Bictegravir, Emtricitabine and Tenofovir Alafenamide in Transwomen for Optimization of ART: The (mo)BETTA Trial

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Bictegravir, **E**mtricitabine and **T**enofovir Alafenamide in **T**ranswomen for Optimization of **A**RT: The (mo)BETTA Trial

Version 1.3 dated 03/25/2019

Investigator-Initiated Protocol

Study Drug:
Bictegravir (GS-9883) + TAF + FTC, provided by Gilead Sciences

Protocol Chair:
Jordan E. Lake, MD, MSc

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Protocol Signature Form

The signatures of the Site Investigator and Monitor below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality and in compliance with the current version of the protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP) and the applicable national and local regulatory requirements.

Investigator's Name	Signature of Investigator	Date

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1.0 Study Hypotheses and Objectives

1.1 Hypotheses

1.1.1 Compared to continued ART, switch to bictegravir + tenofovir alafenamide + emtricitabine will not be associated with an adverse side effect profile and will maintain virologic control in HIV-infected transwomen (TW).

1.1.2 After 48 weeks, switch to bictegravir + tenofovir alafenamide + emtricitabine will be associated with improvements in circulating inflammatory and metabolic biomarker profiles (including mortality-associated biomarkers), bone mineral density, fat and lean mass quantities, hepatic fat and insulin resistance vs continued ART.

1.2 Primary Objective

To determine the safety of bictegravir + tenofovir alafenamide + emtricitabine in HIV-infected TW.

1.3 Secondary Objectives

1.3.1 To compare total, appendicular and trunk fat mass by DXA at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.2 To compare total and appendicular lean mass by DXA at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.3 To compare bone mineral density by DXA at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.4 To compare hepatic fat content, as measured by FibroScan controlled attenuation parameter (CAP) measurement, at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.5 To compare hepatic fibrosis, as measured by FibroScan liver stiffness measurement (LSM), at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.6 To compare frequency of insulin resistance, as measure by the homeostatic assessment model of insulin resistance (HOMA-IR), at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.7 To compare fasting lipid levels at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.8 To compare estimated GFR (using the CKD-Epi equation) at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.9 To compare AST and ALT levels at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

1.3.10 To compare differences in circulating inflammatory and metabolic biomarker levels (including mortality associated biomarkers) at 48 weeks between TW who switch to bictegravir + tenofovir alafenamide + emtricitabine compared to TW who remain on current ART.

2.0 Introduction

2.1 Rationale

Background
Hormone therapy for transgender persons is a critical component of both well-being and harmonizing gender identity and expression; however, female hormone therapy causes fat gain and modulates the body's inflammatory and coagulation pathways. Female hormone therapy has been associated with increased risk of cardiovascular and thromboembolic events (hereafter referred to in aggregate as cardiovascular disease, CVD) in natal females (persons assigned a female sex at birth) and TW,[1-8] although little is known about metabolic disease of other organs in this population.

TW have an extremely high prevalence of HIV infection. A recent meta-analysis reported HIV prevalence rates up to 43.7% among TW, with an odds ratio (OR) for persons of reproductive age of 48.8 (95% Confidence Interval [CI] 21.2-76.3).[9] The reasons underlying the epidemic level of HIV infection among TW are beyond the scope of this proposal, but the burden of HIV disease and its associated comorbidities must be considered in this vulnerable population.

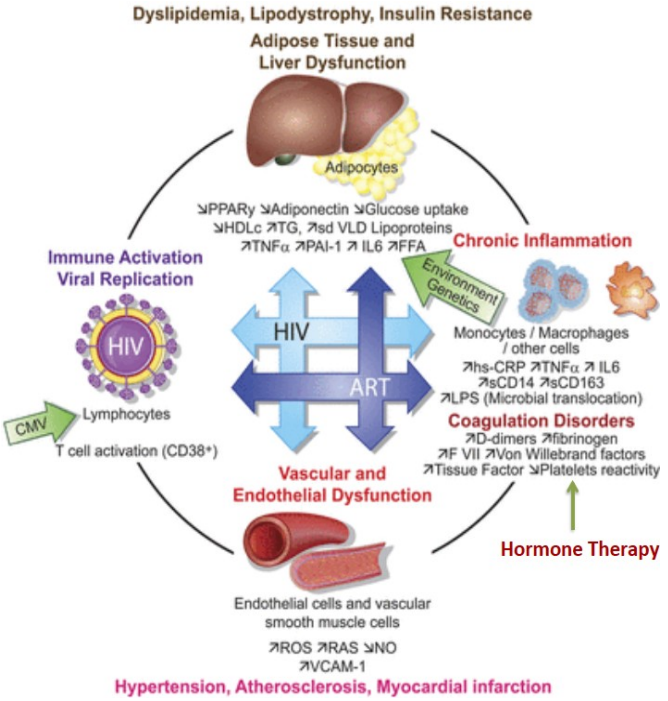

Figure 1. Contributions of HIV and hormone therapy to CVD. Adapted from Hemkens and Bucher. Eur Heart J. 2014 Jun 1;35(21):1373-81.

Non-AIDS events are leading causes of morbidity and mortality among HIV-infected persons well controlled on antiretroviral therapy (ART),[10-15] and these events may occur earlier in life[16,17] or at increased frequency[18-20] in the setting of HIV infection. Both female hormone therapy and ART are associated with fat gain and metabolic disturbances (Figure 1), and the intersection of HIV infection and female hormone therapy among TW may pre-dispose to or exacerbate a number of metabolic diseases, including CVD, fatty liver disease, insulin resistance and osteoporosis. Similarlty, the intersections of HIV-, ART- and female hormone therapy-induced alterations in immuno-metabolic pathways and subsequent metabolic disease risk in TW have not been studied, but could profoundly affect the health of this population.

Preliminary Data
Of 214 TW on hormone therapy (HIV status not reported), 10% experienced a thromboembolic event. TW experience significantly more myocardial infarctions than control women, cerebrovascular disease than control men, and diabetes mellitus than control women and men. Alarmingly, obesity, cerebrovascular disease and myocardial infarction rates dramatically increase with hormone initiation.[1]

Active hormone therapy increases CVD death risk 3-fold.[2] CVD risk appears highest with combined estrogen and progesterone or anti-androgen therapy vs estrogen alone, and is higher with oral vs transdermal estrogens.[21,22] 17-α-ethinyl estradiol is associated with the greatest perturbations of inflammatory biomarkers, coagulation parameters and lipids,[23] and is therefore no longer recommended as first-line hormone therapy for TW. However, no data exist on the incidence, prevalence or associations of modern female hormone therapy with fat or lean mass changes, bone health, liver disease or immuno-metabolic markers among TW, especially HIV-infected TW.

Visceral (including hepatic) fat gain with ART initiation is frequent and occurs with most modern ART regimens.[24,25] The effects of female hormone therapy on metabolic disease prevalence in HIV-infected TW, however, are hard to predict, and data must currently be extrapolated from natal females and HIV-uninfected TW. For example, 40% of natal females initiating selective estrogen receptor modulators for breast cancer develop hepatic steatosis within 2 years,[26-28] possibly from reduced fatty acid oxidation.[29] Estrogen in natal females is associated with improved lipids, reduced fibrogenesis, preservation of mitochondrial function, anti-

oxidant effects that may be lost with menopause, and, with menopause-induced visceral fat gain, contributes to metabolic disease.[30]

Supporting a relationship with metabolic disease, female hormone therapy increases subcutaneous and visceral adipose tissue,[31,32] increases cortisol and triglyceride levels,[33-35] and lowers lipoprotein lipase and insulin sensitivity.[32] Oral estrogens increase IL-1, IL-6, IL-8, CRP and TNF-α levels.[36-38] Additionally, access to appropriate hormone therapy is not widespread, and periods of ineffective androgen suppression and/or supra-physiologic estrogen levels from intermittent or unsupervised dosing may further metabolic and immunologic perturbations in TW.[39,40]

Intervention
Bictegravir (BIC, GS-9883) is a novel, potent, once-daily, unboosted HIV-1 integrase inhibitor. BIC displays a better *in vitro* resistance profile compared to the integrase strand transfer inhibitors raltegravir and elvitegravir, and is comparable to that of dolutegravir.[41] BIC is being studied in Phase III trials with tenofovir alafenamide + emtricitabine as a once daily regimen for the treatment of HIV infection. In Phase II studies, BIC was well-tolerated, and no discontinuations of BIC for adverse events or clinically significant lab abnormalities occurred.[42,43] Lipid and glucose levels, and assessments of lean mass, fat mass and bone mineral density with BIC have not yet been released, but would be expected to be similar or improved compared to other integrase inhibitors.

The integrase inhibitor class of agents may be the optimal ART base for TW, although no data exists in this population. However, given interactions between pharmacokinetic boosters and oral hormone therapy, regimens requiring low-dose ritonavir or cobicistat are likely suboptimal for TW on hormone therapy (excluding Stribild/Genvoya and most protease inhibitors). Similarly, due to increased CVD risk in this population, abacavir-containing regimens should likely be avoided (excluding Triumeq). While once daily dosing or single tablet regimens are preferred by most patients, they are especially important for patients with unstable housing and daily life schedules, which are frequent among TW (excluding traditionally-dosed raltegravir). This is also a population with high rates of food insecurity and depression (excluding Complera/Odefsey and Atripla as preferred options). Given these facts, once daily, unboosted bictegravir may be the ideal ART base for TW women. Additionally, female hormone therapy may have adverse effects on bone mineral density, and agents with improved bone health profiles, such as tenofovir alafenamide, will likely be beneficial in this population.

There is currently no data on the efficacy or tolerability of bictegravir + tenofovir alafenamide + emtricitabine in HIV-infected TW. Therefore, we propose a pilot, two-arm, randomized, open label study of current ART vs switch to bictegravir + tenofovir alafenamide + emtricitabine in HIV+ TW on hormone therapy and suppressive ART with two NRTIs plus a 3rd agent. The goal of this Phase IIb study is to evaluate the safety, tolerability and immuno-metabolic consequences of bictegravir + tenofovir alafenamide + emtricitabine in virologically suppressed, HIV-infected TW.

3.0 Study Design

Participants will be randomized 1:1 to continue current ART or switch to bictegravir + tenofovir alafenamide + emtricitabine for 48 weeks. Blood collection for inflammatory and metabolic biomarker analysis will be performed at weeks 0, 24 and 48. DXA-quantified bone mineral density and lean and fat mass, and Fibroscan-quantified hepatic fat (CAP) and fibrosis (LSM) will be performed at weeks 0 and 48. DXA and Fibroscan will be performed locally at research rates. Blood will be collected on site and stored for batched inflammatory and metabolic biomarker processing.

4.0 Selection and enrollment of participants

4.1 Inclusion Criteria

4.1.1 Self-identified TW

4.1.2 Age 18 or older

4.1.3 Confirmed HIV-1 infection

4.1.4 HIV-1 RNA <50 copies/mL at screening and for ≥24 weeks prior to entry**.** Participants with a single "blips" to HIV-1 RNA <500 copies/mL will be permitted to enroll.

4.1.5 Current ART with 2 NRTIs (TDF, TAF or ABC with FTC or 3TC) *and* a 3rd agent. Study participants are not required to be on their first regimen. However, patients who are not on their first ART regimen must not have previously substituted drugs secondary to known resistance to integrase inhibitors or components of their NRTI backbones. Other reasons for substitution such as medication intolerance or patient preference are acceptable. No changes in ART in the 12 weeks prior to screening.

4.1.6 Current female hormone therapy use.

4.1.7 Ability and willingness of subject to provide informed consent.

4.2 Exclusion Criteria

4.2.1 Current or planned use (within the study period) of any of the following agents, as requested by the Gilead Sciences clinical pharmacology team:

Anticonvulsants: Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antimycobacterial: Rifampin, rifapentine
Herbal Products: St. John's wort, Echinaccea
Antiarrhythmic Agents: Dofetilide
GI Motility Agents: Cisapride
ART: Atazanavir

4.2.2 Change or initiation of lipid- and/or glucose-lowering therapy in the 12 weeks prior to entry, or planned need for such therapy during the study period. Use of stable lipid- and/or glucose-lowering therapy during the study is allowed.

4.2.3 Current use of androgen therapy.

4.2.4 Intent to significantly modify diet or exercise habits, or to enroll in a weight loss intervention during the study period.

4.2.5 Anticipated need to initiate or change doses of medications with anti-inflammatory properties within the study period.

4.2.6 Screening laboratory values as follows:

ANC <500 cells/mm^3
Hemoglobin <10 gm/dL
Cr Cl <30 mL/min (estimated by CKD-Epi equation)
AST or ALT >3x ULN

4.2.9 Evidence of resistance to any component of a subject's current ART regimen (genotypic or phenotypic), with the exception that isolated M184V is not exclusionary.

4.2.10 Current use of bictegravir in another investigational setting.

4.2.11 Current use of other investigational agents that the participant could not receive unchanged, if needed, throughout the study period (unless approved by the study team).

4.2.12 Any condition that the study investigator believes would make the candidate unsuitable for participation.

5.0 Study Treatment

5.1 Regimens, Administration, and Duration

Study treatment is open label bictegravir + tenofovir alafenamide + emtricitabine (only bictegravir is investigational).

At entry participants will be randomized 1:1 by the study team to:

ARM A (immediate switch): Switch current ART to bictegravir + tenofovir alafenamide + emtricitabine for 48 weeks
or
ARM B (no switch): Continue current therapy for 48 weeks

If randomized to ARM A at study entry, the subject will substitute bictegravir + tenofovir alafenamide + emtricitabine for their entry ART regimen.

5.2 Study Product Formulation and Preparation

To be provided by manufacturer.

5.3 Pharmacy: Product Acquisition, Distribution, and Accountability

Study Product Acquisition/Distribution
Bictegravir + tenofovir alafenamide + emtricitabine will be supplied by Gilead Sciences. Participants randomized to Arm B will obtain ART for the study period through the usual means. Bictegravir + tenofovir alafenamide + emtricitabine is commercially available, so participants can receive bictegravir + tenofovir alafenamide + emtricitabine through usual care if they decide to continue it after the 48-week study period.

5.4 Concomitant Medications

Prohibited Medications
The prohibited medications are:

Anticonvulsants: Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antimycobacterial: Rifampin, rifapentine
Herbal Products: St. John's wort, Echinaccea
Antiarrhythmic Agents: Dofetilide
GI Motility Agents: Cisapride
ART: Atazanavir

Precautionary Medications
Use of antacids must be timed to be ≥2 hours from the timing of bictegravir + tenofovir alafenamide + emtricitabine dosing.

6.0 Clinical Evaluations

6.1 Schedule of Events

	Screen	Baseline*	Week 4	Week 12	Week 24*	Week 36	Week 48*	Early Discontinuation
Demographics	X							
Hormone therapy questionnaires		X						
Medical and medication history	X							
Targeted physical exam with weight, vital signs		X	X	X	X	X	X	X
Complete physical exam and height	X							
DXA for bone mineral density, lean and fat mass		X					X	X
FibroScan for hepatic steatosis and fibrosis assessment		X					X	X
HIV-1 RNA	X		X	X	X		X	X
Safety labs**	X	X	X	X	X		X	X
$CD4^+$ T lymphocyte count		X		X	X		X	X
Fasting lipids, banked serum and plasma samples for insulin and biomarkers		X			X		X	X
Medication dispensation		X	X	X	X	X		

* Entry, week 24 and week 48 laboratory evaluations are required to be fasting (at least 8 hours)
**Safety labs include: CBC with differential, chemistry panel including liver enzymes (ALT, AST, Alk Phos), total bilirubin and serum creatinine. All safety labs, HIV-1 RNA, and $CD4^+$ T lymphocyte counts will be performed at local certified laboratories.

6.2 Timing of Study Evaluations

TW ≥18 years of age will be recruited from the Thomas Street Health Center (TSHC, the Harris Health HIV clinic) and community service organizations serving HIV-infected TW.

Visit I Screening
After obtaining informed consent, participants will undergo a series of screening evaluations to determine eligibility (see Section 6.1). If needed, medical records will be requested from the participant's primary physician to confirm eligibility. If eligible, the subject will undergo whole body DXA and FibroScan performance. DXA images will be sent to the reading centers in electronic format. FibroScan data will be interpreted by Dr. Lake and housed locally. Imaging procedures will not be scheduled until eligibility is confirmed by physical exam, medical history and laboratory parameters.

Visit 2 Baseline (within 45 days of screening)
Once eligibility has been confirmed, the subject will be randomized 1: 1 to either:

ARM A: Immediate switch of current ART to bictegravir + tenofovir alafenamide + emtricitabine for 48 weeks.
or
ARM B: Continue current ART unchanged for 48 weeks.

Visit windows for all subsequent visits will be +/- 14 days from the expected date.

Week 48 Visit
At this visit, participants will be referred to their primary provider to determine the best ART regimen for them to continue on off-study.

Discontinuation Visit
A discontinuation visit should occur for any participant who has completed 12 or more weeks of study drug.

6.3 Pregnancy

Not applicable since no participant will be capable of becoming pregnant.

6.4 Discontinuation Evaluations

Evaluations for Randomized or Registered Participants Who Do Not Start Study Treatment
Participants who do not start study treatment will be taken off study with no further evaluations required. The subject will be replaced. All case report forms (CRFs) must be completed and keyed for the period up to and including week 0.

Premature Study Treatment/Background ART Discontinuation Evaluations
Participants who discontinue study drug due to an AE will be followed on-study off drug. The subject will complete all study evaluations and then be taken off study.

Participants who discontinue study drug for ≥14 days or who have confirmed virologic failure (two measurements >200 copies/mL) will complete the Discontinuation Visit evaluations and then be taken off study.

Similarly, participants randomized to Arm B who discontinue their entry ART regimen for ≥14 consecutive days will complete the Discontinuation Visit evaluations will and then be taken off study.

6.5 Clinical Assessments

Documentation of HIV

HIV-1 infection, as documented by any licensed ELISA test kit and confirmed by Western blot at any time prior to study entry. HIV-1 culture, HIV-1 antigen, plasma HIV-1 RNA, or a second antibody test by a method other than ELISA are acceptable alternative confirmatory tests. This does not need to be recorded on a CRF.

Medical History

The medical history must include all AIDS-related diagnoses, any active diagnoses, and history of any major illnesses (eg, coronary artery disease, hypertension, diabetes, stroke, malignancy, auto-immune disorders). Any allergies to any medications and their formulations must be documented. Surgeries that are planned prior to the time of the subject's informed consent will also be documented. Current and previous smoking history and alcohol and drug use history will also be collected.

Medication History

A medication history must be recorded in the source documents and the CRF. The medication history will include the following:

- Complete HIV treatment history, including start and stop dates of any current or past ART regimens (estimated if the exact dates cannot be obtained), immune-based therapy, or HIV-related vaccines, including blinded study medications. For patients who are not on their first ART regimen, documentation must be provided that ART medications were not switched secondary to virologic failure (verbal confirmation okay if documented on the CRF). Any available genotypic or phenotypic information should also be included.
- All prescription medications (in addition to those noted above) taken in the 30 days prior to study entry, including actual or estimated start and stop dates.
- Nonprescription medications taken in the 30 days prior to study entry. Include actual or estimated start and stop dates.
- Alternative therapies and dietary supplements taken in the 30 days prior to study entry. Include actual or estimated start and stop dates.

Complete Physical Exam

A complete physical examination is required at screening and includes: examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac exam; abdominal exam; examination of the lower extremities for edema. The exam also includes documentation of signs and symptoms, diagnoses, vital signs (temperature, pulse, respiration rate, and blood pressure), height and weight.

Targeted Physical Exam

A targeted physical examination at entry and all post-entry visits is to be driven by any previously-identified or new signs or symptoms that the participant has experienced since the last visit. This also includes weight, vital signs (temperature, pulse, respiration rate, and blood pressure), and diagnoses and medication updates at all visits.

Height

Height in stocking feet will be recorded on the CRF at the screening visit only. If not obtained at screening for any reason, height must be documented at the entry visit.

Signs and Symptoms

At entry, record all signs and symptoms occurring in the 30 days prior to entry. After entry, record all signs and symptoms ≥ Grade 2. This study will use the most current DAIDS toxicity grading system. Any signs or symptoms that lead to a change in the study drug, regardless of grade, must also be recorded.

Diagnoses
Record all diagnoses identified in Complete Physical Exam, above. Diagnosis recording should be standardizied by using the ACTG Criteria for Clinical Events and Other Diseases. All confirmed and probable diagnoses made since the last visit will be recorded.

Concomitant Medications
All concomitant medications taken since the last visit will be recorded in the source documents. Only prescription medications will be recorded on the CRFs.

Antiretroviral Medications
All modifications to antiretroviral medications including initial doses, subject-initiated and/or protocol-mandated interruptions, modifications, and permanent discontinuation will be recorded on the CRFs.

Study Treatment Modifications
Modifications of all ART including study treatment, initial dose, subject-initiated, and/or protocol-mandated modifications as well as permanent discontinuation will be recorded on the CRFs. If a subject misses more than 4 consecutive doses, the study treatment is considered modified and this must be reported appropriately on the CRF.

DXA
Whole body DXA will be performed and read locally using standardized procedures. Total lean, appendicular lean, total fat, trunk fat and appendicular fat measurements will be recorded in addition to bone mineral density. These scans are not being performed for clinical care, but TW will be offered a copy of the report to provide to their physician.

FibroScan
FibroScan will be perfomed and interpreted by Dr. Lake, with CAP and LSM measurements recorded. As per standard protocol,[44] 10 measurements with a LSM interquartile range (IQR) <30% per TW will be obtained. Scans will occur in the TSHC procedure room. All TW will have LSM and CAP assessments. These scans are not being performed for clinical care, but TW will be offered a copy of the report to provide to their physician.

Questionnaires
Questionnaires will be administered for 1) self-report of basic demographic information and 2) female hormone therapy type, frequency and mode of acquisition.

6.6. Laboratory Evaluations

Fasting will be required for study entry and weeks 24 and 48. Fasting will be defined as nothing by mouth except water and medications for at least 8 hours prior to the lab draw. At screening and entry, all laboratory values, regardless of grade, must be recorded on the CRFs. For post-entry assessments, record all laboratory values for WBC, Hb, platelet, glucose, creatinine, AST, ALT, lipid profile, $CD4^+$ T lymphocyte count and HIV-1 RNA, and any other $\geq$ Grade 2 laboratory value. Any laboratory value leading to a change in ART treatment must be recorded regardless of grade. Fasting lab studies include: total cholesterol, LDL cholesterol, triglycerides, HDL cholesterol, glucose (at weeks 0, 24 or 48), insulin and all biomarker measurements.

The site must refer to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, which is available on site.

Fasting lipids, glucose, insulin
Fasting total cholesterol, HDL cholesterol, LDL cholesterol (direct), triglycerides and glucose will be performed at entry and weeks 24 and 48 in real time at the local laboratory. Samples for insulin and oxidized LDL measurement will be batched and analyzed at the end of the study.

Plasma HIV-1 RNA
HIV-1 RNA must be performed by a laboratory that possesses a CLIA certification or equivalent. Eligibility will be determined based on the screening value.

$CD4^+$ T Lymphocyte Count
Obtain absolute $CD4^+/CD8^+$ counts and percentages. All laboratories must possess a CLIA certification or equivalent.

Safety Labs
CBC with differential, chemistry panel including liver enzymes (ALT, AST, Alk Phos), total bilirubin, and serum creatinine. All safety labs will be performed at local certified laboratories.

Fasting Stored Serum and Plasma
If participants come to the appointment and are not fasting, they will need to come back in fasting state for these evaluations within a 7-day window.

Serum (three 1 mL aliquots) and plasma (three 1 mL aliquots) will be collected as indicated in the schedule of events (entry, week 24, week48). Additionally, please collect 3mL of both serum and plasma in the event of study discontinuation and/or virologic failure. Frozen specimens will be collected, labeled with patients' PID, study week # and date of draw, and stored in a –70 degrees Celsius until batched processing can occur. The stored samples will be used for future measurements of metabolic and inflammatory markers which may include but are not limited to adiponectin, IL-6, IL-1B, PAI-1, and d dimer.

7.0 Toxicity Management

Criteria for participant management, dose interruptions, modifications, and discontinuation of drug treatment will be mandated only for toxicities attributable to study drug (for Arm A participants). Toxicities due to drugs in the background regimen/entry regimen (for Arm B participants) should be managed according to standard clinical practice, with the goal of maintaining continuous therapy, if possible.

7.1. Grade 1 or 2 Toxicity

Participants who develop a Grade 1 or 2 AE or toxicity may continue study drug.

7.2 Grade 3 Toxicity

Participants who develop a Grade 3 AE or toxicity should have all antiretroviral medications, including study drug, withheld unless the investigator has compelling evidence that the AE has NOT been caused by the study drug. The study chair (Dr. Lake) should be notified of any Grade 3 or greater toxicity. The subject should be re-evaluated closely until the AE returns to Grade ≤ 2, at which time study drug may be reintroduced at the discretion of Dr. Lake or according to standard practice.

If the same Grade 3 AE recurs within 4 weeks following reintriduction and it is thought to be related possibly, probably, or definitely to study drug, then study drug must be permanently discontinued. If the same Grade 3 AE recurs after 4 weeks but is not believed to be related to study drug, the management scheme outlined above may be repeated.

Participants experiencing Grade 3 or greater AEs (requiring permanent discontinuation of study drug) should be followed closely for resolution of the AE to Grade ≤2, and Dr. Lake must be consulted.

Participants with Grade 3 asymptomatic laboratory abnormalities in cholesterol, triglycerides or bilirubin (if on atazanavir) may continue study drug.

7.3 Grade 4 Toxicity

Participants who develop a Grade 4 symptomatic AE or toxicity will have study drug discontinued. If the site investigator has compelling evidence that the AE has not been caused by the study drug, dosing may resume when the AE has resolved and after consulting Dr. Lake. Participants experiencing Grade 4 AEs requiring permanent discontinuation of study drug should be followed closely until resolution of the AE to Grade ≤2, and Dr. Lake must be consulted.

Participants with Grade 4 asymptomatic laboratory abnormalities in cholesterol or triglycerides may continue study drug.

8.0 Criteria For Discontinuation

8.1 Permanent Study Drug Discontinuation

Study drug discontinuation can occur for the following reasons:

- Drug-related toxicity requiring permanent discontinuation (see Section 7.1).
- Requirement for prohibited concomitant drugs (see section 5.4).
- Request by participant to terminate treatment.
- Confirmation of virologic failure (two measurements of HIV-1 RNA >200 copies/mL at least 2 weeks apart).
- Clinical reasons believed life-threatening by the physician, even if not addressed in the toxicity section of the protocol.
- Participant repeatedly noncompliant with study drug as prescribed.
- Participant discontinues study drug for ≥14 consecutive days (Arm A).
- Participant discontinues background entry regimen for ≥14 consecutive days (Arm B).
- Failure by the participant to attend ≥2 consecutive study visits.

8.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant.
- Participant judged by the investigator to be at significant risk of causing harm to self.
- At the discretion of the IRB, Food and Drug Administration (FDA), Office for Protection of Human Research Participants, investigator, or the sponsor.

8.3 Early Discontinuation

Any participant who develops a Grade 3 or 4 symptom or laboratory abnormality (other than bilirubin, cholesterol and triglycerides, UNLESS THE INVESTIGATOR HAS A COMPELLING REASON TO THINK IT IS NOT RELATED TO STUDY DRUG) will be evaluated and will have study treatment withheld until the toxicity resolves (≤ Grade 2). If the abnormality is thought to be related to study treatment, the participant will not be rechallenged without discussion with Dr. Lake (see Section 7.2). Participants who have to discontinue study drug early (for the above listed reasons or confirmed virologic failure) but have been on study drug for at least 12 weeks will undergo a final safety evaluation, blood draw for stored serum and plasma, DXA scan and FibroScan. All participants will remain in follow-up for resolution of Grade 3 or 4 toxicities.

9.0 Sample Size and Endpoints

9.1 Sample size

Since a high percentage of participants are expected to have hepatic steatosis, we will base the sample size around the desired effect size for FibroScan CAP measurement. The sample size for this project is derived

from studies of CAP in HIV-infected but non-TW populations. Using a median baseline CAP of 237 dB/m (standard deviation [SD] 53),[45] 20 TW per arm provides 90% power to detect a minimum between-group CAP difference of 56 dB/m, which is clinically significant. We will enroll 24 TW per arm to allow for up to 20% discontinuation or loss-to-follow-up, which is reasonable for this high-risk population. Therefore, the total sample size will be 48 participants.

Additionally, perturbations of inflammatory, metabolic and coagulation pathways by exogenous female hormone use and the intersections of these perturbations with those associated with HIV are unknown. Therefore, it should not be assumed that the effects of switching ART to bictegravir + emtricitabine + tenofovir alafenamide on immunometabolic biomarkers in transwomen will be similar to those observed with integrase inhibitor or tenofovir alafenamide use in other HIV-infected populations. As such, we will assess the effects of switching ART to bictegravir + emtricitabine + tenofovir alafenamide vs continued ART on multiple biomarkers, including soluble CD14 (sCD14), a monocyte activation and mortality-associated biomarker that has been previously been shown by us and others to decline following switch to an integrase inhibitor.[46,47] If similar declines in sCD14 and variability are observed following switch to bictegravir + emtricitabine + tenofovir alafenamide, 48 participants will provide >99% power to observe this clinically significant effects.

9.2 Randomization and Stratification

Participants will be randomized with equal probability to the two arms of the study. Stratification may occur by entry ART regimen (3rd agent class).

9.3 Primary Endpoint Assessments

The safety (frequency of maintaining HIV-1 RNA <50 copies/mL) and tolerability (frequency of study drug discontinuation due to study-drug related AEs and frequency of study-drug related ≥ Grade 3 lab or clinical events whether or not study drug was discontinued) of bictegravir + tenofovir alafenamide + emtricitabine in HIV-infected TW on female hormone therapy vs continued ART.

9.4 Secondary Endpoints Assessments

- Total lean and fat mass, appendicular lean and fat mass and trunk fat mass, as measured by DXA
- Bone mineral density, as meausured by DXA
- Hepatic steatosis and fibrosis, as measured by FibroScan CAP and LSM
- Total cholesterol, HDL cholesterol, triglycerides, LDL cholesterol (direct), oxidized LDL
- Insulin, glucose, HOMA-IR
- Estimated GFR (CKD-Epi equation)
- AST and ALT
- Inflammatory and metabolic biomarkers

9.5 Study Monitoring

This is an open label study. Accrual and a summary of all Grade ≥2 signs and symptoms and all Grade ≥3 laboratory abnormalities will be prepared by the central data management site at the McGovern School of Medicine, and reviewed by the study team monthly. The AE summary will be divided by treatment arms and reviewed regularly by the team, as will baseline characteristics, early treatment discontinuations, and study discontinuations. The data management center at the McGovern School of Medicine will also prepare a quarterly report of all AEs by treatment arm to be reviewed by the team.

Approximately six-nine months after enrollment of the first participant, an interim review of the study will occur. An independent Study Monitoring Committee (SMC) comprised of three HIV investigators not involved in the study will review accrual, AE summaries, off-treatment, and off-study rates broken down by randomized

treatment arm. A SMC may also be convened if a reason is identified by the study team, the data management center, or in consultation with the sponsor.

9.6 Analyses

A descriptive analysis of demographic and clinical characteristics will be generated. Continuous variables will be expressed as mean ± SD if normally distributed or median with IQR if not normally distributed. Data will be pooled by arm and stratified by ART 3rd drug class. CAP will be used continuously and categorically, using for the latter the following standardized steatosis cut-offs: Grade 1 238 dB/m, Grade 2 260 dB/m and Grade 3 292 dB/m.[48] DXA data will be used continuously for lean and fat mass measurements, and, for bone mineral density, both continuously and categorically, with the latter using standard cutoffs for osteopenia and osteoporosis. Biomarker levels may be log-transformed, where appropriate. Wilcoxon rank-sum and Pearson χ^2 tests will compare continuous and categorical variables, respectively, between and within groups. Although the sample size is small, regression modeling will be attempted to assess if any observed differences persist after adjustment for confounding factors. All statistical tests will be 2-sided (α=0.05). Analysis will be exploratory without adjusting for multiple testing. Dr. Lake and Dr. Miao (statistician) will oversee analysis plan development/implementation.

9.6.1 Primary Analysis

Comparison between treatment arms of the primary endpoint will be undertaken using the Wilcoxon rank-sum test. The primary analysis will be as-treated, excluding participants who do not remain on the study regimen and/or participants who do not have an observed primary endpoint. Partcipiants who discontinue study drug or their background entry regimen for ≥14 consecutive days will no longer contribute data to the primary outcome after the date on which they first discontinued medication. An intent-to-treat analysis will also be performed as a supplement.

9.6.2 Occurrence of Study-Related AE

The number of participants who experience treatment-related AE from the first day of study treatment to Week 48 will be reported by arm.

9.6.3 Proportion of Participants who Discontinue Study Treatment

Proportion of participants who discontinue the study treatment prior to Week 48 will be summarized by arm. Reasons for discontinuing study drug will be listed.

10.0 Data Collection, Monitoring, and Adverse Event Reporting

10.1 Records to Be Kept

Data will be collected onto CRFs, and will be labeled only with a subject's study ID number. CRFs will be stored in a locked cabinet available only to study personnel for a period of time determined by pertinent policies and regulations, and for at least two years after study discontinuation. They key linking study ID #s to personal identifying information will be kept in a separate locked cabinet accessible only by Dr. Lake and the study coordinator.

10.2 Role of Data Management

Instructions concerning the recording of study data on CRFs will be provided by Dr. Lake. The site is responsible for keying the data in a timely fashion within 14 days.

10.3 Clinical Site Monitoring and Record Availability

Local monitoring of this investigator-initiated, non-IND study may occur according to standard McGovern School of Medicine policies, or by the study sponsor.

10.4 Serious Adverse Event Reporting

The serious adverse event (SAE) reporting requirements and definitions for this study will be in keeping with local McGovern School of Medicine policies and in keeping with the sponsor's requirement. The study agent for SAE reporting is bictegravir + tenofovir alafenamide + emtricitabine. SAEs must be documented on the Serious Adverse Event Reporting form (SAE Reporting Form) available in the Manual of Procedure. Dr. Lake must be notified for any Grade 3 or greater toxicity that does not have a clearly documented etiology of not related to study drug. All Grade 4 events, death, persistent or significant disability/incapacity, hospitalization or prolongation of hospitalization, or event that the site investigator deems medically significant and thought to be related possibly, probably, or definitely related to study drug must be reported by completing and faxing the SAE Reporting form to 713-500-5495.

SAEs must be reported during the protocol-defined SAE Reporting period, which is from enrollment until four weeks following the subject's last dose of study drug. After the end of the protocol-defined SAE Reporting Period stated above, the site must report serious, unexpected, clinically-suspected adverse drug reactions if the site staff becomes aware of the event on a passive basis, i.e., from publicly available information.

All confirmed virologic failures will reported immediately to the SMC. The SMC will also receive quarterly SAE reports for review.

11.0 Human Subjects

11.1 Institutional Review Board Review and Informed Consent

This protocol, the informed consent document, and any subsequent modifications will be reviewed and approved by the IRB responsible for oversight of the study. A signed consent form will be obtained prior to screening and prior to study continuation should procotol modifications be required that led to the development of an amended informed consent document. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the signed consent form will be given to the participant, and this fact will be documented in the study record. Consent forms will be available in English and Spanish.

11.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by IRB, SMC, FDA, the office for the protection of human subjects, or the sponsor or their designee.

11.3 Study Discontinuation

The study may be discontinued at any time by the IRB, the sponsor, the FDA, the office for the protection of human subjects, or other government agencies as part of their duties to ensure that research participants are protected.

12.0 Publication of Research Findings

Any presentation, abstract, or manuscript will be made available for review by Gilead Sciences prior to submission.

13.0 Biohazard Containment
As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the National Institutes of Health.

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

14.0 Proposed Sites
The TSHC has experience conducting metabolic studies, HIV expertise and the available population of TW.

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