Orlando Immunology Center

Clinical Protocol

Efficacy, safety and tolerability of switching to dolutegravir/lamivudine in virologically-suppressed adults living with HIV on bictegravir/tenofovir alafenamide/emtricitabine-the DYAD study

Protocol OIC_008; a prospective randomized clinical trial

July 29th 2020

Sponsor: Orlando Immunology Center

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements

Investigator Protocol Agreement Page

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

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Signature

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Clinical Trials.gov Identifier: NCT 04585737

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1. Protocol Synopsis for OIC_008

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Study Title: Efficacy, safety and tolerability of switching to dolutegravir/lamivudine in virologically-suppressed adults living with HIV on bictegravir/tenofovir alafenamide/emtricitabine-the DYAD study

ClinicalTrials.gov Identifier: TBD

Study Centers planned: Orlando Immunology Center

Objectives:

The primary objective of this study is:

- to evaluate the efficacy of switching from B/F/TAF to DTG/3TC versus continuing the baseline regimen of B/F/TAF in HIV-infected, virologically suppressed adults as determined by the proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48

The secondary objectives of this study are to:

- to evaluate the efficacy of switching to DTG/3TC from B/F/TAF as determined by the proportion of participants with HIV-1 RNA≥ 50 copies/mL at Weeks 12 and 24
- to evaluate the efficacy of switching to DTG/3TC from B/F/TAF as determined by the proportion of participants with HIV-1 RNA<50 copies/mL at Weeks 12, 24 and 48
- to evaluate the safety, and tolerability of switching to DTG/3TC from B/F/TAF in HIV-infected, virologically suppressed adults through Week 48

Study Design:

Randomized, open-label, active-controlled study of virologically suppressed participants living with HIV

Participants who provide written informed consent and meet all the eligibility criteria will be randomized in a 2:1 ratio to one of the following 2 treatment groups:

Treatment Group 1 (n=148): FDC of DTG/3TC (50mg/300mg) administered orally, once daily (QD), without regard to food.

Treatment Group 2 (n=74): Stay on baseline regimen consisting of FDC of B/F/TAF (50mg/200mg/ 25mg) (taken as prescribed) without regard to food.

Randomization will be stratified by gender and race at entry given that this study aims to enroll at least 30% of participants who are female and African American.

All participants will be responsible for using their insurance plan to obtain coverage for DTG/3TC and or B/F/TAF, in addition to any labs required by the study. This expectation is clearly outlined in the informed consent. The study team will work with participants to minimize their co-pays for study medications and labs through the use of manufacturer and other external assistance programs.

Study duration will be 48 weeks.

Number of participants planned: Approximately 222 participants

Target Population: HIV-1 infected adult participants who are virologically suppressed (HIV-1 RNA<50 copies/mL) on FDC of B/F/TAF (50mg/200mg/ 25mg) ≥ 3 months prior to screening

Duration of Treatment:

After screening, eligible participants will be treated for at least 48 weeks. Following the Screening and Day 1 visits, participants will be required to return for study visits at Weeks 4, 12, 24, and 48. There are planned participant phone follow-up visits at Weeks 1 and 36. Participants who complete the study through the Week 48 visit will be referred back to their regular HIV clinic provider for routine follow-up upon study completion.

Diagnosis and Main Eligibility Criteria:

Participants must meet all of the following inclusion criteria to be eligible to participate in the study. Eligible participants with chronic hepatitis B infection or chronic hepatitis C infection who are anticipated to need HCV therapy during the study period are not permitted to enroll. Other main inclusion/exclusion criteria are:

- Currently receiving the FDC of B/F/TAF for ≥ 3 months
- Documented plasma HIV-1 RNA < 50 copies/mL x2 during treatment with B/F/TAF at least 3 months apart prior to the enrollment visit (second HIV-1 RNA may be value from the screening visit)
- Have no history of virologic failure of any prior regimen
- Have a stable insurance plan that is not expected to change in the next 48 weeks
- Have no documented or suspected resistance to INSTIs
- History of 1-2 thymidine analogue mutations (TAMs), and other RT substitutions are allowed, with the following exceptions: History of 3 or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), M184V/I, T69-insertions, or K65R/E/N in RT will be excluded
- Estimated glomerular filtration rate (eGFR) ≥50mL/min according to the Cockcroft-Gault formula for creatinine clearance
- Medically stable without an acute or chronic illness deemed by the investigator to limit the subject's ability to participate and complete the study

Study Procedures/Frequency:

After Screening procedures, eligible participants will be randomized 2:1 to Treatment Group 1 or Treatment Group 2 and treated for 48 weeks. Following the Day 1 visit, participants will be required to return for study visits at Weeks 4, 12, 24, and 48. There are planned participant phone follow-up visits at Weeks 1 and 36. Laboratory analyses (chemistry, hematology, and urinalysis), HIV-1 RNA, CD4+ cell count, assessment of adverse events and concomitant medications, and complete or symptom directed physical examinations will be performed at Screening, Day 1 and subsequent study visits. Whole blood for HIV-1 DNA archive testing will be collected at Screening for all participants. Historical HIV-1 RNA genotypes will be collected if available.

Test Product, Dose, and Mode of Administration:

FDC of dolutegravir 50 mg / lamivudine 300 mg (DTG/3TC) administered orally, once daily, without regard to food

Reference Therapy, Dose, and Mode of Administration:

Baseline regimen consisting of FDC of bictegravir 50 mg / emtricitabine 200 mg / tenofovir alafenamide 25mg (B/F/TAF) taken as prescribed

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint is:

- The proportion of participants with HIV-1 RNA≥50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm

The secondary efficacy endpoints are:

- The proportion of participants with HIV-1 RNA ≥50 copies/mL at Weeks 12 and 24 as defined by the US FDA-defined snapshot algorithm
- The proportion of participants with HIV-1 RNA <50 copies/mL at Weeks 12, 24 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in CD4+ cell count and CD4+/CD8+ ratio at Weeks 12, 24 and 48

Safety: Adverse events, clinical laboratory tests, and tolerability of treatment regimens

Patient Reported Outcomes:

HIV Symptoms Distress Module Index (HIV-SI) will be administered at Day 1, Weeks 4, 12, 24, and 48. HIV Treatment Satisfaction Questionnaire Status (HIV-TSQs) will be administered at Day 1 and HIV Treatment Satisfaction Questionnaire Change (HIV-TSQc) will be administered at Weeks 4 and Week 24. Visual Analogue Scale (VAS) Adherence Questionnaire will be administered at Day 1 and at all visits through Week 48.

Statistical Methods:

The primary analysis will consist of a non-inferiority test of switching to the FDC of DTG/3TC versus staying on B/F/TAF with respect to the proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48, as defined by the US FDA-defined snapshot algorithm. It will be concluded that FDC of DTG/3TC is non-inferior to B/F/TAF if the upper bound of the 2-sided 95% confidence interval (CI) of the difference between treatment groups [DTG/3TC –B/F/TAF] in the percentage of participants with HIV-1 RNA≥ 50 copies/mL is less than 6% (i.e., a margin of 6% is applied to the non-inferiority assessment). The 2-sided 95% CIs will be constructed based on the exact method.

The proportion of participants with HIV-1 RNA ≥50 copies/mL at Weeks 12, and 24, and the proportion of participants with HIV-1 RNA <50 copies/mL at Weeks 12, 24 and 48 as defined by the US FDA-defined snapshot algorithm will also be summarized. The 95% CIs at Weeks 12 and 24 will be constructed in the same manner as described for the primary efficacy endpoint.

The change from baseline in CD4+ cell count and CD4+/CD8+ ratio at Weeks 12, 24 and 48 will be summarized by treatment using descriptive statistics. The differences and the associated 95% CIs at Week 48 will be constructed using an Analysis of Variance (ANOVA) model, including treatment (DTG/3TC vs. B/F/TAF).

Adverse events and clinical laboratory assessments will be summarized using descriptive statistics.

Sample sizes of 148 in the DTG/3TC FDC and 74 in B/F/TAF FDC group achieve approximately 80% power to detect a non-inferiority margin difference between the group proportions of 0.06 for HIV-1 RNA≥50 copies/mL at Week 48. The power is computed for the case when the actual treatment group difference is zero (treatment = reference). The test statistic used is the one-sided Score test (Farrington & Manning) with the significance level of 0.025.

2. Background Information and study rationale

DTG/3TC which is FDA-approved as the co-formulated single tablet regimen (STR), Dovato™ is currently approved for the treatment of HIV-1 infection in treatment-naïve adults. This is based on 48-week data from the pooled Gemini 1&2 studies which demonstrated a non-inferior virologic suppression rate of 91% in patients receiving DTG/3TC vs. 93% in patients receiving DTG+TDF/FTC [1]. There was no evidence of treatment-emergent resistance in either arm among confirmed virologic withdrawals. More recently, 96-week data have been reported which confirm the durability of virologic suppression and high genetic barrier to resistance with this 2-drug (2DR) regimen vs. the 3-drug (3DR) comparator [2]. Additional data from these studies reveal a lower frequency of drug-related adverse events (AEs) and an improved safety profile with respect to renal and bone biomarkers in the 2DR arm [1, 2]. This suggests that DTG/3TC may have an advantage with respect to both short and long-term toxicities in comparison to traditional 3DRs while preserving virologic efficacy and barrier to resistance.

Early data from observational studies evaluating the efficacy and safety of switching virologically suppressed adults to DTG/3TC demonstrated virologic suppression rates of 82-97% at Week 48 in the 2DR arm [3-5]. Recently, long-term data from an Italian cohort of 566 patients switched from a variety of regimens to DTG/3TC revealed probabilities of maintaining virologic suppression at Weeks 96 and 144 of 97.5% and 96.5% respectively [6]. Patients in the 2DR also experienced significant increases in CD4+ count and HDL cholesterol and, significant decreases in total cholesterol and triglycerides. Other observational data demonstrates similar safety findings with several studies also revealing significant increases in CD4+ count [7, 8] and improved lipid profiles [5, 7, 8] in those switched to DTG/3TC from other antiretroviral regimens.

Recently, data from a large randomized controlled trial (TANGO) evaluating the efficacy and safety of switching virologically suppressed adults on TAF-based regimens to DTG/3TC reported virologic suppression rates of 93% at Week 48 in both those switched to the 2DR vs. those who remained on their TAF-based regimen [9]. No patients treated with DTG/3TC experienced confirmed virologic withdrawal and there were no significant changes in lipids, AEs and tolerability between treatment arms [9]. Baseline demographics revealed only 7-9% of trial participants were women and only 14-16% were African American or of African heritage [9]. This study also did not enroll patients on B/F/TAF (Biktarvy™), which is currently the most commonly prescribed guideline recommended single tablet regimen in ARV-experienced patients. Registrational studies of B/F/TAF demonstrated non-inferiority to its comparators in virologically suppressed adults [10, 11] with reports of less bothersome symptoms in patients receiving B/F/TAF compared to those receiving ABC/3TC/DTG [12]. To date, there are no studies evaluating the efficacy and safety of switching patients from B/F/TAF to DTG/3TC, and DTG/3TC does not currently have an FDA indication for use in treatment-experienced patients living with HIV.

Further data would be useful to evaluate the efficacy and safety of switching from a 3DR STR to a 2DR STR given the lack of FDA indication for the use of DTG/3TC in treatment-experienced patients living with HIV infection. The need for more information on this switch strategy in certain subgroups i.e. African Americans and females would also be valuable given that these populations are often under-represented in clinical trials of novel HIV therapeutics and are disproportionately affected by the HIV epidemic in the United States.

The DYAD study is a randomized, open-label, prospective switch study to evaluate the efficacy and safety of switching virologically suppressed adults living with HIV on B/F/TAF to DTG/3TC vs. remaining on B/F/TAF through 48 weeks of treatment. This trial will also have a requirement for 30% of participants to be female and 30% of participants to be from communities of color (Black or Hispanic/Latino).

3. Objectives and Endpoints

Objective	Endpoint
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG/3TC once daily compared to continuation of B/F/TAF over 48 weeks in HIV-1 infected, virologically suppressed subjects	Virologic failure endpoint as per FDA snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG/3TC once daily compared to continuation of B/F/TAF over 48 weeks	Proportion of patients with HIV-1 RNA ≥50 copies/mL at Weeks 12 and 24 Proportion of patients with HIV-1 RNA<50 copies/mL at Weeks 12, 24 and 48
To evaluate the immune effects of DTG/3TC once daily compared to continuation of B/F/TAF over 12, 24, and 48 weeks	Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell count ratio at Weeks 12, 24 and 48
To evaluate the safety and tolerability of DTG/3TC once daily compared to B/F/TAF over time	Incidence and severity of AEs and laboratory abnormalities through 48 weeks Proportion of subjects who discontinue treatment due to AEs through 48 weeks
To evaluate the effects of DTG/3TC once daily on fasting lipids over time compared to TBR	Change from Baseline in fasting lipids at Weeks 24, and 48
To evaluate changes in weight, waist circumference and BMI in those treated with DTG/3TC vs. B/F/TAF over time	Change from Baseline in weight, waist circumference and BMI at Weeks 12, 24, and 48
To assess health related quality of life for subjects treated with DTG/3TC compared to B/F/TAF over time	Change from Baseline in health status using the HIV-SI at Weeks 4, 12, 24 and 48 (or Withdrawal from the study)
To assess treatment satisfaction in subjects treated with DTG/3TC compared to B/F/TAF over time	Change from baseline in treatment satisfaction using the HIV TSQs at Weeks 4, and 24 (or withdrawal from the study
To assess viral resistance in subjects meeting Virologic Rebound Criteria	Incidence of observed genotypic resistance to ARVs for subjects meeting Virologic Rebound Criteria
Exploratory	
To evaluate the effect of patient characteristics (e.g., demographic factors, Baseline CD4) on	• Proportion of subjects by subgroup(s) (e.g., by age, gender, Baseline CD4) with

antiviral and immunological responses to DTG/3TC compared to B/F/TAF	plasma HIV-1 RNA ≥50 c/mL using the Snapshot algorithm at Weeks 12, 24, and 48 • Change from Baseline in CD4+ cell counts at Weeks 12, 24, and 48, by patient subgroups
To assess willingness to switch for subjects treated with DTG/3TC compared to B/F/TAF	Reasons for Willingness to Switch at Day 1

4. Study Design

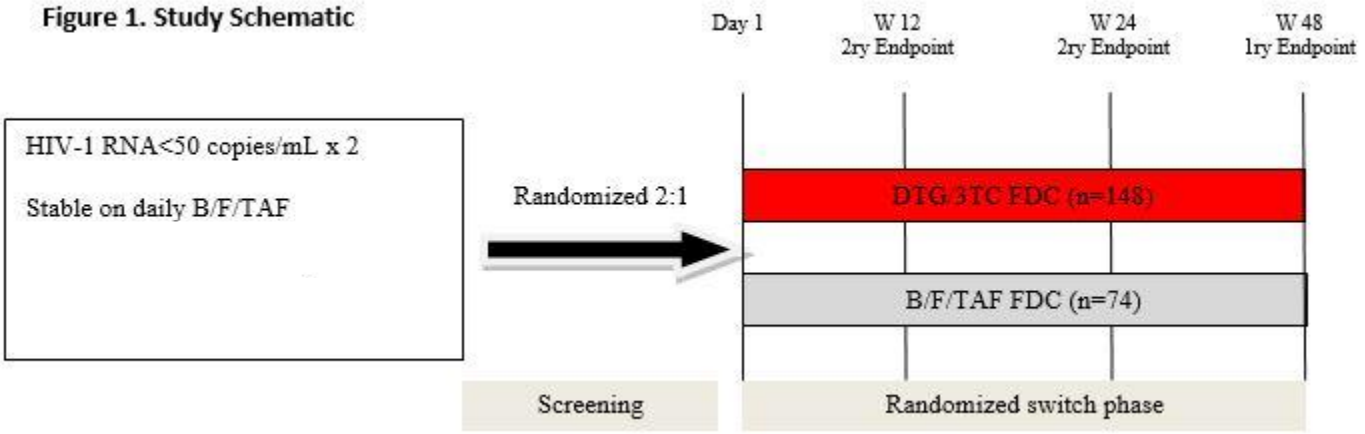
a. Overall Design

This is a 48-week, randomized, open-label, active-controlled, parallel-group study to assess antiviral activity, safety and tolerability of replacing B/F/TAF with a two-drug regimen of DTG/3TC in virologically suppressed adults living with HIV who are stable on B/F/TAF. The study will include a Screening Phase (up to 42 days), and a Switch Phase (Day 1 up to Week 48). Approximately 222 HIV-1 infected adults who are on B/F/TAF will be randomized 2:1 to switch to DTG/3TC once daily (DTG/3TC arm) for up to 48 weeks, or to continue B/F/TAF for 48 weeks. All participants will be responsible for using their insurance plan to obtain coverage for DTG/3TC and or B/F/TAF, in addition to any labs required by the study. This expectation is clearly outlined in the informed consent. The study team will work with participants to minimize their co-pays for study medications and labs through the use of manufacturer and other external assistance programs.

The primary endpoint for the study is the proportion of participants who maintain virologic suppression (defined as an HIV-1 RNA<50 copies/mL) at Week 48 per the FDA snapshot algorithm. The Week 48 primary analysis will take place after the last subject has had their Week 48 viral load assessed, including any retests. All subjects who successfully complete 48 weeks of treatment will complete the study and be referred back to their regular HIV clinic provider for routine management and decisions regarding ARV (antiretroviral) therapy.

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during this study. Adherence to the study protocol, including those specified in the Study Procedures Table (Appendix 1), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these will be communicated promptly to the study PI and any regulatory authorities as appropriate.

Figure 1. Study Schematic



b. Treatment Arms and Duration

Screening Period (Up to 42 days)

Randomization may occur as soon as all screening procedures and entry criteria data are confirmed and available on file at the site. The Screening period of up to 42 days is to allow receipt of all screening assessment results, to enable source document verification of entry criteria and to accommodate scheduling.

Randomized Switch Phase (Day 1 to Week 48)

Subjects who fulfill all eligibility requirements will be randomly assigned 2:1 to receive DTG/3TC FDC once daily up to Week 48 or continue B/F/TAF up to Week 48. The DTG/3TC and B/F/TAF will be administered in an open-label fashion throughout the study. All participants will be responsible for using their insurance plan to obtain coverage for DTG/3TC and or B/F/TAF, in addition to any labs required by the study. The primary analysis will take place after the last subject completes up to 52 weeks on therapy, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at the Week 48 visit. If the retest HIV-1 RNA is <50 c/mL, then the subject will be considered to have met the criteria for virologic responder by the Food Drugs and Administration (FDA)'s Snapshot algorithm at Week 48. If the retest HIV-1 RNA is ≥50 c/mL, then the subject will be considered to be a virologic failure at Week 48 by Snapshot. The secondary analysis at Weeks 12 and 24 will take place after the last subject completes up to 16 and 28 weeks on therapy respectively, as needed, to allow for the collection of a confirmatory viral load measurement in subjects presenting with HIV-1 RNA ≥50 c/mL at Weeks 12 and 24. At the end of the study at Week 48, subjects will referred back to their regular HIV clinic provider for routine management and decisions regarding ARV (antiretroviral) therapy.

c. Type and Number of Subjects

The target population to be enrolled is HIV-1 infected adults who are virologically suppressed on B/F/TAF with no evidence or history of ARV drug-resistance affecting dolutegravir or lamivudine.

Assuming a 15% screen failure rate, approximately 260 HIV-1-infected adult subjects will be screened to achieve 222 randomized subjects for a total of 148 evaluable subjects in Treatment group 1 (DTG/3TC FDC) and 74 evaluable subjects in Treatment group 2 (B/F/TAF FDC).

d. Dose Justification

The DTG/3TC FDC containing DTG (50 mg) and 3TC (300 mg) has been approved by the US-FDA for use once daily for the treatment of human immunodeficiency virus type1 (HIV-1) infection in adults.

e. Benefit:Risk Assessment

All patients with HIV-1 infection should receive effective antiretroviral therapy. Potential risks associated with all classes of ARVs include immune reconstitution syndrome, lipodystrophy, and lactic acidosis with steatosis [13]. The risk of class effects is considered to be low. Potential benefits may include provision

of a new ARV therapy which may have fewer side effects and drug-drug interactions than alternative therapies resulting in improved adherence and long-term virologic suppression. Other potential benefits include the knowledge that patient participation will contribute to the body of knowledge of HIV therapies in African American and female patients. In phase 3 studies of DTG/3TC, the subgroup of participants self-identified as Black or African American had similar outcomes for efficacy and safety compared with the study population as a whole. The overall benefit-risk assessment for DTG/3TC is favorable at this time.

Summaries of findings from both clinical and non-clinical studies conducted with DTG or 3TC can be found in the product labels.

The following section outlines the risk assessment and mitigation strategy for DTG and 3TC in this protocol. For B/F/TAF, please consult the prescribing label for further information on the potential risks and benefits associated with use [18].

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG/3TC] Refer to Product Label for additional information		
DTG: Hypersensitivity reaction (HSR) and rash	**DTG**: HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported.	Subjects with history of allergy/sensitivity to any of the study drugs are excluded. Toxicity management for rash will be left to the discretion of the investigator but specific guidance depending on severity is included in Section 8j. The subject informed consent form (ICF) includes information on this risk and the actions subjects should take in the event of a HSR or associated signs and symptoms
DTG: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations **3TC**: Use in HBV coinfected patients and emergence of HBV variants resistant to 3TC	DTG: Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG-containing ART, along with inadequate therapy for HBV co-infected subjects, likely contributed to significant elevations in liver chemistries.	Subjects meeting any of the following criteria during the screening period are excluded from participating. • Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5x ULN (with >35% direct bilirubin) • Subjects positive for Hepatitis B surface antigen (+HBsAg) • Subjects negative for HBsAg and anti-HBsAg and positive for anti-HBc and HBV DNA.

	There have been rare post-marketing reports of acute hepatic failure in association with DTG-containing regimens 3TC: Current treatment guidelines [13] do not recommend monotherapy with 3TC for patients with HBV infection, which is what subjects randomised to DTG plus 3TC, would effectively be receiving. Emergence of HBV variants associated with resistance to 3TC has been reported in HIV-1 infected patients who have received 3TC-containing antiretroviral regimens in the presence of concurrent infection with HBV. Additionally, discontinuation of 3TC in HBV co-infected subjects can result in severe exacerbations of hepatitis B	• Anticipated need for any hepatitis C virus (HCV) therapy during the first 48 weeks of the study, and for HCV therapy based on interferon or for any drugs that have a potential for adverse drug-drug interactions with study treatment throughout the entire study period. Toxicity management for elevations in liver enzymes will be left to the discretion of the investigator but specific guidance depending on severity is included in Section 8j.
DTG: Psychiatric disorders	DTG: Psychiatric disorders including suicidal ideation and behaviors are common in HIV-infected patients. Events of suicidal ideation, attempt, behaviour and completion were observed in clinical studies of DTG, primarily in subjects with a pre-existing history of depression or other psychiatric illness. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL-or favorable compared with EFV-based regimens. The reporting rate for insomnia was statistically higher for blinded DTG+ abacavir/lamivudine (ABC/3TC) compared to EFV/TDF/FTC in ING114467; however, this was not duplicated in any other Phase IIb/III study conducted with DTG.	Subjects who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating. Because of the elevated risk in the HIV-infected population, treatment emergent assessment of suicidality will be monitored during this study through the end of the continuation phase. Investigators are advised to consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour (See Section 8k). The subject informed consent form includes information on the risk of depression and suicidal ideation and behavior.
DTG: Theoretical serious drug interaction with dofetilide and fampridine/dalfampridine	DTG should not be used with products with narrow therapeutic windows, that are substrates of organic cation transporter 2 (OCT2), including but not limited to the antiarrhythmic agent dofetilide, or the potassium channel blocker fampridine (also known as dalfampridine), due to the potential risk of serious or life-threatening toxicity.	The co-administration of DTG with dofetilide or fampridine (dalfampridine) is prohibited in the study (Section 6j).
DTG and 3TC: Renal function	DTG: Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow.	Toxicity management for declines in renal function will be left to the discretion of the investigator but specific guidance depending on severity is included in Section 8j. Creatinine clearance is calculated in all patients prior to initiating therapy and renal function (creatinine clearance

	3TC: 3TC is eliminated by renal excretion and exposures increase in patients with renal dysfunction.	and serum phosphate) will be monitored at all subsequent study visits. Subjects with creatinine clearance <50 mL/min are excluded from participation in this study.
DTG: Creatine Phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	Toxicity management for elevations in CPK will be left to the discretion of the investigator but specific guidance depending on severity is included in Section 8j.
DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 5/1683 (0.3%) of women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A female subject is eligible to participate if she is not pregnant, not lactating, and, if she is a female of reproductive potential, agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 2) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication. 2. Women who are breastfeeding or plan to become pregnant or breastfeed during the study are excluded. 3. Women who become pregnant, or who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have study treatment discontinued and will be withdrawn from the study. 4. Females of reproductive potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit. 5. Pregnancy status is monitored at every study visit

5. Selection of Study Population and Withdrawal Criteria

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the study medication that may impact subject eligibility is provided in the Product Insert for DTG/3TC (Dovato™) [14].

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

The following are study specific eligibility criteria unless stated otherwise. In addition to these criteria, investigators must exercise clinical discretion regarding selection of appropriate study subjects, taking into consideration any local treatment practices or guidelines and good clinical practice (GCP).

a. Inclusion Criteria

Eligible subjects must:

- be able to understand and comply with protocol requirements, instructions, and restrictions
- be likely to complete the study as planned
- be considered appropriate candidates for participation in an investigative clinical trial with medication (e.g. no active substance abuse, acute major organ disease, or planned long-term work assignments out of the country).

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Aged 18 years or older at the time of signing the informed consent
TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. HIV-1 infected men or women. 3. Must have a stable form of insurance that is expected to continue without significant changes for at least 48 weeks 4. Documented evidence of at least two plasma HIV-1 RNA measurements <50 c/mL at least 3 months apart prior to Day 1 (the screening HIV-1 RNA can count as the second measurement) 5. Plasma HIV-1 RNA <50 c/mL at Screening. 6. Must be on uninterrupted B/F/TAF for at least 3 months prior to screening
SEX
7. Male or female

A female subject is eligible to participate if she is not pregnant [as confirmed by a negative serum human chorionic gonadotrophin (hCG) test at screen and a negative urine hCG test at Day 1/Randomization (a local serum hCG test at Randomization is allowed if it can be done, and results obtained, within 24 hours prior to randomization)], not lactating, and at least one of the following conditions applies:

a. **Non-reproductive** potential defined as:

- Pre-menopausal females with one of the following:

  o Documented tubal ligation

  o Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion

  o Hysterectomy

  o Documented Bilateral Oophorectomy

- Post-menopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment.

b. **Reproductive** potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 2) from 30 days prior to the first dose of study medication and for at least 2 weeks after the last dose of study medication.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception. All subjects participating in the study should be counseled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to an uninfected partner.

INFORMED CONSENT

8. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Eligible subjects must sign a written Informed Consent Form before any protocol-specified assessments are conducted

b. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Women who are breastfeeding or plan to become pregnant or breastfeed during the study. 2. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 disease [15], EXCEPT cutaneous Kaposi's sarcoma not requiring systemic therapy. Historical or current CD4 cell counts less than 200 cells/mm3 are NOT exclusionary. 3. Subjects with severe hepatic impairment (Class C) as determined by Child-Pugh classification [16]. 4. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 5. Evidence of Hepatitis B virus (HBV) infection based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (antiHBc), Hepatitis B surface antigen antibody (anti-HBs) and HBV DNA as follows: • Subjects positive for HBsAg are excluded. • Subjects negative for anti-HBs but positive for anti-HBc (negative HBsAg status) and positive for HBV DNA are excluded. Note: Subjects positive for anti-HBc (negative HBsAg status) and positive for antiHBs (past and/or current evidence) are immune to HBV and are not excluded. AntiHBc must be either total anti-HBc or anti-HBc immunoglobulin G (IgG), and NOT anti-HBc IgM. 6. Anticipated need for any hepatitis C virus (HCV) therapy during the first 48 weeks of the study 7. Untreated syphilis infection (positive rapid plasma reagin [RPR] at Screening without clear documentation of treatment). Subjects who are at least 7 days post completed treatment are eligible. 8. History or presence of allergy or intolerance to the study drugs or their components or drugs of their class. 9. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia. 10.Subjects who in the investigator's judgment, poses a significant suicidality risk.
EXCLUSIONARY TREATMENTS PRIOR TO SCREENING OR DAY 1
11. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening 12. Treatment with any of the following agents within 28 days of Screening • radiation therapy • cytotoxic chemotherapeutic agents • any systemic immune suppressant

13. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of study medication. 14. Use of any regimen consisting of single or dual ART
LABORATORY VALUES OR CLINICAL ASSESSMENTS AT SCREENING
15. Any evidence of major NRTI mutation (defined as history of 3 or more TAMs (M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R), M184V/I, T69-insertions, or K65R/E/N) or presence of any major INSTI resistance-associated mutation [17] in any available prior resistance genotype assay test result 16. Any verified Grade 4 laboratory abnormality 17. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) or ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin). 18. Creatinine clearance of <50mL/min/1.73m2 via CKD-EPI method.
EXCLUSIONARY CRITERIA PRIOR TO SCREENING OR DAY 1
19. Within the 6 to 12-month window prior to Screening and after confirmed suppression to <50 copies/mL, any plasma HIV-1 RNA measurement >200 c/mL. 20. Within the 6 to 12-month window prior to Screening and after confirmed suppression to <50 copies/mL, 2 or more plasma HIV-1 RNA measurements ≥50 c/mL. 21. Within 6 months prior to Screening and after confirmed suppression to <50 c/mL on current ART regimen, any plasma HIV-1 RNA measurement ≥50 copies/mL. 22. Any drug holiday during the 12 months prior to Screening, except for brief periods (less than 1 month) where all ART was stopped due to tolerability and/or safety concerns. 23. Any history of switch to another regimen, defined as change of a single drug or multiple drugs simultaneously, due to virologic failure to therapy (defined as a confirmed plasma HIV-1 RNA ≥400 copies/mL.

c. Screening Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events.

Subjects are allowed to re-screen for this study one time (except where screen HIV-1 plasma RNA ≥50 copies/mL or where exclusionary HIV-1 resistance was present). Re-screening will require a new subject number. A single repeat test (re-test) per analyte or assessment is allowed during the screening period to determine eligibility. However, a repeat HIV-1 RNA, if HIV-1 RNA was ≥50 copies/mL is not allowed.

Laboratory results obtained from a local lab utilizing the participant's insurance plan will be used to assess eligibility. Source documentation to verify entry criteria must be reviewed by the Principal Investigator or designee prior to randomization. Source documents from other medical facilities must be located/retrieved during the screening period. Under no circumstances may a subject be randomized in the absence of source documentation including prior qualifying viral load data (as outlined in the Inclusion Criteria).

d. Withdrawal and Stopping Criteria

Subjects permanently discontinuing study treatments are considered withdrawn from the study. Withdrawn subjects will not be replaced. A subject may withdraw consent and discontinue participation in this study at any time at his/her own request.

The investigator may also, at his or her discretion, discontinue the subject from participating in the study at any time (e.g. safety, behavioral or administrative reasons). If a subject withdraws from the study, he/she may not be able to request destruction of any samples taken, as these are sent for testing and processing at a local laboratory (i.e. Quest, LabCorps, Advent Health), this will be clearly outlined in the informed consent. Subjects are not obligated to state the reason for withdrawal. However, a reason for withdrawal must be documented by the Investigator on the source notes for the Completion/Withdrawal visit. Every effort should be made by the Investigator to follow-up subjects who withdraw from the study.

Subjects may have a temporary interruption to their study treatment for management of toxicities. Such interruption of study treatment does not require withdrawal from the study; however, this decision should be made in conjunction with the Principal Investigator.

Subjects <u>may</u> be prematurely discontinued from the study for any of the following reasons:

- Subject or Investigator non-compliance
- At the request of the subject or Investigator
- The subject requires concurrent prohibited medications during the course of the study. The subject may remain in the study if in the opinion of the Investigator, such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the subject.

Subjects <u>must</u> be discontinued from the study for any of the following reasons:

- Virologic rebound criteria as specified in Figure 2 are met
- Subject is identified as having been mistakenly screened/randomized with exclusionary resistance (see Section 5b)
- Subject requires substitution or dose modification of DTG/3TC or B/F/TAF
- Presence of significant liver toxicity that is possibly drug-related
- Presence of significant renal toxicity that is possibly drug-related
- Grade 4 clinical or laboratory AE that is possibly drug-related
- Allergic reaction or rash that is possibly drug-related at the discretion of the investigator
- Pregnancy (intrauterine), regardless of termination status of pregnancy (Section 5b). As a

reminder, females of reproductive potential who change their minds and desire to be pregnant, or who state they no longer are willing to comply with the approved pregnancy avoidance methods should also be withdrawn from the study

- Subject loses insurance and has no ability to obtain study treatment or cover required study labs through Week 48

If a subject is prematurely or permanently withdrawn from the study, the procedures described in the Study Procedures Table (Appendix 1) for the in-clinic Withdrawal visit are to be performed. All data from the Withdrawal visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any subject from the study. Once the withdrawal visit is completed, the subject will be referred back to their regular HIV clinic provider for further evaluation and management.

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow-up', the investigator or designee must make every effort to regain contact with the subject (where possible, three telephone calls and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

Management of Virologic Rebound

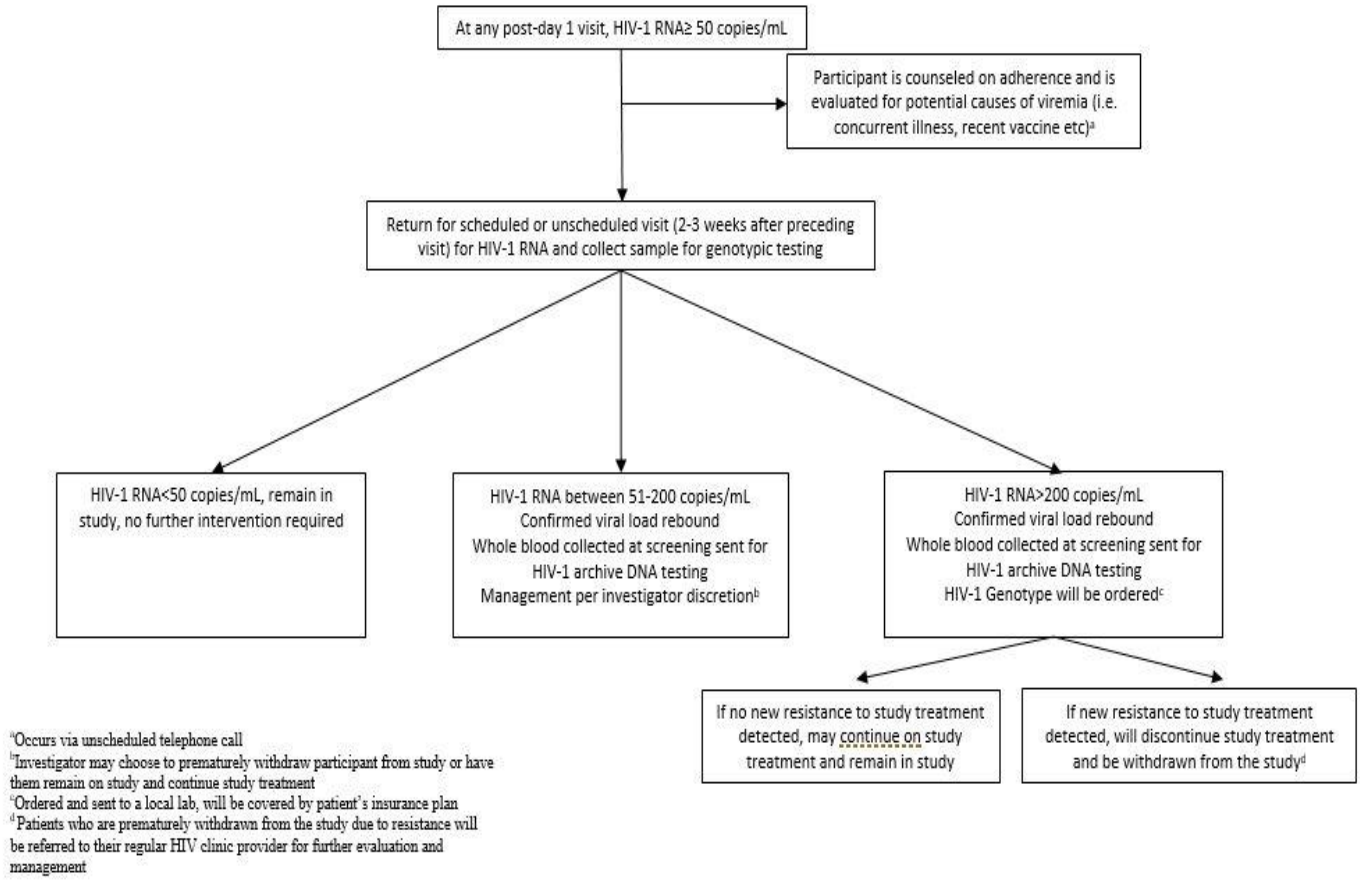
Participants who meet the criteria listed below will be considered to have virologic rebound:

- At any post Day 1 visit, a confirmed rebound in HIV-1 RNA ≥50 copies/mL

Following the initial virologic rebound, participants will be asked to return to the clinic for a scheduled or unscheduled blood draw (within 2 to 3 weeks after the date of the original test that resulted in HIV-1 RNA≥ 50 copies/mL). Participants with HIV-1 RNA values between 50-200 copies/mL should follow the algorithm in Figure 2. If virologic rebound is confirmed at the scheduled or unscheduled visit, whole blood for HIV-1 DNA archive testing (collected at screening) will also be sent to the lab for processing. If virologic rebound is confirmed at the scheduled or unscheduled visit and the HIV-1 RNA is ≥ 200 copies/mL, the plasma sample from the confirmation visit will also be sent for HIV-1 genotypic testing. After a participant's first post-Day 1 resistance test, additional testing will be conducted on a case-by-case basis. Any participant may be discontinued at the investigator's discretion or per local treatment guidelines. If no resistance to study treatment is detected from the genotypes, the participant may remain on study treatment and HIV-1 RNA should be analyzed at a new visit (within 2 to 3 weeks after date of the second test with HIV-1 RNA ≥50 copies/mL). Investigators should carefully evaluate the benefits and risks of remaining on study treatment for each individual participant and document this assessment in the medical record.

Participants who are noncompliant on an ongoing basis will be considered for discontinuation per the investigator's discretion or local treatment guidelines. Participants who are off study treatment may be prematurely discontinued from the study at the discretion of the investigator. Please refer to Figure 2 for the management of participants who meet the criteria for virologic rebound.

Figure 2. Management of Virologic Rebound



<u>Participants with HIV-1 RNA ≥50 copies/mL at Study Drug Discontinuation, Week 12, Week 24, or Week 48</u>

Participants with HIV-1 RNA ≥50 copies/mL at study drug discontinuation, last visit, or last Week 12, 24 or 48 result will be considered virologic rebounders. Participants with HIV-1 RNA ≥50 copies/mL at Week 12, 24 or Week 48 will be asked to return for an unscheduled visit within the visit window for a retest and have whole blood for HIV-1 DNA archive testing (collected at screening) sent to the lab for processing. Participants with HIV-1 RNA ≥200 copies/mL at study drug discontinuation, last visit, or Week 12, 24 or 48 visit, will also have HIV-1 genotype resistance testing conducted.

Management of patients with significant hepatic toxicity

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study drug and the follow-up period (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

For any participant meeting one of the criteria outlined in Table 1 or Table 2, or if the Investigator believes that it is in the best interest of the participants, the investigator will follow the required actions and follow up assessments also outlined in these tables.

Table 1 Liver Chemistry Stopping Criteria - Liver Stopping Event

ALT absolute	*ALT ≥ 8xULN*
ALT increase	*ALT ≥ 5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)*
Bilirubin[1, 2]	*ALT ≥3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)*
INR[2]	*ALT ≥ 3xULN **and** International normalised ratio (INR)>1.5, if INR measured*
Cannot Monitor	*ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for >2 weeks* *(See Table 2 for actions where subjects CAN be monitored weekly for >2 weeks)*
Symptomatic[3]	*ALT ≥ 3xULN (if baseline ALT is <ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity* *ALT ≥ 3x baseline (if baseline ALT>ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity*

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	***Follow Up Assessments***
• **Immediately hold DTG/3TC or B/F/TAF** • **If a causal relationship between the liver event and DTG/3TC or B/F/TAF cannot be ruled out, then DTG/3TC or B/F/TAF must be permanently discontinued and the**	• Viral hepatitis serology, including: Hepatitis A immunoglobulin M (IgM) antibody; HBsAg and hepatitis B core antibody; Hepatitis C RNA;

Subject not rechallenged due to the risk of a recurrent reaction. • Report the event to the ViiV/GSK safety team by telephone within **24 hours**. • Events of possible drug-induced liver injury with hyperbilirubinemia[2] will be reported to ViiV/GSK as serious adverse events (SAEs) using the SAE CRF. • Complete the liver event case report form for all events meeting liver stopping criteria, and submit to ViiV/GSK within one week of first becoming aware of the event • Perform liver event follow up assessments. • Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below). • All participants who experience a liver stopping event in this clinical trial will be permanently withdrawn from the study. **MONITORING:** • Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries (include ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) and perform liver event follow up assessments at the local laboratory as described to the right. • A specialist or hepatology consultation can be considered. • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline.	Hepatitis E IgM antibody. • Cytomegalovirus IgM antibody. • Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing). • Syphilis screening. • Drugs of abuse screen, including alcohol. Record alcohol use on the liver event case report form • Serum acetaminophen adduct High Performance Liquid Chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [19]). • Serum creatinine kinase and lactate dehydrogenase. • Fractionate bilirubin, if total bilirubin ≥1.5xULN. • Obtain complete blood count with differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease. Complete Liver Imaging and/or Liver Biopsy case report form if applicable • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal

	remedies, other over the counter medications.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) **or** ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury **must be reported as a serious adverse event**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia). Record the appearance or worsening of any such clinical symptoms on the adverse event report form.

Table 2 Liver Chemistry Increased Monitoring Criteria

Criteria	Actions
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for >2 weeks.	• Notify the ViiV/GSK safety team **within 24 hours** of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) until resolution, stabilisation (ALT <5×ULN on 2 consecutive evaluations) or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above

Liver Safety- Study Treatment Restart

Participants who meet liver stopping criteria for any reason will be discontinued from study treatment and permanently withdrawn from this clinical trial.

Management of patients with significant renal toxicity

Treatment with DTG/3TC must be discontinued in any subject developing moderate to severe renal impairment during the study, as indicated by confirmed creatinine clearance measuring <50 mL/min via the Cockcroft-Gault method (initial abnormal value must be confirmed by a repeat creatinine clearance assessment within 2 weeks.) These participants will be permanently withdrawn from the study.

e. Subject and Study Completion

Subjects are considered to have completed the study if they satisfy one of the following:

- randomly assigned to either treatment group and completed the Week 48 visit
- the subject no longer derives clinical benefit
- the subject meets a protocol-defined reason for discontinuation

Subjects completing the study will be referred to their regular HIV clinic provider for further evaluation and management.

6. Study Treatment

a. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments. All study treatments will be administered at the approved dosages. Participants will be responsible for utilizing their insurance plan to obtain the study treatment, DTG/3TC FDC (Dovato™) from a local pharmacy. Subjects randomly assigned to continue B/F/TAF up to 48 weeks will also be responsible for utilizing their insurance plan to obtain B/F/TAF (Biktarvy™) from a local pharmacy. The study team will work with all study subjects to minimize out of pocket co pays for drug coverage through the use of manufacturer or other external assistance programs. DTG/3TC must be stored in a secure area under the appropriate physical conditions for the product. For further details on storage, access and administration of study treatments, refer to product labels for Dovato™ [14] and Biktarvy™ [18].

b. Protocol-Permitted Substitutions

There are no protocol-permitted substitutions for DTG/3TC or B/F/TAF allowed for this study.

c. Treatment Assignment

Participants will be assigned a screening number at the time of consent. **Randomization/Day 1 visits cannot occur until participant eligibility has been confirmed.**

Once eligibility has been confirmed and prior to or during the Day 1 visit, the Investigator or designee will randomize the participant using a randomization code developed by the study statistician. Once a participant number has been assigned to a participant, it will not be reassigned to any other participant. The participant number assignment and randomization may be performed up to 3 days prior to the in-clinic Day 1 visit provided that all screening procedures have been completed and participant eligibility has been confirmed.

Participants will be randomized in a 2:1 ratio to Treatment Group 1 or Treatment Group 2.

Treatment Group 1 (n=148):FDC of DTG/3TC (50 mg/300 mg) administered orally, once daily (QD), without regard to food.

Treatment Group 2 (n=74):Stay on FDC of B/F/TAF (50 mg/200 mg/25 mg) administered orally, QD, without regard to food.

No assignment of study drug bottles will occur in this protocol as participants will expected to utilize their insurance plan to obtain commercially available DTG/3TC or B/F/TAF from a local pharmacy.

Randomization will be stratified by race and gender to ensure equal numbers of African Americans and females in each study arm.

d. Planned Dose adjustments

No dose adjustments are permitted in this study for DTG/3TC or for B/F/TAF.

e. Blinding

This will be an open-label study and therefore no blinding is required.

f. Packaging and Labeling

Participants will be responsible for utilizing their insurance plan to obtain commercially available DTG/3TC or B/F/TAF from a local pharmacy. The site and study team will not be responsible for the packaging and labeling of the study treatments.

g. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

Participants will be instructed that all study treatments must be stored in a secure environmentally controlled area in accordance with the labelled storage conditions.

Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to participants or site staff.

Methods to evaluate study treatment accountability will not be used in this protocol as participants will be responsible for utilizing their insurance plan to obtain commercially available DTG/3TC or B/F/TAF from a local pharmacy and will be instructed to store the study treatment at home according to instructions on the label.

h. Compliance with study treatment administration

When subjects self-administer study treatment(s) at home, compliance with study drugs will be assessed through querying the subject during the site visits (i.e. through use of the Visual Analog Scale (VAS) Adherence survey) and documented in the source documents. Treatment start and stop dates also will be recorded in the source documents.

i. Treatment after the end of the study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition. At the end of the study at Week 48, subjects will be referred to their regular HIV clinic provider for further evaluation and management. The clinic provider will be responsible for decisions regarding appropriate HIV therapy once subjects have completed the study.

j. Prior and concomitant medications

Concomitant medications (prescription and non-prescription) should be prescribed by the relevant

health care provider/investigator and administered only as medically necessary during the Randomized phases of the study (except prohibited medications as described below). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the subject and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the source documentation with dates of administration.

Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is highly recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn and only when scheduled visits are ≥4 weeks apart. This approach will minimize the risk of nonspecific increases in the level of HIV-1 plasma RNA at the next scheduled assessment.

DTG/3TC should be administered 2 hours before or 6 hours after taking antacid or laxative products containing polyvalent cations (e.g. aluminum and magnesium), sucralfate, or calcium supplements. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable. Iron supplements can be taken with study treatment provided that all are taken together with a meal. Under fasted conditions, DTG/3TC should be given 2 hours prior to OR 6 hours after iron supplements.

Metformin concentrations may be increased by DTG. A dose adjustment of metformin should be considered when starting and stopping co-administration of dolutegravir with metformin, to maintain glycemic control.

Clinical monitoring is recommended for subjects taking methadone, as methadone maintenance therapy may need to be adjusted in some subjects.

Non-protocol defined treatments or medical interventions (e.g., physical therapy, radiotherapy, surgical procedures) are permitted during the study for appropriate medical management of the subject.

Prohibited Medications and Non-Drug Therapies

The following concomitant medications or therapies are not permitted at any time during the study:

- HIV immunotherapeutic vaccines
- Other experimental agents, ART drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited through Week 48. This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted
- HCV therapy up to Week 48

For more information on prohibited medications and drug-drug interactions in relation to other antiretrovirals used in comparator regimens, please refer to the package insert for B/F/TAF [18].

Prohibited Medications for Subjects Receiving DTG/3TC

Medications (or their equivalents) that may cause decreased concentrations of DTG and/or 3TC and must not be administered concurrently with DTG/3TC:

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- Rifapentine
- St. John's wort
- Dofetilide (DTG may inhibit renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity).
- Fampridine/Dalfampridine

Note: Any prohibited medications that decrease dolutegravir concentrations should be discontinued for a minimum of four weeks or a minimum of three half-lives (whichever is longer) prior to the first dose. Any other prohibited medications should be discontinued for a minimum of two weeks or a minimum of three half-lives (whichever is longer) prior to the first dose.

7. Study Procedures

The study procedures to be conducted for each participant enrolled in the study are presented in tabular form in Appendix 1 and are described in the text that follows.

The investigator must document any deviation from protocol procedures and notify any applicable regulatory agencies.

a. Participant enrollment and treatment assignment

It is the responsibility of the Investigator to ensure that participants are eligible for study prior to enrollment. Please refer to Section 7b below for details about randomization and treatment assignment.

b. Pretreatment Assessments

Screening Visit

Participants will be screened within 42 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 demographic information, including gender at birth, and race
- Obtain screening number using randomization code
- Obtain medical history including history of HIV-1 disease-related events, and prior medications within 30 days of the screening visit
- If available, obtain documentation of historical genotype(s) (not required for entry to study)
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Height
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight and waist circumference measurement
- Obtain blood and urine samples as described in Section 7e
- Review concomitant medications
- Record any SAEs and all AEs related to protocol mandated procedures occurring after signing of the consent form.

Participants meeting all of the inclusion criteria, and none of the exclusion criteria, will return to the clinic within 42 days after screening for the Day 1 Visit. Participants randomized to Treatment Group 1 must continue to take their prior treatment regimen up until the day before their scheduled Day 1 visit. Participants randomized to Treatment Group 2 will continue to take their prior treatment regimen until the end of the study at Week 48. From the time of obtaining informed consent through the first administration of study treatment record all SAEs, as well as any AEs related to protocol-mandated procedures in the source documentation. All other untoward medical occurrences observed during the

screening period, including exacerbation or changes in medical history are to be captured in the medical history in the source documents

Randomization

Once eligibility has been confirmed and prior to or during the Day 1 visit, the Investigator or designee will randomize the participant using the randomization code provided by the study statistician. Once a participant number has been assigned to a participant, it will not be reassigned to any other participant. The participant number assignment and randomization may be performed up to 3 days prior to the in-clinic Day 1 visit, provided that all screening procedures have been completed and participant eligibility has been confirmed. This study aims to enroll 30% of participants who identify as female and African American. Randomization will be stratified by gender and race to ensure equal numbers of females and African American participants in each study arm.

c. Day 1 Assessments

The following evaluations are to be completed at the Day 1 Visit. The Investigator must have confirmed eligibility before proceeding with the Day 1 visit.

Participants must complete all study procedures before being administered FDC of DTG/3TC:

- HIV Symptoms Distress Module Index and HIV Treatment Satisfaction Status (HIV-TSQs) (completed by participants in Treatment group 1&2)
- Visual Analogue Scale (VAS) Adherence Questionnaire is to be completed by participants in Treatment Group 2 only. Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires.
- Willingness to Switch survey (to be completed by participants in Treatment group 1 only)
- Review of AEs and changes in concomitant medications
- Symptom-directed physical examination
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight and waist circumference
- Obtain urine sample for pregnancy testing in female participants of reproductive potential
- Confirmation that participants in Treatment Group 1 were able to obtain DTG/3TC from their local pharmacy using their insurance plan
- Observed first dose administration of FDC of DTG/3TC in Treatment Group 1. If the participant has taken their prior regimen on Day 1, prior to the Study Visit, they should be instructed to take their first dose of DTG/3TC the following day and dosing can be confirmed by phone.
- Participants should be instructed to take FDC of DTG/3TC without regard to food. The participant should be counseled regarding the importance of adherence and taking their study medication at approximately the same time each day as directed by the Investigator.

d. Treatment Assessments (W1-48)

All study visits are to be completed within ± 7 days of the protocol specified visit date (based on the Day 1 visit), unless otherwise specified.

The following evaluations are to be completed at the Weeks 1 and 36* phone call, unless otherwise specified.

- Review of AEs and changes in concomitant medications
- Informal adherence assessment by asking "How many doses of study treatment have been missed in the last 7 days and in inquiring about reasons for missed doses"
- Adherence counseling by investigator or designee

*Week 36 assessment will also include clinical laboratory assessments as specified below

The following evaluations are to be completed at Weeks 4, 12, 24, and 48 unless otherwise specified.

- HIV Symptoms Distress Module Index is to be completed by the participant at Weeks 4, 12, 24 and 48. HIV Treatment Satisfaction Change (HIV-TSQc) is to be completed at Weeks 4 and 24 only. VAS Adherence Questionnaire is to be completed by the participant at Weeks 4, 12, 24 and 48. The Columbia-Suicide Severity Rating Scale (C-SSRS) is to be completed by the participant at Weeks 4, 12, 24 and 48. Participant is to read questionnaire by himself/herself and write/mark answers directly onto questionnaires
- Review of AEs and changes in concomitant medications
- Complete physical examination (Weeks 24 and 48) (urogenital/anorectal exams will be performed at the discretion of the Investigator) or symptom-directed physical examination, as needed
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight and waist circumference
- Obtain blood and urine samples as described in Section 7e
- Document any changes in insurance and confirm participant ability to still obtain DTG/3TC or B/F/TAF from their local pharmacy
- Participants who meet the criteria for virologic rebound will be managed according to the Management of Virologic Rebound Schema found in Figure 2

After completion of the Week 48 assessment, participants will exit the study and be referred to their regular HIV clinic provider for further evaluation and management.

e. Clinical Laboratory Assessments

Blood and urine samples will be collected throughout the study as outlined below, and in the Study Procedures Table found in Appendix 1.

Blood Samples

Blood sample collection for the following laboratory analyses will be performed at the visits specified below:

Serum pregnancy test (all female participants). If the test is positive at the screening visit, the participant will not be enrolled **(Screening)**

- FSH test: Only required for female participants who are <54 years old and have stopped menstruating for ≥ 12 months but do not have documentation of ovarian hormonal failure

(Screening only)

Chemistry profile: alkaline phosphatase, AST, ALT, total bilirubin, total protein, albumin, bicarbonate, blood urea nitrogen (BUN), chloride, creatinine, eGFR, glucose, potassium, sodium and calcium **(Screening, Weeks 4, 12, 24, 36 and 48)**

Metabolic assessments: Fasting (no food or drinks, except water, at least 8hours prior to blood collection) glucose and lipid panel (total cholesterol, HDL, direct LDL, and triglycerides) **(Screening, Weeks 24, and 48)**

- If the participant has not fasted prior to the visit, the visit may proceed, but the participant must return within 72 hours in a fasted state to draw blood for the metabolic assessments

Hematology profile: complete blood count (CBC) with differential and platelet count **(Screening, Weeks 4, 12, 24, 36 and 48)**

CD4+ cell count and percentage **(Screening, Weeks 24, 36, 48)**

Plasma HIV-1 RNA. Any subsequent HIV-1 genotype testing will be performed as described in Section 5d **(Screening, Weeks 4, 12, 24, 36 and 48)**

Whole blood for HIV-1 DNA archive testing as described in Section 5d **(sample collected at Screening and stored for potential future testing)**

HBV blood panel: Hepatitis B virus surface antigen (HBsAg), Hepatitis B virus surface antibody (HBsAb) and Hepatitis B virus core antibody (HbcAb) **(Screening, Weeks 24, 48)**. If screening results reveal the patient is HBV immune (HBsAb positivity), the HBV blood panel will not be collected for the remainder of the study period.

- The following tests will be conducted if the following criteria are met:
    - *If positive HBsAg*: reflex testing for plasma HBV DNA, Hepatitis B virus e-antigen (HBeAg) and Hepatitis B virus e-Antibody (HBeAb). Patients who test positive for HBsAg and are randomized to the DTG/3TC arm will be prematurely discontinued from the study.
    - *If positive HBcAb with negative HBsAg and negative HBsAb*: reflex testing for plasma HBV DNA, HBeAg and HBeAb. Patients who test positive for any of these markers and are randomized to the DTG/3TC arm will be prematurely discontinued from the study.

HCV antibody (Ab) serology **(Screening, Weeks 24, and 48)**. Participants who are HCV Ab positive will have an HCV RNA test performed.

Urine Samples

Urine sample collection for the following laboratory analyses will be performed at the visits specified below:

Urinalysis **(Screening, Weeks 4, 12, 24, 36 and 48)**

Urine pregnancy testing for persons of childbearing potential (**Day 1, Weeks 4, 12, 24, 36 and 48)**. If the

urine pregnancy test is positive, a serum pregnancy test will also be performed.

f. Assessments for Premature Discontinuation from Study

If the participant discontinues their study regimen prior to the Week 48 visit, the participant will be asked to return to the clinic within 72 hours of stopping study treatment for the Early Study Drug Discontinuation Visit which will also serve as the End of Study visit.

The following evaluations are to be completed at the Early Study Drug Discontinuation Visit:

- Review of AEs and changes in concomitant medications
- Complete physical examination (urogenital/anorectal exams will be performed at the discretion of the Investigator)
- Vital signs measurement (blood pressure, pulse, respiration rate, and temperature), including weight and waist circumference
- Obtain blood and urine samples as described for the Week 48 visit above

At the Early Study Drug Discontinuation Visit, any evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study treatment regimen, will be evaluated and managed by the participant's regular HIV clinic provider. The study team will request these clinical records to follow and document the resolution of any abnormal results that developed during the study.

g. End of Study

The end of study will be the last patient's last observation (or visit). After the end of study visit, any ongoing AEs or evaluations showing abnormal results indicating that there is a possible or probable causal relationship with the study treatment regimen, will be evaluated and managed by the participant's regular HIV clinic provider. The study team will request these clinical records to follow and document the resolution of any abnormal results that developed during the study.

h. Post Study Care

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

i. Management of virologic rebound

Participants with virologic rebound will be managed according to the Management of Virologic Rebound schema in Figure 2.

8. Safety

a. Adverse Events (AEs) and Serious Adverse Events (SAEs)

Definitions of Adverse Events and Serious Adverse Events

Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical study participant administered a medicinal product, which does not necessarily have a causal relationship with the treatment. An AE can therefore 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, overdose, 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 as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an adverse event and must be reported
- Pre-existing 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 and/or convenience admissions)
- Overdose of study treatment *without* clinical sequelae
- 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 pre-existing and should be documented on the medical history case report form (CRF).

Serious Adverse Events

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

- Death
- Life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- All events of possible drug-induced liver injury with hyperbilirubinemia defined as ALT greater than or equal to 3xULN and bilirubin greater than or equal to 2xULN (>35% direct)
- A medically important event or reaction: such events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes constituting SAEs. Examples of medically

important events include intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; and development of drug dependency or drug abuse.

Assessments of Adverse Events and Serious Adverse Events

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

Assessment of Causality for Study Drugs and Procedures

The investigator or qualified sub investigator is responsible for assessing the relationship to study treatment using clinical judgment and the following considerations:

- **No**: Evidence exists that the adverse event has an etiology other than the study treatment. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Yes**: There is reasonable possibility that the event may have been caused by the study treatment. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

The relationship to study procedures (eg, invasive procedures such as venipuncture or biopsy) 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, (eg, venipuncture)

Assessment of Severity

AE severity should be recorded and graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events [20]. For adverse events associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

b. Time period and frequency of collecting AE and SAE info

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to study treatment will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact at the timepoints specified in the Study Procedures Table in Appendix 1.
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section on the source documents.
- All SAEs considered possibly related to study treatment will be recorded and reported to ViiV/GSK within 24 hours of first becoming aware of the event. The ViiV Healthcare (VH) CRF with toxicity Grade (SAE) and VH CRF with intensity (SAE) forms will be used to record and report these events.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must notify ViiV/GSK within 24 hours of first becoming aware of the event utilizing the methods described above.

c. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

d. Follow up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

e. Reporting requirements for AEs and SAEs

SAEs will be reported to ViiV/GSK per applicable guidelines for Investigator Sponsored studies utilizing ViiV/GSK products as specified above in Section 8b.

SAEs will be reported to applicable regulatory authorities per IRB SAE reporting guidelines.

f. Pregnancy

Information on the occurrence of pregnancies in female subjects will be collected over the period starting at Screening and ending at the final Follow-up visit. Pregnancies that occur following the first dose of study drug will be reported to the Antiretroviral Pregnancy Registry and ViiV/GSK within 24 hours of first becoming aware of the event. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). The VH pregnancy initial report and pregnancy follow-up report CRF will be used to record and report these events. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as SAEs. Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment must be reported to ViiV/GSK within 24 hours of first becoming aware of the event.

Any female who becomes pregnant (intrauterine) while participating in this study must be withdrawn from the study and must discontinue study drug immediately.

g. Physical Exams

Physical exams should be conducted as part of normal routine clinical care per the Study Procedures Table (Appendix 1) and findings will be recorded in the source documents. Abnormalities noted during any exam may be captured in the current medical conditions or AE logs.

h. Vital Signs

Vital sign collection including, weight and waist circumference should be conducted as part of normal routine clinical care per the Study Procedures Table (Appendix 1) and findings will be recorded in the source documents. Abnormalities in vital signs during any visit may be captured in the current medical conditions or AE logs.

i. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Section 7e must be performed by the local lab preferred by the patient's insurance plan. All blood and urine samples will be collected at the study visit and will be transported to the local lab for processing. Laboratory assessments must be

conducted in accordance with the Study Procedures Table (Appendix 1). Laboratory requisition forms must be completed, and samples must be clearly labelled with the subject name, date of birth, and visit date. Details for the preparation and shipment of samples will be provided by the local laboratory

and are generally available on the local laboratory website. Reference ranges for all safety parameters will be provided by the local laboratory. If additional *non-protocol specified laboratory assessments* are performed at the local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g. AE, SAE or dose modification) the results must be recorded in the source documents. Labs will be graded by the investigator according to the DAIDS toxicity scales [20].

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (i.e. clinical chemistry, hematology, and urinalysis) that require medical or

surgical intervention or lead to study treatment interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

j. Toxicity Management

In the event of a discontinuation of study treatment for suspected drug induced liver injury, other clinically significant liver chemistry elevations, severe skin reaction or hypersensitivity reaction, subjects should not be rechallenged with study treatment due to the risk of a recurrent reaction. These subjects should be permanently discontinued from the study and referred to their routine HIV provider for alternative ARV selection and management.

Hypersensitivity and rash

Allergic Reaction

Subjects may continue study treatment for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The subject should be advised to contact the Investigator immediately if there is any worsening of symptoms or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Subjects with Grade ≥3 allergic reactions that are considered to be possibly or probably related to study treatment should permanently discontinue the study treatment and be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the adverse event.

Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing antiretroviral therapy. Episodes generally occur within the first ten weeks of treatment, rarely require interruptions or discontinuations of therapy and tend to resolve within two to three weeks. The index case of a hypersensitivity reaction with DTG involved a profuse, purpuric and coalescing leukocytoclastic vasculitis as well as clinically significant liver chemistry elevations. Other than this case, no other instances of serious skin reaction, including Stevens-Johnson Syndrome, toxic epidermal necrolysis and erythema multiforme have been reported for DTG in clinical trials.

Subjects with an isolated Grade 1 rash may continue study treatment at the Investigator's discretion. The subject should be advised to contact the Investigator immediately if there is any worsening of the rash, if any systemic signs or symptoms worsen, or if mucosal involvement develops.

Subjects may continue study treatment for an isolated Grade 2 rash. However, the study treatment (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The subject should be advised to contact the physician immediately if rash fails to resolve (after more than two weeks), if there is any worsening of the rash, if any systemic signs or allergic symptoms develop, or if

mucosal involvement develops.

Subjects should permanently discontinue study treatment (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 or 4 rash, and the subject should be withdrawn from the study. Subjects should be treated as clinically appropriate and followed until resolution of the adverse event.

The rash and any associated symptoms should be reported as adverse events (see Section 8e) and appropriate toxicity ratings should be used to grade the events (based on DAIDS [Division of ADS] toxicity gradings).

If the etiology of the rash can be diagnosed as being unrelated to study treatment and due to a specific medical event or a concomitant non-study medication, routine management should be performed, and documentation of the diagnosis provided.

Liver safety criteria

Liver Chemistry Stopping and Follow up Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology during administration of study drug and the follow-up period (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

For any participant meeting one of the criteria outlined in Table 1 or Table 2, or if the Investigator believes that it is in the best interest of the patients, the Investigator must follow the required actions and follow up assessments also outlined in these tables.

Table 3 Liver Chemistry Stopping Criteria - Liver Stopping Event

ALT absolute	*ALT ≥ 8xULN*
ALT increase	*ALT≥ 5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)*
Bilirubin[1, 2]	*ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)*
INR[2]	*ALT ≥ 3xULN and International normalised ratio (INR)>1.5, if INR measured*
Cannot Monitor	*ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for >2 weeks* *(See Table 2 for actions where subjects CAN be monitored weekly for >2 weeks)*
Symptomatic[3]	*ALT ≥3xULN (if baseline ALT is £ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity* *ALT ≥ 3x baseline (if baseline ALT>ULN) with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity*
Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	*Follow Up Assessments*
• Immediately hold DTG/3TC or B/F/TAF. • If a causal relationship between the liver event	• Viral hepatitis serology, including: Hepatitis A immunoglobulin M (IgM)

and DTG/3TC or B/F/TAF cannot be ruled out, then DTG/3TC or B/F/TAF must be permanently discontinued and the Subject not rechallenged due to the risk of a recurrent reaction. • Report the event to the GSK/ViiV safety team by telephone within 24 hours. • Events of possible drug-induced liver injury with hyperbilirubinemia[2] will be reported to GSK/ViiV as SAEs using the SAE CRF. • Complete the liver event CRF for all events meeting liver stopping criteria, and submit to GSK/ViiV within one week of first becoming aware of the event • Perform liver event follow up assessments. • Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below). • All participants who experience a liver stopping event in this clinical trial will be permanently withdrawn from the study. MONITORING: • Make every reasonable attempt to have subjects return to clinic within 24 hours for repeat liver chemistries (include ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) and perform liver event follow up assessments at the local laboratory as described to the right. • A specialist or hepatology consultation may be considered. • Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline.	antibody; HBsAg and hepatitis B core antibody; Hepatitis C RNA; Hepatitis E IgM antibody. • Cytomegalovirus IgM antibody. • Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing). • Syphilis screening. • Drugs of abuse screen, including alcohol. Record alcohol use on the liver event case report form • Serum acetaminophen adduct High Performance Liquid Chromatography assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [19]). • Serum creatinine kinase and lactate dehydrogenase. • Fractionate bilirubin, if total bilirubin≥1.5xULN. • Obtain complete blood count with differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (or gamma globulins). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease. Complete Liver Imaging and/or Liver Biopsy case report form if applicable • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) **or** ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury **must be reported as a serious adverse event**; INR

measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants

New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia). Record the appearance or worsening of any such clinical symptoms on the adverse event report form.

Table 4 Liver Chemistry Increased Monitoring Criteria

Criteria	Actions
ALT ≥5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for >2 weeks.	• Notify the medical monitor within 24 hours of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, aspartate aminotransferase, alkaline phosphatase, bilirubin) until resolution, stabilisation (ALT <5×ULN on 2 consecutive evaluations) or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above

Liver Safety- Study Treatment Restart

Participants who meet liver stopping criteria for any reason will be discontinued from study treatment and permanently withdrawn from this clinical trial.

Suicidal Risk Monitoring

Subjects with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some reports of depression, suicidal ideation and behaviour (particularly in patients with a pre-existing history of depression or psychiatric illness) in some patients being treated with integrase inhibitors, including DTG. Therefore, it is appropriate to monitor subjects for suicidality before and during treatment.

Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour, or any other unusual changes in behaviour. It is recommended that the investigator consider mental health consultation or referral for subjects who experience signs of suicidal ideation or behaviour.

Assessment of treatment-emergent suicidality will be monitored during this study using the paper version of the Columbia Suicidality Severity Rating Scale (C-SSRS). The definitions of behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [21]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Day 1 (Baseline) visit questions will be in relation to lifetime experiences and current experiences (within the past 2 months); all subsequent questioning is in relation to the last assessment. The C-SSRS is to be administered as a patient completed questionnaire specified in the Study Procedures Table (Appendix 1). The C-SSRS will be conducted manually with participants completing a paper survey. Additionally, the investigator will

collect and document information regarding any subject that experiences a possible suicidality-related AE (PSRAE) while participating in this study.

If any subject experiences a PSRAE while participating in this study that is considered by the Investigator to meet ICH E2A [22] definitions for seriousness, the Investigator will collect information using a PSRAE CRF (or agreed alternative) in addition to reporting the event on a SAE CRF. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to the GSK/ViiV safety team within one week of the investigator diagnosing a possible suicidality-related serious adverse event.

Management of patients with significant renal toxicity

Treatment with DTG/3TC must be discontinued in any subject developing moderate to severe renal impairment during the study, as indicated by confirmed creatinine clearance measuring <50 mL/min via the Cockcroft-Gault method (initial abnormal value must be confirmed by a repeat creatinine clearance assessment within 2 weeks.) These participants will be permanently withdrawn from the study.

9. Data Management

- For this study, subject data will be entered into OIC defined CRFs, and will be maintained on a secure internal server at the study site.
- Management of clinical data will be performed in accordance with applicable GCP standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- CRFs (including queries and audit trails) will be retained by Orlando Immunology Center, and deidentified copies can be sent upon request to ViiV/GSK for verification and review.

10. Statistical Considerations and Data Analyses

a. Analysis Objectives

The primary objective of this study is to evaluate the efficacy of switching from B/F/TAF to DTG/3TC versus continuing the baseline regimen of B/F/TAF in HIV-infected, virologically suppressed adults as determined by the proportion of participants with HIV-1 RNA ≥50 copies/mL at Week 48.

The secondary objectives of this study are

1. To evaluate the efficacy of switching to DTG/3TC from B/F/TAF as determined by the proportion of participants with HIV-1 RNA≥50 copies/mL at Weeks 12 and 24
2. To evaluate the efficacy of switching to DTG/3TC from B/F/TAF as determined by the proportion of participants with HIV-1 RNA<50 copies/mL at Weeks 12, 24 and 48
3. To evaluate the safety, and tolerability of switching to DTG/3TC from B/F/TAF in HIV-infected, virologically suppressed adults through Week 48

Primary Endpoint

The primary efficacy endpoint is:

- The proportion of participants with HIV-1 RNA≥50 copies/mL at Week 48 as defined by the US FDA-defined snapshot algorithm

Secondary Endpoint

The secondary efficacy endpoints are:

- The proportion of participants with HIV-1 RNA ≥ 50 copies/mL at Weeks 12 and 24 as defined by the US FDA-defined snapshot algorithm
- The proportion of participants with HIV-1 RNA <50 copies/mL at Weeks 12, 24 and 48 as defined by the US FDA-defined snapshot algorithm
- The change from baseline in $CD4^+$ cell count at Weeks 12, 24 and 48

b. Demographic Data and Baseline Characteristics

Demographic and baseline characteristics will be summarized using standard descriptive methods, including sample size, mean, SD, median, Q1, Q3, minimum, and maximum for continuous variables, and frequency and percentages for categorical variables.

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

Baseline characteristics including body weight, height, BMI, GFR, HIV-1 infection, and enrollment distribution will be summarized.

For categorical demographic and baseline characteristics, the Cochran–Mantel–Haenszel test will be used to compare treatment groups. For continuous demographic and baseline characteristics, the Wilcoxon rank sum test will be used to compare treatment groups.

c. Efficacy Analysis

The primary analysis will consist of a non-inferiority test of switching to DTG/3TC versus staying on B/F/TAF with respect to the proportion of participants 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 full data set (to include all patients in the study).

US FDA-defined Snapshot Algorithm: All HIV-1 RNA data collected on-treatment (ie, including data collected up to 1 day after the last dose date of study drug) will be used in the snapshot algorithm.

Virologic outcome will be defined as the following categories:

- HIV-1 RNA ≥ 50 copies/mL: this includes participants a) Who have the last available on-treatment HIV-1 RNA ≥ 50 copies/mL in the Week 48 analysis window, or b) Who do not have on-treatment HIV-1 RNA data in the Week 48 analysis window and 1. Who discontinue study treatment prior to or in the Week 48 analysis window due to lack of efficacy, or 2. Who discontinue study treatment prior to or in the Week 48 analysis window due to reason other than lack of efficacy and have the last available on-treatment HIV-1 RNA ≥50 copies/mL
- HIV-1 RNA < 50 copies/mL: this includes participants who have the last available on-treatment HIV-1 RNA < 50 copies/mL in the Week 48 window

Analysis of Primary Efficacy Endpoint

The **null hypothesis** is that the proportion of participants achieving HIV-1 RNA ≥ 50 copies/mL (as defined by the US FDA-defined snapshot algorithm) at Week 48 in DTG/3TC is at least 6% lower than the response rate in the B/F/TAF arm; the **alternative hypothesis** is that the response rate in the DTG/3TC arm is less than 6% lower than that in the B/F/TAF arm. Non-inferiority will be assessed using the conventional confidence interval (CI) approach. The point estimate of treatment difference (DTG/3TC–B/F/TAF) and the associated 2-sided 95% CI will be constructed based on the exact method.

It will be concluded that DTG/3TC is non-inferior to B/F/TAF if the upper bound of the 2-sided 95% CI of the difference between treatment groups [DTG/3TC –B/F/TAF] in the percentage of participants with HIV-1 RNA ≥50 copies/mL is less than 6% (i.e., a margin of 6% is applied to non-inferiority assessment).

Secondary Analyses

The proportion of participants with HIV-1 RNA≥ 50 copies/mL at Weeks 12 and 24, and the proportion of participants with HIV-1 RNA< 50 copies/mL at Weeks 12, 24 and 48 as defined by the US FDA-defined snapshot algorithm will also be summarized.

The changes from baseline in $CD4^+$ cell count at Weeks 12, 24 and 48 will be summarized by treatment using descriptive statistics. The differences between treatment groups at Week 48 and the associated 95% CIs will be constructed using an Analysis of Variance (ANOVA) model, including treatment (DTG/3TC vs. B/F/TAF) as a fixed effect in the model.

d. Safety Analysis

All safety data collected on or after the date that the study treatment was first administered up to the date of the last dose of study treatment will be summarized for participants in the safety analysis set according to the study treatment received

Adverse Events

Events will be summarized on the basis of the date of onset for the event. A treatment-emergent adverse event will be defined as any adverse event with onset date on or after the study treatment start date and no later than 30 days after the study drug stop date; or any adverse event leading to study drug discontinuation. Summaries (number and percentage of participants) of treatment-emergent adverse events will be provided by treatment. Additional summaries will include summaries for adverse events by grade, Investigator's assessment of relationship to study treatment, and effect on study dosing.

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.

e. Patient Reported Outcomes (PRO)

The PRO measures based on questionnaires will be summarized by treatment and visit using descriptive statistics.

f. Sample Size Calculation

Sample Size Sample sizes of 148 in DTG/3TC switch arm and 74 in the B/F/TAF arm achieve approximately **80**% power to detect a non-inferiority margin difference between the group proportions of 0.06 for HIV-1 RNA <50 copies/mL at Week 48. The power is computed for the case when the actual treatment group difference is zero (treatment = reference). The test statistic used is the one-sided Score test (Farrington & Manning) with the significance level of 0.025.

g. Analysis Schedule

The Week 48 analyses will be conducted after all participants either complete their Week 48 visits or prematurely discontinue from the study treatment, respectively.

11. Study Governance and Considerations

a. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

b. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of the study, Orlando Immunology Center will obtain favorable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with Orlando Immunology Center Standard of Operating Procedures (SOP). The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki.

This includes, but is not limited to, the following:

- IRB review and favorable opinion/approval of the study protocol and amendments as applicable
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB)
- Signed informed consent must be obtained for each subject prior to participation in the study

c. Quality Control (Study Monitoring)

In accordance with applicable regulations including GCP, and Orlando Immunology Center procedures, the study principal investigator will meet with the study team prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and OIC requirements.

- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the OIC CRF will serve as the source document.

The OIC will appoint a senior member of the research department who is not affiliated with the study to monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

d. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, the study funder ViiV Healthcare may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

e. Study and Site Closure

- Upon completion or premature discontinuation of the study, the OIC monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and OIC SOP.
- OIC reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance.
- If the study is suspended or prematurely discontinued for safety reasons, OIC will promptly inform all investigators, the study funder (ViiV/GSK) and the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB promptly and provide the reason for the suspension or premature discontinuation.

f. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a ViiV/GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- The Investigator's Site Files must be retained for 5 years from the date of the final clinical study report or publication, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval

of the sponsor.

- The investigator must notify ViiV/GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

g. Provision of Study Results, Posting of Information on Publicly Available Clinical Trials Registers and Publication

No summaries of the study data according to actual randomized treatment groups will be available prior to the planned Week 24 preliminary analysis. Public presentation of the Week 24 analysis may be done prior to last subject's week 48 visit. The investigator is encouraged to share the summary results with the study subjects, as appropriate. The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance to the following timeline:

Study Approval, IRB processing and final contracts/budgeting: 6 months (January 2020 -June 2020)

Enrollment period and data collection: 18 months (July 2020-January 2022)

Data Collation and analysis of Results: 4 months (January 2022-May 2022)

IDWeek Abstract Preparation and Submission: 2 months (May 2022)

IDWeek Abstract Presentation: October 2022

Manuscript preparation and submission: 4 months: Target date October 2022 (post IDWeek)

12. References

1. Cahn, P., et al., Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. Lancet, 2019. **393**(10167): p. 143-155.
2. Cahn, P., et al., Durable efficacy of dolutegravir (DTG) plus lamivudine (3TC) in antiretroviral treatment-naïve adults with HIV-1 infection - 96-week results from the GEMINI studies. Presented at the 10th International AIDS Conference on HIV Science (IAS 2019), 21-24th July 2019, Mexico City, Mexico., 2019.
3. Joly, V., et al., Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL). J Antimicrob Chemother, 2019. **74**(3): p. 739-745.
4. Corado, K.C., M.R. Caplan, and E.S. Daar, Two-drug regimens for treatment of naive HIV-1 infection and as maintenance therapy. Drug Des Devel Ther, 2018. **12**: p. 3731-3740.
5. Hidalgo-Tenorio, C., et al., DOLAMA study: Effectiveness, safety and pharmacoeconomic analysis of dual therapy with dolutegravir and lamivudine in virologically suppressed HIV-1 patients. Medicine (Baltimore), 2019. **98**(32): p. e16813.
6. Baldin, G., et al., Long term data on the efficacy and tolerability of lamivudine plus dolutegravir as a switch strategy in a multicenter cohort of HIV1-infected, virologically suppressed patients. Int J Antimicrob Agents, 2019.
7. Maggiolo, F., et al., Lamivudine/dolutegravir dual therapy in HIV-infected, virologically suppressed patients. BMC Infect Dis, 2017. **17**(1): p. 215.
8. Borghetti, A., et al., Efficacy and tolerability of lamivudine plus dolutegravir compared with lamivudine plus boosted PIs in HIV-1 positive individuals with virologic suppression: a retrospective study from the clinical practice. BMC Infect Dis, 2019. **19**(1): p. 59.
9. Van Wyk, J., et al., Switching to DTG/3TC fixed dose combination (FDC) is non-inferior to continuing a TAF-based regimen (TBR) in maintaining virologic suppression through 24 weeks (TANGO study). Presented at the 10th International AIDS Conference for HIV Science (IAS 2019), 21-24 July 2019, Mexico City, Mexico., 2019.
10. Daar, E.S., et al., Efficacy and safety of switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor-based regimens in virologically suppressed adults with HIV-1: 48 week results of a randomised, open-label, multicentre, phase 3, non-inferiority trial. Lancet HIV, 2018. **5**(7): p. e347-e356.
11. Molina, J.M., et al., Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. Lancet HIV, 2018. **5**(7): p. e357-e365.
12. Wohl, D., et al., Patient-Reported Symptoms Over 48 Weeks Among Participants in Randomized, Double-Blind, Phase III Non-inferiority Trials of Adults with HIV on Co-formulated Bictegravir, Emtricitabine, and Tenofovir Alafenamide versus Co-formulated Abacavir, Dolutegravir, and Lamivudine. Patient, 2018. **11**(5): p. 561-573.
13. Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. 2018:298
14. Dovato Package Insert USPI. ViiV Healthcare. 2020.
15. Selik RM, Mokotoff ED, Branson B, Owen SM, Whitmore S, Hall HI. Morbidity and Mortality Weekly Report (MMWR). Revised Surveillance Case Definition for HIV Infection -United States

2014. Centers for Disease Control and Prevention, 2014.
16. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg. 1964;1:1-85.
17. Wensing AM., Calvez V., Ceccherini-Silberstein F., et al., 2019 Update of the Drug Resistance Mutations in HIV-1. Top Antivir Med . 2019 Sep;27(3):111-121.
18. Biktarvy Package Insert USPI. Gilead Sciences. 2019.
19. FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. July 2009. Accessed 07 January 2015 at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022145s032,203045s010,205786s001lbl.pdf
20. U.S. Department of Health and Human Services, National Institutes of Health, National Institute of Allergy and Infectious Diseases, Division of AIDS. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. [July 2017]. Available from: https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf
21. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164:1035–43.
22. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals For Human Use. ICH Harmonized Tripartite Guideline. Clinical safety data management: Definitions and standards for expedited reporting. ICH E2A. 1994

13. Appendices

Appendix 1. Study Procedures Table

Study Procedure	Screening	Day 1	Week 1 (Phone Call)	Week 4	Week 12	Week 24	Week 36 (Phone Call)[c]	Week 48[a]
Informed Consent	X							
HIV Symptoms Distress Module		X		X	X	X		X
HIV-TSQ		X		X	X	X		X
Vas Adherence Questionnaire		X		X	X	X		X
C-SSRS		X		X	X	X		X
Medical History	X		X				X	
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Complete/Symptom-Directed Physical Exam	X	X		X	X	X		X
Height	X							
Weight/Waist Circumference	X	X		X	X	X		X
Vital Signs	X	X		X	X	X		X
Urine Pregnancy Test[b]		X		X	X	X	X	X
Serum Pregnancy Test[b]	X							
FSH Test	X							
Chemistry Profile	X			X	X	X	X	X
Metabolic Assessments	X					X		X
Hematology Profile	X			X	X	X	X	X
Plasma HIV-1 RNA	X			X	X	X	X	X
CD4+ Cell Count and Percentage	X					X	X	X
Urinalysis	X			X	X	X	X	X
HBV Blood Panel	X					X		X
HCV Serology	X					X		X
HIV-1 Genotype								
Obtain Screening number	X							
Randomization		X						

[a]Procedures at Withdrawal visit are identical to those at Week 48
[b]Performed in females of child-bearing potential
[c]Participants will present to the research center for laboratory assessments only

Appendix 2. Pregnancy Precautions, Definition for Persons of Childbearing Potential, and Contraceptive Requirements

1) Definitions

a. Definition of Childbearing Potential

For the purposes of this study, a female born participant is considered of childbearing potential following the initiation of puberty (Tanner stage 2) until becoming post-menopausal, unless permanently sterile or with medically documented ovarian failure.

Women are considered to be in a postmenopausal state when they are >54 years of age with cessation of previously occurring menses for >12 months without an alternative cause. In addition, women < 54 years of age with amenorrhea of ≥ 12 months may also be considered postmenopausal if their FSH level is in the postmenopausal range, and they are not using hormonal contraception or hormonal replacement therapy.

Permanent sterilization includes hysterectomy, bilateral oophorectomy, or bilateral salpingectomy in a female participant of any age.

b. Definition of Male Fertility

For the purposes of this study, a male born participant is considered to be fertile after the initiation of puberty unless permanently sterile by bilateral orchiectomy or medical documentation.

2) Contraception Requirements for Persons of Childbearing Potential

The inclusion of persons of childbearing potential requires the use of highly effective contraceptive measures. They must have a negative serum pregnancy test at Screening and a negative pregnancy test on the Baseline/Day 1 visit prior to randomization. In the event of a delayed menstrual period (over one month between menstruations), a pregnancy test must be performed to rule out pregnancy. This is true even for persons of childbearing potential with infrequent or irregular periods. Female participants must also agree to one of the following from Screening until 30 days after the last dose of study drug.

- Complete abstinence from intercourse of reproductive potential. Abstinence is an acceptable method of contraception only when it is in line with the participant's preferred and usual lifestyle.

Or

- Consistent and correct use of 1 of the following methods of birth control listed below.
    - Intrauterine device (IUD) with a failure rate of <1% per year
    - Intrauterine hormone-releasing system (IUS) with a failure rate of <1% per year
    - Tubal sterilization
    - Essure micro-insert system (provided confirmation of success by hysterosalpingogram three months after procedure and where permitted and used per local prescribing label)

  - Vasectomy in the male partner (provided that the partner is the sole sexual partner and had confirmation of surgical success 3 months after procedure)

Persons of childbearing potential who wish to use a hormonally based contraceptive method must use it in conjunction with a barrier method, preferably a male condom. Persons of childbearing potential who utilize a hormonal contraceptive as one of their birth control methods must have consistently used the same method for at least three months prior to study dosing. Hormonally based contraceptives and barrier methods permitted for use in this protocol are as follows:

- Barrier methods (each method must be used with a hormonal method)
  - Male condom (with or without spermicide)
  - Female condom (with or without spermicide)
  - Diaphragm with spermicide
  - Cervical cap with spermicide
  - Sponge with spermicide

- Hormonal methods (each method must be used with a barrier method, preferably male condom)
  - Oral contraceptives (either combined or progesterone only)
  - Injectable progesterone
  - Subdermal contraceptive implant
  - Transdermal contraceptive patch
  - Contraceptive vaginal ring

Persons of childbearing potential must also refrain from egg donation and in vitro fertilization during treatment and until at least 30 days after the end of relevant systemic exposure.

3) Contraception Requirements for Male Participants

During the study, male participants should use condoms when engaging in intercourse of reproductive potential with persons of childbearing potential.

4) Unacceptable Contraceptive Methods

Contraceptive methods that are unacceptable include periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). Female condom and male condom should not be used together.

5) Procedures to be Followed in the Event of Pregnancy

Participants will be instructed to notify the investigator if they become pregnant, or are concerned they may be pregnant, at any time during the study, or if they become pregnant within 30 days of last study drug dose. Participants who become pregnant or who suspect that they are pregnant during the study must report the information to the investigator and discontinue study drug immediately.

Participants who become pregnant while on study should receive appropriate monitoring and care until the conclusion of the pregnancy. Subjects who become pregnant while on study who are not

engaged in pre-natal care that includes a routine second trimester ultrasound will be referred for ultrasonography as part of study follow-up. Instructions for reporting pregnancy and pregnancy outcomes are outlined in Section 8f.