEARCH-RELATED INJURY

We do not anticipate any research related injury. However, if you feel you are injured from participating in this study, you will be offered care at the study clinic, free of charge. For research related injury, please call the 24-hour emergency number: 0736464299.There is not a program of monetary compensation through this institution. If you need medical care that we cannot provide, we will refer you to the appropriate services or organizations that can provide care for the injury. You do not give up any legal rights by signing this consent form. You do not waive any right to seek payment or give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

If you ever have any questions about this study, or if you have a research-related injury, you should contact Catherine Kiptiness at the Thika Partners in Prevention Study clinic at Tel. 067 2222561/0725 641110. For research related injury, please call the 24-hour emergency number: 0736464299. If you have questions about your rights as a research participant, you should contact: The Head, Scientific and Ethics Review Unit (SERU) Kenya Medical Research Institute (KEMRI), P.O Box 54840-00202 Nairobi Phone No. 0717719477, Email address: seru@kemri.org. A description of this study will also be available on https://www.clinicaltrials.gov. as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

STATEMENT OF CONSENT AND SIGNATURES

I have read the study enrollment consent for this study, or had it read to me. I have discussed the information with study staff. My questions have been answered. I understand that my decision whether or not to take part in the study is voluntary. I understand that if I decide to join the study I may withdraw at any time. If I refuse to be in the study or decide to stop being in the study I will have no loss of benefits to which I am already entitled. By signing this form, I do not give up any rights that I have as a research participant.

_____	_____	_____
Participant Name (print)	Participant Signature/Thumbprint	Date
_____	_____	_____
Study Staff Name (print)	Study Staff Signature	Date

Witness Name (print)	Witness Signature	Date

SPECIMEN SHIPMENT, STORAGE AND USE OF YOUR DATA AND SAMPLES FOR FUTURE STUDIES:
Please initial and date one option:

_____ I agree for my specimen to be shipped, and for my specimen/information to be used for future research and shared with other researchers without my additional consent without identifiers

_____ I DO NOT agree for my specimen to be shipped and for my specimen/information to be used for future research or shared with other researchers with or without identifiers

STATEMENT OF CONSENT: BIOMETRIC FINGERPRINT
Please initial and date one option:

_____ I agree to have my fingerprint taken

_____I DO NOT agree to have my fingerprint taken

Participant Name (print)	Participant Signature/Thumbprint	Date
Study Staff Name (print)	Study Staff Signature	Date
Witness Name (print)	Witness Signature	Date

RECEIVING OFF-SITE VISITS, PLEASE TICK YOUR CHOICE BELOW
We would like to conduct your study visits at home or at a mutually agreed location, to make the visits more convenient for you.

☐ I DO agree to arranging study visits at a mutually agreed location.

☐ I DO NOT want to have visits at other locations other than the clinic.

Copies to;
1. Investigators
2. Study participant