Efficacy, Safety, and Tolerability of Switching EFV/TDF/FTC to BIC/FTC/TAF in Virologically Suppressed Adults with HIV-1 Infection.

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ABBREVIATIONS

ABC	Abacavir
AE	Adverse event
ATR	Atripla®, EFV/FTC/TDF
BIC	Bictegravir
BMI	Body Mass Index
CD4	Helper T lymphocytes positive for surface glycoprotein CD4
CI	Confidence interval
DLP	Distal symmetrical polyneuropathy
DM2	Diabetes mellitus 2
EFV	Efavirenz
FDC	Fixed dose combination
HAART	Highly active antiretroviral therapy
HBsAg	Hepatitis B virus surface antigen serology
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HTN	Hypertension
IRB	Institutional review board
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
PI	Protease inhibitor
PIN	Patient identification number
PVR	Pure virologic response
PRO	Patient reported outcomes
RAL	Raltegravir
RPV	Rilpivirine
RTV	/R, Ritonavir
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
VL	HIV viral load

1. INTRODUCTION

Human Immunodeficiency Virus-1 (HIV) is a life threatening and serious infection throughout the world. The World Health Organization estimates between 30-43 million people are living with HIV worldwide. The natural progression of the disease cripples the immune system, leading to unchecked infections and ultimately death.

With the advent of highly active antiretroviral therapy (HAART), we saw HIV transform from a terminal infection into a chronic disease that was managed with drugs. This transformation, however, required three drug combination regimens to prevent HIV from developing resistance to the drug. This resulted in numerous pills taken at strict dosing intervals frequently throughout the day. As treatments evolved, therapy required fewer pill numbers and decreased dosing intervals. This trend eventually gave way to efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) co-formulated into a single tablet, ATRIPLA®. This was the advent of the single tablet regimen—one pill, once a day. ATRIPLA® has many years of proven efficacy and improved patient adherence[1]

With the continued evolution of potent HAART, virologically suppressed HIV-infected patients are often switched to safer and better tolerated drugs[1]. Both older patients with age associated comorbidities and younger patients, who can fairly expect to be on antivirals for many years to come, are rightly concerned about side effects and toxicities of long term exposure to highly potent medications. Patients depend on their providers to optimize long term safety and tolerability in their antiretroviral therapy.

1.1 Rationale for the Study

Therapeutic dosage of the tenofovir disoproxil fumarate (TDF) component of ATRIPLA® requires plasma concentrations of the drug that are associated with nephrotoxicity and decreased bone mineral density[3]. Tenofovir alafenamide fumarate (TAF) has a unique metabolism that results in higher intracellular levels of the active phosphorylated moiety tenofovir-diphosphate[2]. Compared with TDF, the therapeutic dosage of TAF reduces tenofovir plasma concentrations by over 90%. This reduction in plasma concentration results in decreased renal and bone risks. TAF has the potential to improve on the efficacy and safety profile of TDF.

Efavirenz, another component of ATRIPLA® is widely associated with neuropsychiatric side-effects, including sleep disturbances, depression, and anxiety[4]. Switching from Efavirenz to an integrase inhibitor is associated with improvements in mood[5,6].

Bictegravir (BIC) is a novel, once daily integrase inhibitor. It has been shown to have potent antiviral activity, a favorable pharmacokinetic profile, good tolerability and an improved resistance profile when compared to previous integrase inhibitors.[10,11.] In a phase 2 trial investigating previously untreated people with HIV, bictegravir plus emtricitabine and tenofovir alafenamide (BIKTARVY®) vs dolutegravir, plus emtricitabine and tenofovir alafenamide both showed high efficacy up to 24 weeks and both regimens were well tolerated.[12]

Additionally, switching HAART experienced patients to BIKTARVY® has been shown to be non-inferior to continuation of regimens containing Atazanavir or Darunavir, when they were given with either lamivudine/abacavir or FTC/TDF.[13]

We plan to evaluate in a real world setting the efficacy, safety and tolerability of switching from the older, established single tablet regimen of ATRIPLA® (EFV/FTC/TDF) to a new single tablet regimen of BIKTARVY® (BIC/FTC/TAF).

Within the limitations of a real-world study, we have attempted to replicate the protocol of Gilead Science's Phase 3 study evaluating a switch to BIC/FTC/TAF from dolutegravir plus either FTC/TAF or FTC/TDF[14]. This will have the potential benefit of comparing different regimen switches as well as potentially adding robustness to the body of data regarding BIC/FTC/TAF.

2. STUDY OBJECTIVES

2.1. The primary objective of the study is:

- To evaluate the proportion of participants with virologic failure determined by HIV-1 RNA ≥ 50 copies/mL at week 48 in virologically suppressed patients with HIV-1 infection switching from ATRIPLA® to BIKTARVY®.

2.2. The secondary objectives of the study are:

- To determine the safety of switching from ATRIPLA® to BIKTARV®Y in virologically suppressed patients with HIV-1 infection as determined by the proportion of participants with virologic failure, a rise in serum creatinine values, a change in lipid parameters, and change in CD4 cell count from baseline.
- To determine the efficacy of switching from ATRIPLA® to BIKTARVY® in virologically suppressed patients with HIV-1 infection as determined by the proportion of participants with HIV-1 RNA < 50 copies/Ml.
- To evaluate tolerability, durability of BIKTARVY® in virologically suppressed patients with the aid of 2 Patient Reported Outcomes (PRO) questionnaires (see appendix 3).

3. STUDY ENDPOINTS

3.1. Primary Endpoint

- The primary efficacy endpoint is the proportion of subjects that have HIV-1 RNA ≥ 50 copies/mL at week 48, as defined by the FDA snapshot analysis.

3.2. Secondary Endpoints

- The proportion of subjects that have HIV-1 RNA < 50 copies/mL at week 48, as defined by the FDA snapshot analysis.
- The change from baseline in serum creatinine at Week 48
- The change from baseline in CD4 cell count at Week 48
- The change from baseline in lipid parameters at Week 48
- The change in responses to the PROs from baseline at Week 4, 12, and 48

4. STUDY DESIGN

4.1. Study Summary

Prospective 48 week single cohort study to evaluate the efficacy and safety of switching from ATRIPLA to BIKTARVY® in HIV-1 infected adult subjects who are virologically suppressed (HIV-1 RNA < 50 copies/mL).

4.2. Study Design

This protocol describes a prospective study involving the switch of HIV infected patients currently on ATRIPLA® that are virologically suppressed (HIV-1 RNA < 50 copies/mL) to BIKTARVY® and monitoring them over a 48-week period.

4.3. Sample Size

All patients meeting eligibility will be included in the study, the expected sample size being a total number of subjects: 100 HIV-infected adults.

4.4. Target Population

HIV-1 infected adults (≥ 18 years) with HIV-1 RNA < 50 copies/mL on a stable ATRIPLA® regimen prior to screening.

4.5. Eligibility Criteria:

4.5.1. Inclusion Criteria.

Subjects must meet <u>all,</u> of the following criteria:

- ≥18 years of age
- HIV positive
    - On a stable antiretroviral regimen consisting of ATRIPLA® for at least the 6 consecutive months preceding Screening Visit.
- Plasma HIV-1 RNA concentrations at undetectable levels for at least 6 consecutive months prior to the screening visit and have HIV RNA< 50 copies/mL at the Screening Visit.
- Estimated GFR ≥30mL/min according to the Cockcroft-Gault formula for creatinine clearance.
- Hepatic transaminases (AST and ALT) ≤5x upper limit of normal (ULN)
- Total bilirubin ≤1.5 mg/dL, or normal direct bilirubin.
- Adequate hematologic function (hemoglobin ≥ 8.5g/dL; platelets ≥ 50,000/mm^3; absolute neutrophil count ≥1,000/mm^3)
- Female subjects of reproductive potential using a reliable and consistent method of birth control for at least three months prior to study dosing. Male subjects should use condoms when engaging in intercourse of reproductive potential.
- The ability to understand and sign a written informed consent form, which must be obtained prior to initiation of study procedures.

4.5.2. Exclusion Criteria

- A new AIDS-defining condition diagnosed within 30 days prior to screening.
- Individuals with decompensated cirrhosis. (i.e. ascites, encephalopathy, etc.)
- Pregnancy
- A history of malignancy within the past 5 years (prior to screening) or ongoing malignancy other than cutaneous Kaposi's sarcoma (KS), basal cell carcinoma, or resected, noninvasive cutaneous squamous carcinoma. Individuals with cutaneous KS are eligible but must not have received any systemic therapy for KS within 30 days prior to baseline.
- Active, serious infections (other than HIV-1 infection) requiring parenteral antibiotic or antifungal therapy within 30 days prior to baseline.
- Life expectancy < 1 year.
- Subject participation in any clinical trial without prior approval from the Investigator.
- Concomitant use of disallowed agents from Table 2
- Participation in any other investigation study 30 days prior to enrollment.

4.6. Risks/ Benefits

There are potential risks for adverse reactions and for patient intolerance to the investigational drug. Benefits include the potential loss of neuropsychiatric effects of efavirenz as well as the documented reduced nephrotoxicity and bone mineral loss with switching from TDF to TAF.

5. STUDY DATA

Demographic summaries will include sex, race/ethnicity, age, prior antiviral therapies and (if available) pertinent prior mutations. Data relevant to endpoint evaluation includes subject HAART regimen, viral load (VL), CD4 T-cell count, fasting lipid panel, serum creatinine, PRO, at initial screening, weeks 4, 8, 12, 24, 36 and 48.

6. STUDY DRUG/STUDY PROCEDURES

6.1 STUDY DRUG

6.1.1 Formulation

The BIKTARVY® (BIC/FTC/TAF 50/200/25 mg) tablets are capsule-shaped, film coated purplish-brown, debossed with “GSI” on one side of the tablet and “9883” on the other side of the tablet. Each tablet core contains 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide. In addition to the active ingredients the BIKTARVY® tablets contain croscarmellose sodium, magnesium stearate, and microcrystalline cellulose. The tablet cores are film-coated with iron oxide red, iron oxide black, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide.

6.1.1.1 Packaging and Labeling

BIKTARVY® is packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets, silica gel desiccant and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant polypropylene screw cap with an induction-sealed and aluminum-faced liner.

6.1.1.2 Storage and Handling

Study drug will be stored at controlled room temperature of 25°C (77°F); excursions are permitted between 15°C and 30°C (59°F and 86°F). Storage conditions are specified on the label. Until dispensed to the subjects, all bottles of study drugs should be stored in a securely locked area, accessible only to those authorized site personnel.

To ensure the stability and proper identification, study drug should not be stored in a container other than the container in which they were supplied. Keep the bottle tightly closed to protect from moisture.

Consideration should be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions should be followed to avoid direct eye contact or exposure through inhalation when handling.

6.1.2 Dosage and Administration

BIKTARVY® will be provided by Gilead. Study drug is taken once daily, at approximately the same time every day. Each BIKTARVY® tablet contains 50mg of bictegravir (BIC), 200mg of emtricitabine (FTC), and 25mg of tenofovir alafenamide (TAF).

6.1.3 Prior and Concomitant Medications

With the following exceptions, subjects should continue to receive treatment for other conditions, prophylactic vaccines as per local medical guidelines and primary provider recommendations.

The use of medications for the treatment of HIV, other than the study drug, is prohibited.

Medications and herbal/natural supplements listed in the following table are disallowed or should be used with caution while subjects are participating in the study. Subjects will refrain from consumption of grapefruit juice and Seville orange juice throughout participation in the study.

Table 1 Prior and Concomitant Medications

Drug Class	Use for a minimum of 2 hours before and 2 hours after any dose of study drug
Antacids	Tums or Rolaids
Buffered medications	The ulcer medication sucralfate (Carafate), supplements that contain calcium, iron or zinc
Drug Class	**Agents Disallowed-- must be discontinued at least 30 days prior to the Day 1 visit and for the duration of the study.**
Antiarrhythmic Agent	Dofetilide
Anticonvulsants	Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine
Antimycobactrerials	Rifampin, Rifapentine, Rifabutin
Antiretrovirals	Any antiretroviral that is not part of the study regimen
GI motility Agents	Cisapride
Herbal/Natural Supplements	St. John's Wort, Echinacea

If subjects need to initiate treatment with any excluded concomitant medication, the Investigator must be consulted prior to initiation of the new medication.

6.1.4 Accountability for Study Drug

Subjects will be instructed to bring all study medication in the original container at each clinic visit for drug accountability. The Investigator will be responsible for maintaining accurate records for all study drug bottles dispensed and tablets returned. The inventory and dispensing logs must be available for inspection. Study medication supplies, including partially used or empty bottles, must be accounted for by the study staff prior to destruction of return.

The Investigator is responsible for ensuring adequate accountability of all used and unused study drug. This included acknowledgement of receipt of each shipment of study drug (quality and condition). All used and unused study drug dispensed to subjects must be returned to the site.

Study Drug accountability records will:

- Date received and quantity of IP kits
- Date, subject number, subject initials, the IP kit number dispensed
- Date, quantity of used and unused IP returned, along with the initials of the person recording the information

6.1.5 Product Return or Disposal

Study drug return or disposal will be performed on site. Unopened drugs that were not dispensed will be returned to Gilead.

6.2 Study Procedure

The study procedures to be conducted for each subject enrolled are as follows (also in table form in appendix 2).

6.2.1 Subject Enrollment

It is the responsibility of the Investigator to ensure that subjects are eligible for study prior to their enrollment.

6.2.2 Assessments

6.2.2.1 Screening Visit

Subjects will be screened within 30 days before Day 1 to determine eligibility for participation in the study. The following will be performed and documented at screening:

- Obtain written informed consent(s)
- Obtain medical history, including history of HIV-1 disease related events and current medications as well as any medications within 30 days of the screening visit
- If available, obtain documentation of historical genotype(s) and Hepatitis B immunity.
- Obtain measurements of blood pressure, pulse, temperature, height and weight
- Complete physical exam (genital/rectal exam, if clinically indicated)
- Obtain blood and urine samples as described in section 6.2.9
- Record all AE/SAE's to any protocol mandated procedures occurring after signing of the consent form

Subjects meeting all inclusion criteria and no exclusion criteria will return to the clinic within 30 days for the Day 1Visit. Subjects must continue their current HAART up until their scheduled Day 1 Visit

6.2.2.2 Day 1/Baseline Visit

The Investigator must have confirmed eligibility before proceeding with the Day 1 Visit.

The subject must complete prior to being administered the study drug:

- Subject will read PRO questionnaires (appendix 3) and write/mark answers directly onto questionnaire.
- Review/record SAE/AE's and changes in concomitant medications
- Obtain measurements of blood pressure, pulse, temperature, height and weight
- Complete physical exam (genital/rectal exam, if clinically indicated)
- Obtain blood and urine samples as described in section 6.2.9
- Dispense study drug
- Observe first dose administration of study drug.
- Subjects will be counseled regarding the importance of adherence and taking the study medication at the same time each day.
- Record all AE/SAE's to any protocol mandated procedures

6.2.2.3 Treatment Assessments (Week 4-48)

The following evaluations are to be completed at Weeks 4, 8, 12, 24, 36, and 48.

Study visits are to be completed within ±2 days of the protocol specified visit date (based on the Day 1 visit) through Week 12, visits for Week 12, 24, 36 and 48 should be completed ±6 days of the protocol specified date. If the subject is not evaluated within the visit window, the database will reflect missing/no available data for that visit.

Regularly scheduled evaluations will be made on all the subjects, even if they no longer are receiving study drug.

The following will be completed at each visit:

- Subject will read PRO questionnaires (appendix 3) to themselves and write/mark answers directly onto questionnaire.
- Review/record of SAE/AE's and changes in concomitant medications

- Obtain measurements of blood pressure, pulse, temperature, height and weight
- Complete or symptom directed physical exam, as clinically indicated
- Subjects will be reminded of the importance of adherence and taking the study medication at the same time each day
- Obtain blood and urine samples as described in section 6.2.4.1
- Document dispensing of study drug and accountability for all study drugs.
- Subjects should be reminded of the importance of adherence and taking the study medication at the same time each day.
- Record all AE/SAE's to any protocol mandated procedures
- Subjects who meet criteria for virologic failure will be managed according to the Management of Virologic Rebound Section 6.2.5.

A prescription will be provided for continuation of antiviral therapy at the final study appointment. The subject will receive an additional 7 day supply of the study drug to prevent lapse in therapy.

6.2.2.4 Early Study Drug Discontinuation Assessment

If the subject discontinues the study drug prior to the Week 48 Visit, the subject will be asked to return to the clinic within 5 days of stopping study drug for the Early Study Drug Discontinuation Visit. Every attempt should be made to keep the subject in the study and continue to perform the required follow ups and procedures through to the Week 48 Visit (see Section 6.2.2.3). If this is not acceptable to the subject or investigator, the subject may be withdrawn from the study.

If the subject discontinues the study drug and without notifying the Investigator within 5 days, the subject may be withdrawn from the study, at the Investigator's discretion.

At the Early Study Discontinuation Visit, any evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study drug will be repeated weekly (or as often as deemed prudent by the Investigator) until the abnormality is resolved/returns to baseline (based on Day 1 Visit) or is otherwise explained.

The following will be completed:

- Review/record of SAE/AE's and changes in concomitant medications
- Obtain measurements of blood pressure, pulse, temperature, height and weight
- Complete or symptom directed physical exam, as clinically indicated
- Obtain blood and urine samples as described in section 6.2.4.1
- Document accountability for all study drugs.

6.2.2.5 Criteria for Discontinuation of Study Treatment

Study Medication will be discontinued in the following instances

- Unacceptable toxicity, or toxicity that in the judgement of the investigator compromises the ability to continue study specific procedures or is considered to not be in the subject's best interest
- Subject request to discontinue for any reason
- Pregnancy during the study
- Development of active tuberculosis
- Discontinuation of the study at the request the IRB

Study medication may be discontinued in the following instances:

- Intercurrent illness that would in the judgement of the investigator affects assessments of clinical status to a significant degree. Following resolution of the intercurrent illness, the subject may resume study dosing at the discretion of the investigator.
- Lack of efficacy

- Subject noncompliance

6.2.3 Post Study Care

After a subject has completed/terminated their participation in the study, long-term care for the subject will remain the responsibility of their primary treating provider.

6.2.4 Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined below, within Section 6.2, and also in Appendix 1 Study Procedure Table.

6.2.4.1 Blood Samples

Blood sample collection for the following:

- Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, direct and indirect bilirubin, total protein, albumin, CPK, bicarbonate, blood urea nitrogen (BUN), chloride, creatinine, glucose, potassium, sodium
- Fasting glucose and lipid panel (total cholesterol, HDL, LDL, and triglycerides) at Day 1, Weeks 12, 24, 48.
    - If the patient is not fasting (no food or drinks except water for at least 8 hours prior to blood collection.
    - If the subject has not fasted prior to the visit, the visit may proceed but the subject must return within 72 hours in a fasted state to draw labs
- Hematology profile: complete blood count (CBC) with differential and platelet counts
- CD4+ cell count and percentage
- Plasma Quantitative HIV-1 RNA
- If no documented Hepatitis B immunity: Hepatitis B surface antigen, surface antibody and core antibody at Screening, Week 48.
    - The following tests will be conducted if the following criteria are met:
        - *If positive surface antigen*: plasma qualitative and quantitative HBV DNA, Hepatitis B virus e-antigen and antibody
        - *If positive core antibody with negative surface antigen and surface antibody:* plasma qualitative and quantitative HBV DNA, Hepatitis B virus e-antigen and antibody
- For subjects who are coinfected with Hepatitis B, plasma quantitative Hepatitis B DNA
- Hepatitis C Virus (HCV) antibody (subjects who are HCV antibody positive will have HCV RNA test performed) at Screening and Week 48.
- Plasma and serum storage sample for safety or virology testing (all visits except Screening Visit).

6.2.4.2 Urine samples

Urine samples will be collected for the following:

- Urinalysis
- Urine pregnancy testing (If positive at screening, subject will not be enrolled. If positive at subsequent visit, study medication will be discontinued)

6.2.5 Virologic Failure

Virologic failure is defined as virologic rebound or having HIV-1 RNA ≥ 50 copies/mL at study discontinuation or week 48

6.2.5.1 Management of Viral Rebound

Subjects who meet either of the criteria listed below will be considered to have virologic rebound:

- At any post Day 1 Visit, an HIV-1 RNA ≥ 50 copies/mL which is subsequently confirmed at the following visit (scheduled or unscheduled)
- Any subject with HIV-1 RNA ≥ 50 copies/mL at study drug discontinuation

Following the unconfirmed virologic rebound, subjects will be asked to return to the clinic for a blood draw, 4 weeks after the date of the original test that had an RNA ≥50 copies/mL. If virologic rebound is confirmed

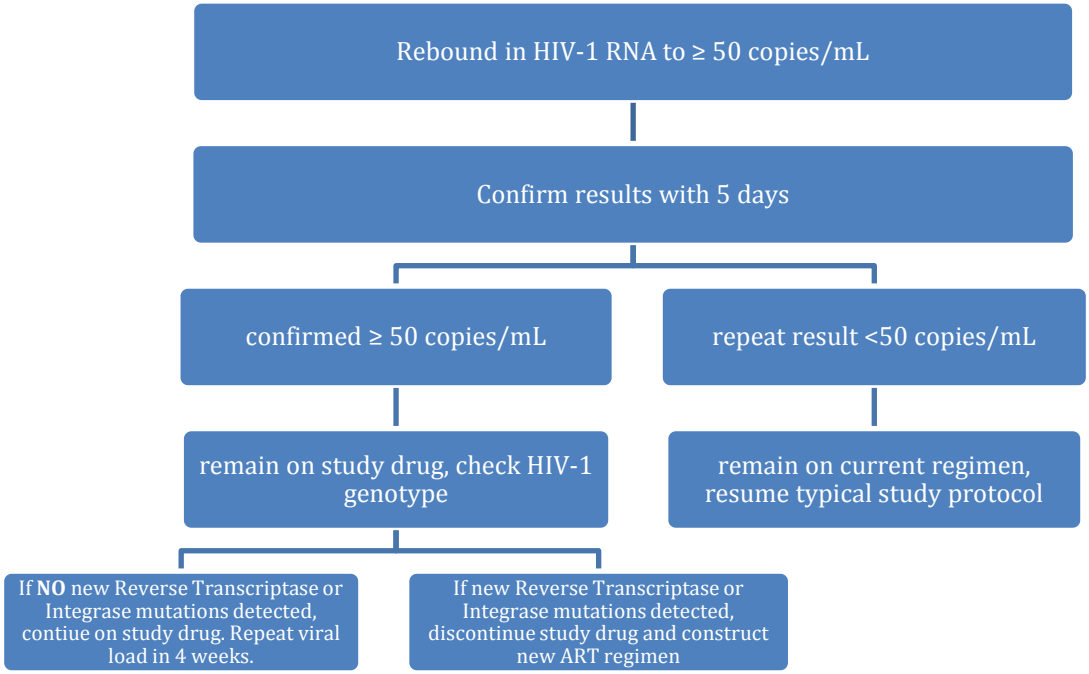
and the HIV-1 RNA is ≥ 200 copies/mL, the blood sample from the confirmation visit will be the primary sample used for HIV-1 genotypic and phenotypic testing. After a subject's first post-baseline resistance test, additional testing will be conducted on a case-by-case basis. Any subject may be discontinued at Investigator's discretion or per local treatment guidelines.

If no resistance is detected from the genotype or phenotype, the subject may remain on study drug and HIV-1 RNA test should be again repeated 2-3 weeks later. If HIV-1 RNA ≥ 50 copies/mL remains Investigators should carefully evaluate the risks and benefits of remaining on study drug and document this assessment in the on-site medical record.

Subjects who are nonadherent on an ongoing basis will be considered for discontinuation per the Investigator's discretion or local treatment guidelines. Sub-investigators who opt to discontinue study drugs for an individual subject must discuss with the Investigator prior to study drug discontinuation.

For subjects who are off study drug but remain in study, it will be the Investigator's discretion to manage virologic rebound.

Figure 1



6.2.5.2 Subjects with HIV-1 RNA ≥ 50 copies/mL at Study Drug Discontinuation or Week 48

Subjects with HIV-1 RNA ≥ 50 copies/mL at Study Drug Discontinuation, last Visit, or Week 48 will be considered virologic failures. Subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 will be asked to return for an unscheduled visit within 4 weeks for a retest as detailed in Section 6.2.5. Subjects with HIV-1 RNA ≥ 200 copies/mL will also have resistance testing as detailed in Section 6.2.5.

7 ADVERSE EVENTS AND TOXICITY MANAGEMENT

7.1 Definition of Adverse Events, Adverse Reactions, and Serious Adverse Events

7.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study subject which does not necessarily have a causal relationship with the medicinal product. An AE can be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. AEs may also include pre or post treatment complications that occur, as a result of protocol specified procedures, lack of efficacy, over dose, drug abuse/misuse reports, or occupational exposure. Preexisting events that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

An AE does not include the following:

- Medical or surgical procedures such a surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported.
- Preexisting diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social or convenience admissions)
- Overdose without clinical sequalae (see Section 7.6.1)
- Any Medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol associated procedure is not an AE. It is considered to be preexisting and should be documented in the medical record.

7.1.2 Serious Adverse Events

A serious adverse event (SEA) is defined as an event that, at any dose, results in the following:

- Death
- Life-threatening event in which the subject is at risk of death at the time of event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of an existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in offspring of study subject born after subject received study drug
- A medically important event or reaction that may not immediately result in death, hospitalization, or life-threatening event but may jeopardize the subject or may require intervention to prevent an SAE from occurring. Medical and scientific judgement must be exercised to determine whether such an event is reportable under expedited reporting rules. Examples of this type of occurrence would include intensive treatment for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency/abuse. For the avoidance of doubt, infections resulting from contaminated medical product will be considered a medically important event and subject to expedited reporting requirements.

7.1.3 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug interruption, modification or discontinuation must be recorded as an AE or SAE. In addition, laboratory or other abnormal assessments (e.g., EKG, x-rays, and vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition detailed in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis, not the laboratory result (i.e. “anemia,” not “decreased hemoglobin”).

For specific information on handling of clinical laboratory abnormalities in this study, please refer to Section 7.5.

7.2 Assessment of Adverse Events

The investigator or qualified sub-investigator is responsible for assessing AEs and SAEs for causality and severity as well as for final review and confirmation of accuracy of event information and assessments.

7.2.1 Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub-investigator is responsible for assessing the relationship to the study drug using clinical judgement and the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Yes:** There is reasonable possibility that the event may have been caused by the study drug.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture) should be assessed using the following considerations:

- **No:** Evidence exists that the adverse event has an etiology other than the study procedure.
- **Yes:** The adverse event occurred, as a result of protocol procedures.

7.2.2 Assessment of severity

AE severity should be recorded and graded according to the Grading Scale for Severity of Adverse Events and laboratory Abnormalities (Appendix 2). For AE associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; which might not be in agreement with the grading of the laboratory abnormality.

The distinction between the seriousness and the severity of an AE should be noted. Severe is a measure of intensity; a severe reaction is not necessarily a serious reaction. For example, a subject might have a headache that is described as severe but would not be considered a SAE unless it met one of the criteria for serious events.

7.3 Adverse Events and Serious Adverse Events

7.3.1 Adverse Events

Following initiation of study medication, all AEs regardless of cause or relationship until end of study must be reported to the study database.

All AEs should be followed up until resolution/return to baseline or until the adverse event is stable, if possible.

7.3.2 Serious Adverse Events

All SAEs regardless of cause or relationship that occurs after the subject signs the informed consent and until the duration of the study, including the protocol defined follow-up period, must be reported. This also includes any SAEs resulting from protocol associated procedures performed after informed consent is signed.

Investigators are not obligated to actively seek SAEs after the protocol defined follow up period; however, if the investigator learns of any SAEs that occur after study participation has concluded and the event is deemed relevant to the use of the study drug, they should promptly document and report the event.

7.4 Toxicity Management

All clinical events and clinically significant laboratory toxicities will be managed according to uniform guidelines detailed in Appendix 2 and as outlined below.

- Clinical events and clinically significant laboratory abnormalities will be graded according to the Grading Scale for Severity of Adverse Events and laboratory Abnormalities (Appendix 2).

- Grade 3 and 4 clinically significant laboratory abnormalities should be confirmed by repeat testing within 7 calendar days of receiving results and before study drug discontinuation, unless such a delay is not consistent with good medical practice.

Any questions regarding toxicity management should be directed to the Investigator.

7.4.1 Grades 1 and 2 Clinical Event or Laboratory Abnormality

Continue study drug at the discretion of the Investigator

7.4.2 Grade 3 Clinical Event or Laboratory Abnormality

For Grade 3 clinical event or clinically significant laboratory abnormality, study drug may be continued if the event is considered to be unrelated to study drug.

For a Grade 3 clinical event or clinically significant laboratory abnormality confirmed by repeat testing that is considered to be related to the study drug, study drug will be withheld until the toxicity returns to ≤ grade 2. When restarting study drug following resolution of the adverse event, the study drug should be restarted at full dose.

If following re-challenge with study drug a laboratory abnormality returns to ≥ Grade 3 and is considered to be related to the study drug, then the study drug will be permanently discontinued and the subject managed according to local practice. Recurrence of laboratory abnormalities considered unrelated to the study drug may not require permanent discontinuation.

7.4.3 Grade 4 Clinical Events or Laboratory Abnormality

For a Grade 4 clinical event or clinically significant laboratory abnormality confirmed by repeat testing that is considered to be related to the study drug, the study drug will be permanently discontinued and the subject managed according to local practice. The subject should be followed as clinically indicated until the laboratory abnormality returns to baseline or is otherwise explained, whichever occurs first.

A clinically significant Grade 4 laboratory abnormality that is not confirmed by repeat testing should be managed according to the algorithm for the new toxicity grade.

Study drug may be continued without dose interruption for a clinically non-significant Grade 4 laboratory abnormality (e.g., elevated CK after significant exercise or triglyceride elevation on a non-fasting specimen) or a clinical event considered unrelated to the study drug, but must be discussed with the Investigator.

7.4.4 ALT Flare

Defined as: serum ALT > 10 x upper limit of normal (ULN) and > 2 times Day 1 value, confirmed with repeat testing within 3 days of original results receipt, with or without associated symptoms

7.4.4.1 Management of ALT Flare

When initial results are received, schedule subject to return to the clinic as soon as possible (ideally within 3 days of initial blood draw). During the visit, in addition to redrawing blood for repeat CMP testing, clinical assessment of the subject will be performed. The assessment should include a physical examination and evaluation of the subject's mental status.

If ALT elevation is confirmed, the following labs should be performed: plasma HBV DNA, HBV serology (HBsAg and HBsAb), HAC IgM, HCV serology, quantitative HDV RNA.

Based on the results of the confirmatory tests, the following treatment modifications are recommended:

Elevated liver enzymes, normal or stable total bilirubin relative to Day 1

If ALT levels are elevated (as specified in Section 7.4.4) with normal or stable total bilirubin, the subject may remain on the study drug and should be monitored weekly until ALT levels return to normal or Day 1 level. During monitoring, if the ALT values remain persistently elevated, the Investigator considers whether the study drug should be discontinued.

Elevated liver enzymes, elevated total bilirubin

If ALT levels are elevated (as specified in Section 7.4.4) and total bilirubin is confirmed to be ≥ 2 x Day 1 value and is > ULN, the investigator should consider discontinuing the study drug. The subject should be monitored weekly until ALT and total bilirubin levels return to normal or Day 1 level.

During monitoring, if the ALT values and the liver function tests remain persistently elevated, the Investigator should consider discontinuing the study drug.

7.4.5 Management of Potential Hepatobiliary Toxicity

Any subject exhibiting signs/symptoms or laboratory abnormalities suggestive of possible hepatobiliary toxicity should undergo thorough examination and clinical workup as deemed appropriate by the Investigator. Consideration should be given to appropriate imaging studies (e.g., ultrasound of the liver and biliary tree) and potential consultation with a gastroenterologist with specialty training in hepatobiliary diseases.

7.5 Hepatitis C Management

If a subject, tests positive for HCV RNA at screening or develops signs or symptoms of active Hepatitis C Virus, local medical practice is followed at the discretion of the Investigator. Study drug may be continued without interruption. Should the Investigator decide to initiate Hepatitis C treatment the investigator confirms that no drug-drug interactions are expected. Subjects should return to the clinic for scheduled or unscheduled follow up visits according to local medical practice for laboratory evaluations.

7.6 Special Situations Reports

7.6.1 Definitions of Special Situations

Special situation reports include all reports of medication error, abuse, misuse, overdose, reports of adverse events associated with product complaints, reports of adverse reactions in infants following exposure from breastfeeding, occupational exposure with an adverse event, and pregnancy reports regardless of an associated AE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, subject or consumer.

Abuse is defined as persistent or sporadic intentional excessive use of a medicinal product by a subject.

Misuse is defined as any intentional and inappropriate use of a medicinal product that is not in accordance with the protocol instructions or the local prescribing information.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively which is above the maximum recommended dose per protocol or in the product labelling (as it applies to the daily dose of the subject in question). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken the excess dose(s). Overdose cannot be established when the subject cannot account for the discrepancy except in cases in which the investigator has reason to suspect that the subject has taken the additional dose(s).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

Occupational exposure is defined as exposure to a medicinal product as a result of one's professional or non-professional occupation.

7.6.2 Instructions for Reporting Special Situations

7.6.2.1 Instructions for Reporting Pregnancies

The Investigator will report pregnancies in subjects that are identified after initiation of the study drug and throughout the study to Gilead.

The subject should receive appropriate monitoring and care until the conclusion of the pregnancy.

The pregnancy itself is not considered an AE nor is an induced elective abortion to terminate a pregnancy without medical reasons.

Any premature termination of pregnancy (e.g., spontaneous abortion, induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an SAE. The underlying medical reason for this procedure should be recorded as the AE term.

A spontaneous abortion is always considered to be an SAE and will be reported as described in section 7.3. Furthermore, any SAE occurring as an adverse pregnancy outcome post study will be reported to Gilead.

The outcome should be reported to Gilead via email or fax to:

Email: Safety_FC@gilead.com

Fax: 650-522-5477

7.6.2.2 Reporting Other Special Situations

Any inappropriate use of concomitant medications prohibited by this protocol should not be reported as "misuse," but may be more appropriately documented as a protocol deviation.

Refer to Section 7.3 for full instructions on the mechanism of special situation reporting.

All clinical sequelae in relation to these special situation reports will be reported as AEs or SAEs at the same time using the AE EMR and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome will be reported, when available.

8. STATISTICAL CONSIDERATIONS

8.1 Analysis

The efficacy analysis endpoints are as follows:

8.1.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects that have HIV-1 RNA ≥ 50 copies/mL at week 48, as defined by the FDA snapshot analysis.

8.1.2 Secondary Endpoints

1. The proportion of subjects that have HIV-1 RNA <50 copies/mL at Week 48, as defined by the FDA snapshot analysis.
2. The change in serum creatinine from Day 1 to Week 48
3. The change in CD4 cell count at Day 1 to Week 48
4. The change in lipid parameters at Day 1 to Week 48
5. The change in responses to the PRO at Day 1, Week 4, 12, and 48

8.2 Analysis Conventions

8.2.1 Analysis Sets

8.2.2 Full Analysis Set

The primary analysis set for efficacy analyses is defined as FAS, which will include all subjects who have received at least 1 dose of study drug. Subjects who do not receive at least 1 dose of study drug will be excluded from all analysis.

8.2.3 Safety

The primary analysis set for safety analysis is defined as safety analysis set, which will include all subjects who have received at least 1 dose of study drug. All the data collected up to 30 days after subjects permanently discontinue their study drug will be included in the safety summaries, unless specified otherwise.

8.3 Data Handling Conventions

For analysis purposes, laboratory data that are continuous in nature but are ≤ the lower limit or ≥ the upper limit of quantitation will be inputted to the value of the lower limit minus 1 or upper limit plus 1 significant digit, respectively (e.g., If HIV-1 RNA results of 'No HIV-1 RNA detected' and '≤ 50 copies/mL HIV-1 RNA detected' will be inputted as 49 copies/mL).

Missing data can have an impact upon the interpretation of the trial data. In general, values for missing data from the specified visit will not be inputted. However, a missing pre-treatment laboratory result would be treated as normal (i.e. No toxicity grade) for the laboratory abnormality summary.

All available data for subjects that do not complete the study will be included in data listings.

8.4 Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods including sample size, mean, SD, median, minimum, and Maximum for continuous variables and frequency and percentages for categorical variables.

Demographic data will include sex, race, ethnicity, and age.

Baseline characteristics will include body weight, height, creatinine, lipid parameters and CD4 at baseline.

8.5 Efficacy Analysis

8.5.1 Primary Analysis

The primary analysis will consist of a descriptive analysis of switching from EFV/TDF/FTC to BIC/FTC/TAF with respect to the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm. The primary analysis of the efficacy endpoint will be based on the FAS.

8.5.1.1 US FDA-defined Snapshot Algorithm

All HIV-1 RNA data collected on-treatment (i.e. including data collected up to 1 day after the last dose date of the study drug) will be used in the snapshot algorithm. Virologic outcome will be defined as the following categories:

- **HIV-1 RNA < 50 copies/mL**: subjects who meet this criteria by result of the last available on-treatment laboratory result in the Week 48 analysis window
- **HIV-1 RNA ≥ 50 copies/mL**: subjects who meet this criteria by result of the last available on-treatment laboratory result in the Week 48 analysis window or do not have laboratory results in the Week 48 window and who discontinue study drug either:
    - due to lack of efficacy or
    - for reason other than lack of efficacy and have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL
- **No virologic Data in the Week 48 Analysis Window:** subjects who do not have on-treatment HIV-1 RNA data in the Week 48 window because
    - Discontinuation of the study drug for reason other than lack of efficacy and have the last available on-treatment HIV-1 RNA < 50 copies/mL or
    - Missing data during the Week 48 window but remain on study drug

8.5.1.2 Analysis of Primary Efficacy Endpoint

The evaluation will be based on the proportion of subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48.

8.5.2 Secondary Analyses

The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm will also be summarized.

The Change from baseline in CD4+ cell count at Week 48 will be summarized by treatment using descriptive statistics.

8.6 Safety Analysis

All safety analyses will be performed using the full analysis set.

All safety a data collected on or after the date of the study drug was first administered up to the date of the last dose of study drug plus 30 days, unless specified otherwise, will be summarized for subjects in the safety analysis set.

Data for the pretreatment period and the period past the date of last dose of study drug plus 30 days will be included in data listings for all enrolled subjects.

8.6.1 Extent of Exposure

Duration of exposure to study drug will be expressed as the number of weeks between the first and last dose of the study drug, inclusive, regardless of temporary interruptions in study drug administration and summarized by treatment.

8.6.2 Adverse Events

Clinical and laboratory adverse effects will be coded using the definitions detailed in Appendix 2 and recorded in the study database.

Summaries (number and percentages of subjects) of treatment-emergent adverse events (by SOC, HLT [if applicable], and PT) will be provided by treatment. Additional summaries will include summaries for adverse events by grade, Investigator's assessment of relationship to study drug and effect on study drug dosing.

On an ongoing basis adverse events will be reviewed for event that might meet the definition of Stage 3 Opportunistic Illnesses in HIV that are indicative of an AIDS-Defining Diagnosis. The Principal Investigator will review the possible Stage 3 events and approve the events that meet the definition. Those events that do meet the Stage 3 Opportunistic Illnesses definition of an AIDS-Defining Diagnosis will be listed in Appendix 2.

8.6.3 Laboratory Evaluations

Selected laboratory data (using conventional units) will be summarized using only observed data. Absolute values and changes from baseline at all scheduled visits will be summarized.

Graded laboratory abnormalities will be defined using the Grading of Laboratory Abnormalities in Appendix 2.

Incidence of treatment-emergent laboratory abnormalities, defined as values that increase at least 1 toxicity grade from baseline at any time post baseline up to and including the date of last dose of study drug plus 30 days will be summarized. If baseline data are missing, then any graded abnormality (i.e., at least a Grade1) will be considered treatment emergent. The maximum post baseline toxicity grade will be summarized by laboratory parameter.

Laboratory abnormalities that occur before the first dose of study drug or after the last dose of study drug plus 30 days will be included in a data listing.

8.6.4 Other Safety Evaluations

Vital signs will be summarized as appropriate

8.7 Patient Reported Outcomes

The PRO measures based on questionnaires (HIV Symptom Index and Pittsburg Sleep Quality Index, see Appendix 2) may be summarized by visit using descriptive statistics.

8.8 Sample Size

A total of approximately 100 HIV-1 infected subjects

8.9 Analysis Schedule

The Week 48 analysis will be conducted after all subjects either complete their Week 48 visit or prematurely discontinue from the study drug, respectively. Final analysis will be performed after all subjects complete the study or prematurely discontinue from the study

9. RESPONSIBILITIES

9.1 Good Clinical Practice

The rights and welfare of the individual clinical research subject must always be the paramount consideration in conducting clinical research. Accordingly, clinical research must be conducted in a manner that protects the rights, welfare and confidentiality of the human subject and also assures data credibility by protecting the integrity of accurate data that has been demonstrably collected according to the approved protocol.

9.2 Investigator Responsibilities

9.2.1 General Responsibilities

The Investigator is responsible for:

- Ensuring that the study is conducted according to the signed investigator statement/agreement, the investigational plan (study protocol), applicable regulations
- Ensuring that all persons assisting with the trial are adequately informed about the protocol, the study drug, their trial-related duties and functions
- Protection of the rights, safety, and welfare of subjects under the investigator's care
- Control of the study drug included in the investigation.
- Assuring that each subject's informed consent is obtained appropriately
- Proper delegation of authority for the conduct of various aspects of the study so that the investigator retains control and knowledge of the study

9.2.2 Control of Study Drug

The investigator shall control the study drug. The Investigator is responsible to ensure that:

- The study drug is administered only to subjects under the investigator's personal supervision or under the supervision of a qualified sub-investigator responsible to the investigator.
- The study drug is not to be supplied/provided to any person not authorized to receive it.
- Adequate records of the disposition of the study drug are maintained, including dates, quantity, receipt, distribution to subjects, and disposition.

9.2.3 Medical Decision Making

An MD/DO must be designated as responsible for all trial-related medical decisions. Medical decisions must be made by a qualified person permitted by state licensure laws to make or enact such decisions. The investigator should:

- Ensure that adequate medical care is provided to a subject for any adverse events related to the trial, during and as follow-up to a subject's participation.
- Inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.
- Inform the subject's primary physician about the subject's participation in the trial if the subject agrees to the primary physician being informed and has signed a HIPAA Authorization form permitting such disclosure.

9.2.4 IRB/IEC Review and Approval

The investigator shall assure that initial and continuing review of the proposed clinical study is performed according to the policies and procedures of the Central Institutional Review Board (IRB), as well as with any other IRB that has jurisdiction.

Continuous approval from the IRB must be maintained.

All unanticipated problems involving risk to human subjects or others are promptly reported to the IRB. All serious adverse events are reported to the IRB within twenty-four hours of time investigator is aware of the event.

Any changes in the research activity are promptly reported to the IRB.

No changes are made in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

9.2.5 Informed Consent

The Investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study related procedures. The investigator must use the most current IRB/IEC-approved consent form for documenting written informed consent. Each informed consent (or assent as applicable) will be appropriately signed and dated by the subject's legally authorized representative and the person conducting the consent discussion, and also by an impartial witness if required by IRB/IEC or local requirements. The consent form will inform subjects about sample retention.

9.2.6 Confidentiality

The investigator will assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. All information and data will be collected by the investigator. All collected data concerning participants or their participation in this study will be considered confidential and maintained in a HIPAA-compliant electronic medical recording system. Subject data pertinent to the study will be de-identified and access limited only to personnel directly involved in this research study. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the participant. Study data will not be transmitted nor disclosed to a third-party. Paper records will be kept in secure files and electronic records will be password protected.

9.2.7 Study Files and Retention of Records

The investigator shall keep and maintain adequate and accurate records, including:

- Case histories on each individual study subject that record all observations and other data pertinent to the investigation
- Screening, enrollment, and informed consent documentation; demonstrating that informed consent was obtained prior to participation in the study
- Study reports, including reports of progress, safety, financial disclosure and final completion

9.2.7.1 Records Retention as Required

Midland Research Group, Inc. will use on-site facility and if storage becomes unavailable due to capacity of documents, then Midland Research Group, Inc., will use an offsite facility once documents are ready to be retained for retention, if applicable.
FDA regulation requires an investigator to retain records a minimum of two years after the close of the study or after the records are no longer required to support a drug or marketing application, whichever is longer. Contract commitments must be met.

9.2.7.2 Record Transfer or Record Destruction

All record transfers or record destruction will be verified and documented.

9.2.8 Case Report Forms

For each subject consented, a study file will be completed by an authorized study staff member who has completed training for this function. The study file will only capture the data required per the protocol schedule of events and procedures. The Inclusion/Exclusion Criteria and Enrollment should be completed only after all data related to eligibility have been received. Subsequent to data entry, a second staff member will perform source data verification.

9.2.9 Study Drug Accountability and Return

Unused study drug supplies will be returned to Gilead. Investigator will assist with disposal procedures and provide appropriate instruction for destruction of used study drug supplies.

9.2.10 Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

9.3 Sponsor Responsibilities

9.3.1 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Investigator, who must submit all protocol modifications to the IRB in accordance with local requirements and receive documented IRB approval before modifications can be implemented.

9.3.2 Study Report and Publications

The Investigator is responsible for submitting any reports within time periods and according to procedures called for by:

- Midland Research Group, Inc. or applicable division or departmental policy or procedures, including the Institutional Review Board (IRB)
- Contractual agreements with collaborators, etc.

9.3.3 Payment Reporting

Investigators and their study staff may be asked to provide services performed under this protocol. If required under applicable statutory and regulatory requirements, Midland Research Group Inc. will capture and disclose to Federal and State agencies any expenses paid or reimbursed for such services, including any clinical trial payments, meal, travel expenses or reimbursements, consulting fees, and any other transfer of value.

9.3.4 Access to Information for Monitoring

As per Gilead contract

9.3.5 Access to Information for Auditing or Inspection

9.3.6 Study Discontinuation

The investigator reserves the right to terminate the study at any time. Should this be necessary, they will arrange discontinuation procedures and notify the appropriate regulatory authorities and the IRB. In terminating the study, the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

10. PUBLICATIONS

Midland Research Group, Inc. shall adhere to the *Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals* established by the International Committee of Medical Journal Editors.

11. REFERENCES

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APPENDIX 1. SCHEDULE OF STUDY VISITS

	SCREENING VISIT	DAY 1 [a]	WEEK 4 [a]	WEEK 8 [a]	WEEK 12 [b]	WEEK 24 [b]	WEEK 36 [b]	WEEK 48 [c]	EARLY DISCONTINUATION
Informed Consent	X								
Patient Questionnaires		X	X		X			X	X
Height	X								
Weight	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Complete Medical History & Physical Exam	X								
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Assess for Adverse Experiences			X	X	X	X	X	X	X
Abbreviated History & Physical Exam		X	X	X	X	X	X		
Hematology	X	X	X	X	X	X	X	X	X
Chemistry	X	X	X	X	X	X	X	X	X
CD4 Profile	X	X	X	X	X	X	X	X	X
HIV- RNA Quantitative	X	X	X	X	X	X	X	X	X
Fasting Lipid Profile		X			X	X	X	X	X
Plasma and serum Storage Sample		X	X	X	X	X	X	X	X
Urinalysis	X		X	X	X	X	X	X	X
Hepatitis B Surface antigen, Surface antibody, and Core Antibody [d]	X								X
Hepatitis C antibody [e]	X								X
Plasma Hepatitis B viral load [f]	X		X	X	X	X	X	X	X
Females of childbearing potential: Pregnancy Test (Urine)	X	X	X	X	X	X	X	X	X
Dispensing or Administration of Study Drug		X	X	X	X	X	X		
Counting of Returned Study Drug			X	X	X	X	X	X	X

[a] ±2 days
[b] ±6 days
[c] ±6 weeks
[d] If Hepatitis B Surface antigen positive or if Ag/Ab negative with Core antibody positive: plasma qualitative and quantitative HBV DNA, Hepatitis B virus e-antigen and antibody
[e] If Hepatitis C antibody positive, HCV RNA will be performed
[f] If Hepatitis B coinfected

APPENDIX 2. GRADING SCALE FOR SEVERITY OF ADVERSE EVENTS AND LABORATORY ABNORMALITIES

	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	8.5-10.0	7.5-8.49	6.5-7.49	<6.5
ANC	1000-1300	750-999	500-749	<500
Platelets	100-125	50-99	25-49	<25
WBC	2.0-2.5	1.5-1.99	1.0-1.49	<1
Hyponatremia	>130	125-129	121-124	<121
Hypernatremia	<150	150-154	154-159	>159
Hypokalemia	>3	2.5-3.0	2.0-2.49	<2.0
Hyperkalemia	5.6-6.0	6.01-6.5	6.51-7.0	>7.0
Hypoglycemia	55-64	40-54.9	30-39.9	<30
Hyperglycemia, Fasting	110-125	126-250	251-500	>500
Hypocalcemia (corrected)	Below normal but above 7.8	7.0-7.8	6.1-6.9	<6.1
Hypercalcemia (corrected)	Above normal but below 11.5	11.5-12.5	12.6-13.5	>13.5
Total Bilirubin	Up to 1.5 ULN	1.5-2.5 x ULN	2.5-5.0 x ULN	>5.0 x ULN
BUN	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
Creatinine	1.5-2.0	2.01-3.00	3.01-6.00	>6.00
Bicarb	16-LLN	11-15.9	8-10.9	<8.0
Triglycerides (fasting)	NA	500-750	751-1200	>1200
LDL (fasting)	130-160	161-190	>190	NA
CK	3-6 x ULN	6.1-10 x ULN	10.1-20 ULN	>20 x ULN
AST	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
ALT	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
GGT	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
Alk Phos	1.25-2.5 x ULN	2.6-5.0 x ULN	5.1-10 x ULN	>10 x ULN
lipase	1.0-1.5 x ULN	1.51-3.0 x ULN	3.01-5.0 x ULN	>5.0 x ULN
Albumin	NA	2.0 to <LLN	<2.0	NA
Hematuria	>ULN-10	>10-75	>75	NA
Proteinuria	1+	2-3+	4+	NA
Glycosuria	1+	2-3+	4+	NA

Cardiac Arrhythmia	Asymptomatic and no intervention indicated	Asymptomatic and non-urgent intervention indicated	Symptomatic and non-urgent intervention indicated	Life threatening or urgent intervention indicated
Cardiac ischemia/infarct	NA	NA	Stable angina or testing with ischemia	Unstable angina or acute MI
Hemorrhage	NA	Symptomatic, no transfusion indicated	Symptomatic, ≤ 2 units PRBC's transfusion indicated	Life threatening or > 2 units PRBC's transfusion indicated
Hypertension	Systolic: 140-159 Diastolic: 90-99	Systolic: 160-179 Diastolic: 100-109	Systolic: >179 Diastolic: 110	Life threatening (i.e. malignant hypertension) or requiring hospital admission
Hypotension	NA	Symptomatic, corrected with oral fluids	Symptomatic, IV fluids indicated	Refractory shock
Pericardial effusion	Asymptomatic, small	Asymptomatic, mod-large	Physiologic consequences, no urgent intervention indicated	Physiologic consequences, urgent intervention indicated
PR prolongation	0.21-.025	>0.25	Type II 2nd degree AV block	Complete AV block
Prolonged QTc	450-470 Or increase <30 above baseline	471-499 Or increase 30-50 above baseline	>499 Or increase >50 above baseline	Life threatening dysrhythmia
Thrombus	NA	DVT, no intervention or anticoagulation indicated	DVT, intervention or anticoagulation indicated	PE or life-threatening embolism
Vasovagal episode	No LOC	LOC	NA	NA
Ventricular dysfunction	NA	Asymptomatic and intervention indicated	New/worsening symptomatic CHF	Life threatening CHF
Bronchospasm	FEV1 70-80%	FEV1 50-69%	FEV1 25-49%	FEV1<25%, cyanosis or intubation
Dyspnea	On exertion, minimal, without impact on activities	On exertion, moderate, with impact on activities	At rest, unable to perform typical activities	Resp. failure with vent support indicated
Uveitis	Asymptomatic	Symptomatic or intervention indicated	Posterior or pan-uveitis or	Disabling visual loss

			operation indicated	
Visual changes from baseline	minimal, without impact on activities	moderate, with impact on activities	unable to perform typical activities	Disabling visual loss
Alopecia	Thinning detectable by subject	Thinning/patchy hair loss detectable by provider	Complete hair loss	NA
Rash	Localized macular rash	Diffuse rash or target lesions; no vesicles, bulla or ulceration. No mucosal involvement	Diffuse rash or target lesions; with vesicles, few bulla or superficial ulceration. mucosal involvement of one site	Extensive bullous lesions/more than one site of mucosal involvement, Stevens-Johnson syndrome or toxic epidermal necrolysis
Pigmentation changes	Slight or localized	Marked or generalized	NA	NA
pruritus	minimal, without impact on activities	moderate, with impact on activities	Severe, unable to perform typical activities	NA
Anorexia	Mild, not decreasing intake	Decreased intake, no significant weight loss	Significant weight loss	Aggressive intervention indicated (i.e. feeding tube) or life threatening
Ascites	Asymptomatic	Symptomatic, Intervention indicated	Symptomatic despite intervention	Life threatening consequences
Cholecystitis	NA	Medical intervention indicated	Procedure indicated	Life threatening consequences (sepsis/perforation)
Constipation	NA	Persistent, requiring regular use of diet modification, laxatives/enemas	Obstipation with manual evacuation indicated	Life threatening consequences (obstruction)
Diarrhea	Transient/ intermittent or increase of >3 stools over baseline/24 hr.	Persistent or increase of 4-6 stools over baseline/24 hr.	Bloody diarrhea or increase of >6 stools over baseline/24 hr.	Life threatening consequences (shock)
Dysphagia	Able to eat usual diet	Causes alteration of diet, but no medical	Causes severe alteration of diet, medical	Life threatening reduction of oral intake

		intervention indicated	intervention indicated	
Mucositis/stomatitis	Erythema	Patchy Ulcerations or pseudo-membranes	Confluent Ulcerations or pseudo-membranes or mucosal bleeding	Tissue necrosis or diffuse mucosal bleeding or life threatening consequences
Nausea	Transient or intermittent	Persistent resulting in decreased oral intake 24-48 hours	Persistent resulting in minimal oral intake >48 hours or aggressive rehydration indicated	Life threatening consequences
Pancreatitis	NA	Symptomatic, no hospitalization indicated	Symptomatic, hospitalization indicated	Life threatening consequences
Proctitis	Discomfort	Minimal interference with usual activities or medical intervention indicated	Unable to perfume usual activities or operative intervention indicated	Life threatening consequences
Vomiting	Transient or intermittent	Persistent resulting in decreased oral intake 24-48 hours	Persistent resulting in minimal oral intake >48 hours or aggressive rehydration indicated	Life threatening consequences
Psychiatric issues (i.e. anxiety, agitation, depression, mania, psychosis)	minimal, without impact on activities	moderate, with impact on activities	Severe, unable to perform typical activities	Behavior potentially harmful to self/others or unable to perform self-care
AMS	minimal, without impact on activities	lethargy, with impact on activities	Confusion, memory impairment lethargy, or somnolence, unable to perform typical activities	Delirium/obtundation or coma
Ataxia	Minimal but detectable on exam, without impact on activities	moderate, with impact on activities	marked, unable to perform typical activities	Disabling causing inability to care for self
Cognitive and behavior (including	Minimal, without impact on	moderate, with impact on	marked, unable to perform typical	Disabling causing inability to care for

dementia and ADD)	activities. No special resourced indicated	activities or part-time special resourced indicated	activities or full-time special resourced indicated	self or institutionalization
CNS Ischemia	NA	NA	Transient ischemic attach	CVA/stroke with neurological deficit
headache	Minimal but detectable on exam, without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or hospitalization indicated
Insomnia	NA	moderate, with impact on activities or part-time special resourced indicated	marked, unable to perform typical activities or full-time special resourced indicated	Disabling causing inability to care for self
Neuromuscular Weakness	Asymptomatic but detectable on exam, without or minimal impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure
Sensory alteration	Asymptomatic but detectable on exam, without or minimal impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure
Seizure, new onset	NA	1 seizure	2-4 seizures	Prolonged or repetitive seizures or difficult to control
Seizure, pre-existing	NA	Increased frequency, no change in character	Change from baseline in either duration or quality	Prolonged or repetitive seizures or difficult to control
Syncope (not associated with a procedure)	NA	Present	NA	NA
vertigo	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure
Arthralgia	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure

Bone Mineral Loss	BMP t-score or z-score -2.5 to -1.3	BMP t-score or z-score <-2.5	Pathological fracture	Pathological fracture causing life threatening consequences
myalgia	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Disabling causing inability to care for self or respiratory failure
Osteonecrosis	NA	Asymptomatic but with radiologic findings and no surgical intervention indicated	symptomatic with radiologic findings or surgical intervention indicated	Disabling bone pain with radiologic findings causing inability to care for self
Acute systemic allergic reaction	Localized urticaria with no medical intervention indicated	Localized urticaria with mild angioedema with no medical intervention indicated	Gen urticaria or angioedema with medical intervention indicated or bronchospasm	Anaphylaxis, laryngeal angioedema, laryngeal edema or life threatening bronchospasm
chills	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	NA
Fatigue/malaise	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Incapacitating symptoms, unable to perform basic self-care
Fever	99.8-101.5	101.6-102.8	102.9-104.9	>104.9
pain	without impact on activities	moderate, with impact on activities	severe, unable to perform typical activities	Incapacitating symptoms, unable to perform basic self-care
Unintentional weight loss	NA	5-9% loss of body weight	10-19% loss of body weight	>19% loss of body weight or aggressive intervention indicated (feeding tube, TPN)
Lipodystrophy or lipoatrophy	detectable by subject	Detectable by provider	Obvious or disfiguring	NA
Diabetes mellitus (new onset)	NA	without indication for medications	Medications indicated	Life threatening consequences
Diabetes mellitus (existing)	NA	Requiring modification of medications	Lack of control despite medication modification	Life threatening consequences
gynecomastia	detectable by subject	Detectable by provider	Obvious or disfiguring	NA

Hyperthyroidism	asymptomatic	Symptoms causing moderate impact of activities OR medication indicated	Symptoms causing inability to perform activities OR medication indicated	Life threatening consequences
hypothyroidism	asymptomatic	Symptoms causing moderate impact of activities OR medication indicated	Symptoms causing inability to perform activities OR uncontrolled despite medication	Life threatening consequences
Intermenstrual bleeding	Spotting	≤ typical menstrual cycle	≥ typical menstrual cycle	Hemorrhage with life threatening hypotension
Urinary obstruction (i.e. stone)	NA	Without hydro-nephrosis or acute kidney injury	With hydro-nephrosis or acute kidney injury	Life threatening consequences
Infection (other than HIV)	Localized, no systemic antimicrobial treatment indicated AND symptoms causing minimal impact on activities	Systemic antimicrobial treatment indicated OR symptoms causing >minimal impact on activities	Systemic antimicrobial treatment indicated AND symptoms inability to perform activities OR operation intervention indicated (beyond simple I&D)	Life threatening consequences (i.e. septic shock)

APPENDIX 3. PRO QUESTIONNAIRES

Self-completed HIV Symptom Index[15]

INSTRUCTIONS: The following questions ask about symptoms you might have had during the **past four weeks**. Please answer the following questions by placing a checkmark in the appropriate box.

Symptom	Did not have this symptom	Symptom did not bother me	Symptom bothers me a little	Symptom bothers me	Symptom bothers me a lot
Fatigue or loss of energy					
Fevers, chills or sweats					
Feeling dizzy or lightheaded					
Pain, numbness or tingling in the hands or feet					
Trouble remembering					
Nausea or vomiting					
Diarrhea or loose bowel movements					
Felt sad, down, or depressed					
Felt nervous or anxious					
Difficulty falling or staying asleep					
Skin problems, such as rash, dryness or itching					
Cough or trouble catching your breath					
Headache					
Loss of appetite or a change in the taste of food					
Bloating, pain, or gas in your stomach					
Muscle aches or joint pain					
Problems with having sex, such as loss of interest or lack of satisfaction					
Changes in the way your body looks such as fat deposits or weight gain					
Problems with weight loss or wasting					
Hair loss or changes in the way your hair looks					

Pittsburgh Sleep Quality Index[16]

Instructions: The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights of the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

BEDTIME_____

2. During the past month, how long (in minutes) has it usually takes you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

GET UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (this may be different than the number of hours you spent in bed.)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you…	Not during past month	Less than once a week	Once or twice a week	Three or more times a week
a) Cannot get to sleep within 30 minutes				
b) Wake up in the middle of the night or early morning				
c) Have to get up to use the bathroom				
d) Cannot breathe comfortably				
e) Cough or snore loudly				
f) Feel too cold				
g) Feel too hot				
h) Had bad dreams				
i) Have pain				
j) Other reason(s), please describe and mark how often it occurs:				

6. During the past month, how would you rate your sleep quality overall?

Very Good _____

Fairly Good _____

Fairly Good_____

Very Good_____

	Not during past month	Less than once a week	Once or twice a week	Three or more times a week
7. During the past month, how often have you taken medicine to help you sleep (prescribed or “over the counter”)?				
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?				

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or a roommate?

No bed partner or room mate _____

Partner/roommate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a roommate or bed partner, ask him/her how often in the past month you have had…	Not during past month	Less than once a week	Once or twice a week	Three or more times a week
a) Loud snoring				
b) Long pauses between breaths while asleep				
c) Legs twitching or jerking while you sleep				
d) Episodes of disorientation or confusion during sleep				
e) Other restlessness while you sleep; please describe and mark how often it occurs:				