Objectives and Endpoints:

Objectives	Endpoints
Primary	
To demonstrate the non-inferior antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 48 weeks in virologically suppressed adults living with HIV-1	Virologic failure endpoint as per Food and Drug Administration (FDA) snapshot category at Week 48
Secondary	
To demonstrate the antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 48 weeks	Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the intent-to-treat exposed (ITT-E) population
To evaluate the antiviral activity of switching to DTG/3TC FDC once daily compared to continuation of CAR over 24 weeks	• Virologic failure endpoint as per FDA snapshot category at Week 24 • Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm for the ITT-E population
To evaluate the immune effects of DTG/3TC FDC once daily compared to continuation of CAR	• Change from Baseline in CD4+ cell count and in CD4+/CD8+ cell counts ratio at Weeks 24 and 48 • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS], and death) through Weeks 24 and 48
To evaluate the safety and tolerability of DTG/3TC FDC once daily compared to CAR over time	• Incidence and severity of adverse events (AEs) and laboratory abnormalities • Proportion of participants who discontinue treatment due to AEs
To evaluate the safety and tolerability of DTG/3TC FDC once daily in those with creatinine clearance of between 30-49 mL/min/1.73m^2 compared to those with a creatinine clearance of $\geq$50 mL/min/1.73m^2	• Incidence and severity of AEs and laboratory abnormalities • Proportion of participants who discontinue treatment due to AEs
To evaluate the effects of DTG/3TC FDC once daily on fasting lipids over time compared to CAR	Change from Baseline in fasting lipids at Weeks 24 and 48
To assess viral resistance in participants meeting Confirmed Virologic Withdrawal (CVW) Criteria	Incidence of observed genotypic and phenotypic resistance to antiretrovirals (ARVs) for participants meeting CVW Criteria

Procedures	**Screening Visit[a]**	**Randomized Phase**							**Continuation Phase[c]**	**Withdrawal**	**Follow-up[d]**
		Baseline/ Day 1	**4**	**12**	**24**	**36**	**48[b]**	**52**	**Every 12 Weeks After Week 52**		
Willingness to Switch[o]		X[o]									
HIV TSQ[p]		X	X		X		X			X	
Symptom Distress Module[p]		X	X		X		X		X (every 24 weeks)	X	
Laboratory Assessments											
Quantitative plasma HIV-1 RNA[q]	X	X	X	X	X	X	X		X	X	
Lymphocyte subset[r]	X	X	X	X	X	X	X			X	
Plasma for storage[s]	X	X	X	X	X	X	X		X	X	
Clinical chemistry[t]	X	X	X	X	X	X	X			X	X
Hematology	X	X	X	X	X	X	X			X	X
PT/INR (for Child-Pugh)	X										
Fasting lipids and glucose[u]		X			X		X			X[v]	
Urinalysis and spot urine for protein analysis[w]		X			X		X			X	X
Pregnancy test[x, y]	S	U/S[z]	S	S	S	S	S	S	S	S	
HBsAg, anti-HBc, Anti-HBs, and HBV DNA[aa]	X										
HCV antibody	X										
RPR	X										
Renal, bone and inflammatory marker analytes (blood/urine) and HbA1c, insulin and glucose[bb]		X			X		X			X	
Whole Blood (Virology)[cc]		X					X			X	
Whole Blood (Telomere Length)[dd]		X					X			X[ee]	

Objectives	Endpoints
To evaluate the effects of DTG/3TC FDC once daily on fasting lipids over time compared to CAR	Change from Baseline in fasting lipids at Weeks 24 and 48
To assess viral resistance in participants meeting Confirmed Virologic Withdrawal (CVW) Criteria	Incidence of observed genotypic and phenotypic resistance to ARVs for participants meeting CVW Criteria
To assess health related quality of life for participants treated with DTG/3TC FDC compared to CAR	Change from Baseline in health status using HIV TSQ at Weeks 24 and 48 (or Withdrawal from the study) and SDM at Weeks 24, 48 and every 24 weeks during the continuation phase (or Withdrawal from the study)
Exploratory	
To assess willingness to switch for participants treated with DTG/3TC FDC compared to CAR	Reasons for Willingness to Switch at Day 1
To evaluate renal (in urine and blood), bone (in blood), inflammatory (in blood) biomarkers and insulin resistance in participants treated with DTG/3TC FDC compared to CAR	Change from Baseline in renal, bone and inflammatory biomarkers and homeostasis model of assessment-insulin resistance (HOMA-IR) at Weeks 24 and 48
To evaluate biomarkers of telomerase function in participants treated with DTG/3TC FDC compared to CAR.	Change from baseline in biomarkers of telomerase function at Week 48

4.2. Number of Participants

Assuming 20% screen failure rate, approximately 622 adult participants living with HIV will be screened to achieve approximately 490 randomized participants for a total of 245 evaluable participants per treatment group (See Section 9.3).

A goal of this study is to enrol populations who are underrepresented in clinical studies including at least 20% women and approximately 20% of participants who are ≥50 years of age. To provide sufficient data to determine whether women respond differently than male participants and whether participants who are ≥50 years of age respond differently than those < 50 years of age, sites are expected to consider women and participants ≥50 years of age in their screening strategies. Another goal of the study is to enrol approximately 20% of participants taking efavirenz/emtricitabine/tenofovir disoproxil fumarate to reflect on its continued use as first line ARV of choice in many countries. Enrolment may be allowed to continue at select sites to attempt to reach targets in these key study populations.

The study will limit the enrolment of participants with current or prior exposure to DTG to approximately 20%.

4.3. Participant and Study Completion

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

- Randomly assigned to either treatment group, completed the Randomized Phase including the Week 52 visit, and did not enter the Continuation Phase;

- Randomly assigned to DTG/3TC FDC, completed the Randomized Phase including the Week 52 visit, entered and completed the Continuation Phase, defined as remaining on study until:

    - DTG and 3TC are each locally approved for use as part of a 2-drug regimen, and each of the single entities of DTG and 3TC are available through public health services or through the participant's usual health insurance payer, or
    - the actual DTG/3TC FDC tablet, if required by local regulations, is available, or
    - the participant no longer derives clinical benefit, or
    - the participant meets a protocol-defined reason for discontinuation, or
    - development of the DTG plus 3TC 2-drug regimen is terminated

The Continuation Phase is not applicable for participants in Sweden and Denmark.

An in-clinic Follow-Up visit will be conducted approximately 4 weeks after the last dose of study medication for participants with ongoing AEs, serious adverse events (SAEs) regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit. Assessments at the Follow-up visit should reflect any ongoing complaints (e.g., blood draws to follow a

inclusion of participants with creatinine clearance of ≥30 mL/min/1.73m^2 to confirm these earlier observations. The protocol includes extensive serum and urine renal function laboratory tests collected at each study visit, and has management procedures for specified change (decrease) in renal function.

This study will aim to enrol 20% females to provide safety and efficacy data to help inform clinicians about use of this ART regimen in women. While women comprise approximately 50% of people living with HIV globally, the number of women in most HIV clinical trials remains low, and recruiting and retaining women into antiretroviral clinical studies remains a challenge. The reasons are multiple, but may reflect differences in lifestyle, care commitments, behaviour and socioeconomics between women and men living with HIV. Additionally, women may metabolize and respond to antiretroviral agents differently than men; women may have higher drug exposure, be at greater risk for some adverse events (i.e., lactic acidosis, hepatotoxicity/rash, and osteoporosis), and have an added potential for drug-drug interactions (i.e., oral hormonal contraceptives/or estrogen).

The open-label design best suits the objectives of this study. A double-dummy design could not be undertaken given the increase in pill burden that would result from blinding, the differing requirements for dosing a variety of CAR with food, and wide variety of potential DDIs. An increase in pill burden could hinder compliance substantially and discourage participant enrolment. The use of the FDA snapshot algorithm for assessing the proportion of participants with virologic failure as an objective primary endpoint will help reduce biases inherent to an open-label study design.

4.5. Justification for Dose

To date, the efficacy, PK, safety, and drug interaction potential of DTG and 3TC as individual agents have been evaluated in two extensive clinical development programs of Phase I to III clinical trials. As individual agents, DTG and 3TC are both approved and marketed as TIVICAY 50 mg once daily and EPIVIR 300 mg once daily, respectively. These doses will be used in the current study.

Comprehensive clinical studies have been conducted with the individual DTG and 3TC products, including clinical pharmacology studies evaluating potential DDIs between each of these active ingredients and other agents. There are no known clinically relevant PK interactions between DTG and 3TC with concomitant dosing.

A summary of the overall clinical development for both products is available in the most recent version of the IBs and or Product Insert(s) for the respective products [see DTG IB: GlaxoSmithKline Document Number RM2007/00683/11; GlaxoSmithKline Document Number 2017N352880_00; GlaxoSmithKline Document Number 2017N352880_01; Dolutegravir (TIVICAY) Product Insert; 2017; EPIVIR Product Insert, 2017].

Based on the preliminary results of the pivotal bioequivalence study (204994), a bilayer tablet formulation with a core which utilizes the same formulation in the respective layers as the single entity tablets was selected. When administered in the fasted state, the bilayer tablet demonstrated bioequivalence to the single entity tablets for dolutegravir area under the curve zero to infinity (AUC(0-∞)) & maximum concentration (Cmax) and

will complete the Screening period up to 28 days prior to Baseline (Day 1) during which all clinical and laboratory assessments of eligibility must be performed and reviewed. The Screening period of up to 28 days is to accommodate availability of all Screening assessment results, completion of source document verification to satisfy the Inclusion and Exclusion Criteria including the required previous HIV-1 RNA values, and scheduling. All Screening results **must** be available prior to randomization.

All information about the participant's current and any past regimen must be available for review by the Principal Investigator or designee prior to randomization. Source documents from other medical facilities must be located/received during the 28-day screening period and under no circumstances may the participant be randomized in the absence of source documentation, even if there are delays in receipt of this information. A participant may be re-screened if the source documentation is obtained after the screening window closes.

Details regarding prior resistance data must be noted in the source documentation. Resistance testing reports with genotypic data **must** be provided to ViiV after screening and before randomization for review by ViiV. Sites must wait for the study virologists to confirm the lack of exclusionary resistance mutations, which will be provided to the site before the screening window closes. Details for tracking historic resistance report availability and sending to ViiV Virology for evaluation are described in the SRM. Details regarding baseline or prior resistance data must be noted in the source documentation. **If a participant is identified as having been mistakenly screened/randomized with exclusionary resistance, they will be withdrawn.**

Participants with chronic active hepatitis B virus infection are excluded. Evidence of Hepatitis B virus (HBV) infection is based on the results of testing at Screening for Hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs), and HBV DNA. HBV DNA testing will only be performed for participants with positive anti-HBc and negative HBsAg and negative anti-HBs (past and/or current evidence).

All participants will be screened for syphilis at screening. Participants with untreated syphilis infection, defined as a positive Rapid Plasma Reagin (RPR) without clear documentation of treatment, are excluded unless they complete treatment during the 28-day screening window and 7 days prior to randomization. Participants who complete treatment after the screening window closes may be rescreened.

Participants who meet all entry criteria are randomized and assigned a randomization number. Participants not meeting all inclusion and exclusion criteria at initial screen may be rescreened and receive a new participant number one time unless they were excluded for reason of having exclusionary historic genotypic resistance or for a viral load ≥50c/mL at time of screening. Participants who are randomized into the trial and subsequently withdrawn from the study for any reason may not be rescreened.

failure will include the following events; data in window not below 50 c/mL, discontinued for lack of efficacy, discontinued for other reason while not below 50 c/mL, and change in background therapy.

8.1.2. Secondary Efficacy Endpoints

- Proportion of participants with plasma HIV-1 RNA <50 c/mL at Weeks 24 and 48 using the Snapshot algorithm for the ITT-E population
- Percentage of participants with viral failure endpoint as per FDA snapshot category at Weeks 24
- Change from Baseline in CD4+ lymphocyte count and in CD4+/CD8+ cell counts ratio at Weeks 24 and 48
- Incidence of disease progression (HIV-associated conditions, AIDS and death).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (SoA) (Section 1.3).

8.2.1. Physical Examinations

Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Abnormalities noted during any exam must be recorded in the eCRF (e.g. in the current medical conditions or AE logs).

8.2.2. Vital Signs

- At the Screening visit, vital signs including height, weight and Body Mass Index (BMI) will be measured. The systolic and diastolic blood pressure will be measured in semi-supine position after 5 minutes rest. Body weight and BMI will also be assessed at each visit according to the Schedule of Activities (SoA) (Section 1.3).

8.2.3. Electrocardiograms

- A baseline 12-lead ECG will be conducted at the Screening visit, for possible use as a reference during the study (i.e. in evaluation of any pertinent cardiovascular event).

8.2.4. Clinical Safety Laboratory Assessments

Refer to Appendix 7 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency. All protocol required laboratory assessments must be performed by central laboratory services, with the exception of exceptional circumstances during screening noted in Section 5. Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic. Laboratory assessments must be conducted in accordance with the Laboratory Manual, and SoA (Section 1.3). Laboratory requisition forms must be completed and samples

must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Q^2 Solutions and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by Q^2 Solutions.

- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification) the results must be recorded in the eCRF. Please refer to Appendix 14 in Section 11.14 for study management information during the COVID-19 pandemic.
- Labs will be graded automatically by the central lab according to the DAIDS toxicity scales (See Section 11.11 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events").
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Section 11.7.

8.2.5. Suicidal Risk Monitoring

Participants with HIV infection occasionally may 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 people with a pre-existing history of depression or psychiatric illness) in some people being treated with INIs, including DTG. Therefore, it is appropriate to monitor participants for suicidality before and during treatment.

Participants should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 8.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 11.8.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

The Death eCRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 11.12) will be recorded on the HIV-Associated Conditions eCRF page if they occur. However, these individual events or outcomes, as well as any sign, symptom, diagnosis, illness, and/or clinical laboratory abnormality that can be linked to any of these events or outcomes are not reported to ViiV/GSK as AEs and SAEs even though such event or outcome may meet the definition of an AE or SAE, **unless the following conditions apply**:

- The investigator determines that the event or outcome qualifies as an SAE under part 'f' of the SAE definition (see Section 11.8), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual participant, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

8.4. Treatment of Overdose

For this open-label study, any tablet intake exceeding the randomized daily number of tablets for DTG/3TC FDC will be considered an overdose [Dolutegravir (TIVICAY) Product Insert, 2017; EPIVIR Product Information, 2017]. ViiV Healthcare does not recommend specific treatment for an overdose of DTG/3TC FDC. As appropriate, the Investigator should use clinical judgment and also refer to the prescribing information for the individual drugs used for CAR in treating overdose in the CAR arm.

For the purposes of this study, an overdose is not an AE unless it is accompanied by a clinical manifestation associated with the overdose. If the clinical manifestation presents with serious criteria, the event is a SAE (see Section 11.8). If an overdose occurs and is associated with an adverse event requiring action, all study medications should be temporarily discontinued until the adverse event resolves.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/SAE and laboratory abnormalities until DTG/3TC FDC can no longer be detected systemically (at least 2 days).
- Obtain a plasma sample for PK analysis within 60 hours from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).

- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Liver Event

As part of the follow-up for any liver stopping event, a blood sample for PK analysis will be collected if it can be obtained within 60 hours of the last dose (See Section 11.9.1).

Overdose

Only if requested by the Medical Monitor, as part of the follow-up for any suspected overdose, a blood sample for PK analysis will be collected if it can be obtained within 60 hours from the date of the last dose of study intervention (See Section 8.4).

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Blood and urine are being collected to perform renal, bone and inflammatory biomarker assessments.

Renal biomarkers:

- Cystatin C (blood)
- Retinol Binding Protein (RBP, urine),
- Beta-2-Microglobulin (B2M, urine)
- Urine RBP/creatinine ratio
- Urine B2M/creatinine ratio
- urine albumin/creatinine ratio,
- urine protein/creatinine ratio,

- To assess the reason(s) for their participation and facilitate an understanding of participant's willingness to switch, participants will be asked a single item question prior to randomization.
- The HIV treatment satisfaction questionnaire (HIV TSQ) (status version) [Woodcock, 2001; Woodcock, 2006] is a 10-item self-reported scale that measures overall satisfaction with treatment and by specific domains e.g., convenience, flexibility.
- The Symptom Distress Module (also called the HIV Symptom Index or Symptoms Impact Questionnaire) is a 20-item self-reported measure that addresses the presence and perceived distress linked to symptoms commonly associated with HIV or its treatment [Justice, 2001].

8.10. HIV-1 Polymerase Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide plasma for storage samples according to the Schedule of Activities (for potential viral genotypic and phenotypic analyses). Participants meeting CVW criteria will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from samples collected at the time of meeting SVW criteria; these results will be reported to the investigator as soon as available to provide guidance for election of an alternative regimen

Details concerning the handling, labelling and shipping of these samples will be supplied separately. Genotypic and phenotypic analyses may be carried out by Monogram Biosciences using, but not limited to, their Standard PhenoSense and GenoSure testing methods for PRO, RT, and integrase assays.

A secondary endpoint of the study will be the incidence of observed genotypic and phenotypic resistance to DTG or 3TC and to CAR for participants meeting Virologic Withdrawal criteria. The virologic endpoint may also be assessed based on third-agent class.

8.10.1. HIV-1 Exploratory Analysis

HIV-1 exploratory analysis may be carried out for participants meeting virologic failure criteria, and for all participants to more broadly assess the contribution of Baseline genotypic information on study results. These tests may be carried out on whole blood or stored plasma samples collected at Baseline and/or on stored plasma samples from other relevant time points as long as this is feasible per local country and laboratory practices. These exploratory tests and analyses may include but are not limited to additional viral genotyping and/or phenotyping, as well as other virologic evaluations such as linkage and minority species analyses, low level HIV-1 RNA quantitation, viral DNA quantitation and measurement of viral replicative capacity. HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype will also be determined on the last on-treatment isolates from participants who have HIV-1 RNA ≥400 c/mL regardless of confirmatory HIV-1 RNA.

eGFR	Estimated glomerular filtration rate
EVG	Elvitegravir
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FTC	Emtricitabine
GCP	Good Clinical Practice
GCSP	GSK's Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
GFR	Glomerular Filtration rate
HAART	Highly active ART therapy
HbA1c	Glycated hemoglobin
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HIV TSQ	HIV treatment satisfaction questionnaire
HLA	Human leukocyte antigen
HOMA-IR	Homeostasis model of assessment – insulin resistance
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IVRS/IWRS	Interactive Voice/Web Recognition System
LDL	Low density lipoprotein
LPV	Lopinavir
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram per deciliter
m-ITT	Modified Intent to Treat

- ART drug regimen(s) that participants started after withdrawal from the main study due to meeting CVW or PVW criteria
- Plasma HIV-1 RNA levels after regimen switch and up to 12 months after CVW or PVW date
- Reasons for virologic failure when the subsequent treatment regimen is changed nonadherence, tolerability, adverse event, etc.
- Reasons for switching when the subsequent treatment regimen is changed - virologic failure, tolerability, safety, adherence, convenience, etc.
- Adverse Events, SAEs or Death leading to ARV discontinuation
- Adverse Drug Reactions, SAEs or Death related to ViiV Healthcare products
- Pregnancy while on ViiV Healthcare products
- Concomitant Medications

Schedule of Activities

Procedures	**Baseline (after regimen switch upon withdrawal from 208090 main study)**	**3 months**	**6 months**	**12 months**
Written Informed Consent	X			
Current ART regimen	X	X	X	X
Plasma HIV-1 RNA (if available)	X	X	X	X
Reasons for Virologic Failure		X	X	X
Reasons for Switch (if subsequent regimen is changed)		X	X	X
Adverse Events, SAEs, or Death leading to ARV discontinuation	X	X	X	X
Adverse Drug Reactions, SAEs, or Death related to ViiV Healthcare products	X	X	X	X
Pregnancy while on ViiV Healthcare products[a]	X	X	X	X
Concomitant Medications	X	X	X	X

a. Investigator must collect pregnancy information on the appropriate form and submit to ViiV/GSK/PPD

11.3.1.2. Restarting Study Intervention

Refer to Section 11.9.2 for details on drug restart following transient resolving liver events not related to study intervention.

11.3.1.3. Decline in Renal Function

Participants who experience an increase in serum creatinine from Baseline of 45 micromoles/liter (μMol/L) (or 0.5 milligrams/deciliter [mg/dL]) should return for a confirmatory assessment within 2 to 4 weeks. A urinalysis, urine albumin/creatinine and urine total protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker, 2012] should also be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

Participants who experience progression to an estimated GFR (using the CKD-EPI-creatinine) of <30 mL/min/1.73m^2 must return for a confirmatory assessment within 2 weeks [Levey, 2009]. A urinalysis, urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker, 2012] should be done at this confirmatory visit. If an estimated GFR of <30 mL/min/1.73m^2 is confirmed using the CKD-EPI (cystatin C), then study intervention should be discontinued and the participant withdrawn from the study (as dose adjustment is needed for NRTIs, which is not possible in a study of a fixed-dose combination tablet).

11.3.1.4. Proteinuria

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, >300 mg/g, or >34 mg/mmol) that represents a change from Baseline and no associated increase in creatinine, should have a repeat spot urine albumin/creatinine ratio performed within 2-4 weeks. If confirmed, then consideration should be given to additional evaluation after consultation with the study medical monitor. Additional evaluation may include a 24-hour urine protein and creatinine measurement and nephrology referral.

Participants with an abnormal urine albumin/creatinine ratio (>0.3 mg/mg, 300 mg/g, or >34 mg/mmol and representing a change from Baseline) and a serum creatinine increase >45 μmol/L (or 0.5 mg/dL) should have confirmation of both results within 2 weeks. If confirmed, the study medical monitor should be contacted immediately. Agreement on further management should be agreed between the investigator and medical monitor.

11.3.1.5. Allergic reaction

Participants may continue study intervention for Grade 1 or 2 allergic reactions at the discretion of the Investigator. The participant 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.

basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Table 3 List of Highly Effective Contraceptive Methods

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner   • *Note: Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.*
Highly Effective Methods[b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation
  • oral
  • injectable

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

MCV = mean corpuscular volume, MCH = mean corpuscular haemoglobin, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO_2 = carbon dioxide, HDL = high density lipoprotein, LDL = low density lipoprotein, HbsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio, HbA1c = glycated haemoglobin, HOMA-IR = homeostasis model of assessment – insulin resistance, IL-6 = interleukin-6, hs-CRP = high-sensitivity C reactive protein, sCD = soluble CD.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
c) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI-creatinine) [Levey, 2009]. In addition, GFR will be estimated by the central laboratory using the CKD-EPI-cystatin C [Inker, 2012] at day 1 and when indicated by renal toxicity criteria.
d) For fasting lipids assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
e) For participants meeting virologic withdrawal criteria, plasma samples will be analyzed in attempt to obtain genotype/phenotype data.
f) Urine pregnancy test/ serum pregnancy test will be performed according to the Schedule of Activities.
g) The intention is to utilize these biomarker data for research purposes; the sponsor will not be reporting real-time results of these assessments to the investigator, except for Cystatin C (Day 1 only) and HbA1c.

References

Levey AS, Stevens LA, Schmid CH, et.al. A new equation to estimate glomerular filtration rate. *Ann Int Med*. 2009;150:604-12.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.8.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening 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, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from

11.8.4. Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to ViiV/GSK/PPD in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by ViiV/GSK/PPD. In this case, all participant identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to ViiV/GSK/PPD.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the categories in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") in Section 11.10:

- Grade 1/ Mild
- Grade 2/ Moderate
- Grade 3/ Severe
- Grade 4/ Potentially life threatening
- Grade 5/ Death

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

11.9. Appendix 9: Liver Safety: Required Actions and Follow-up Assessments and Study Intervention Restart Guidelines

Study treatment refers to all drugs evaluated in the study and therefore includes ViiV study intervention and non-ViiV ART therapies that can be used in combination with ViiV products or other ART interventions.

A liver stopping event is an occurrence of predefined liver chemistry changes (ALT, bilirubin and or INR) that trigger discontinuation of study treatment and requirement of additional actions and follow up assessments to be performed.

A liver monitoring event is as an occurrence of predefined liver chemistry changes (ALT, bilirubin and or INR) that triggers increased monitoring of the participant's liver chemistries, but no action is taken with study treatment unless liver chemistry stopping criteria are met.

11.9.1. Liver Chemistry Stopping Criteria: Required Actions and Follow up Assessments

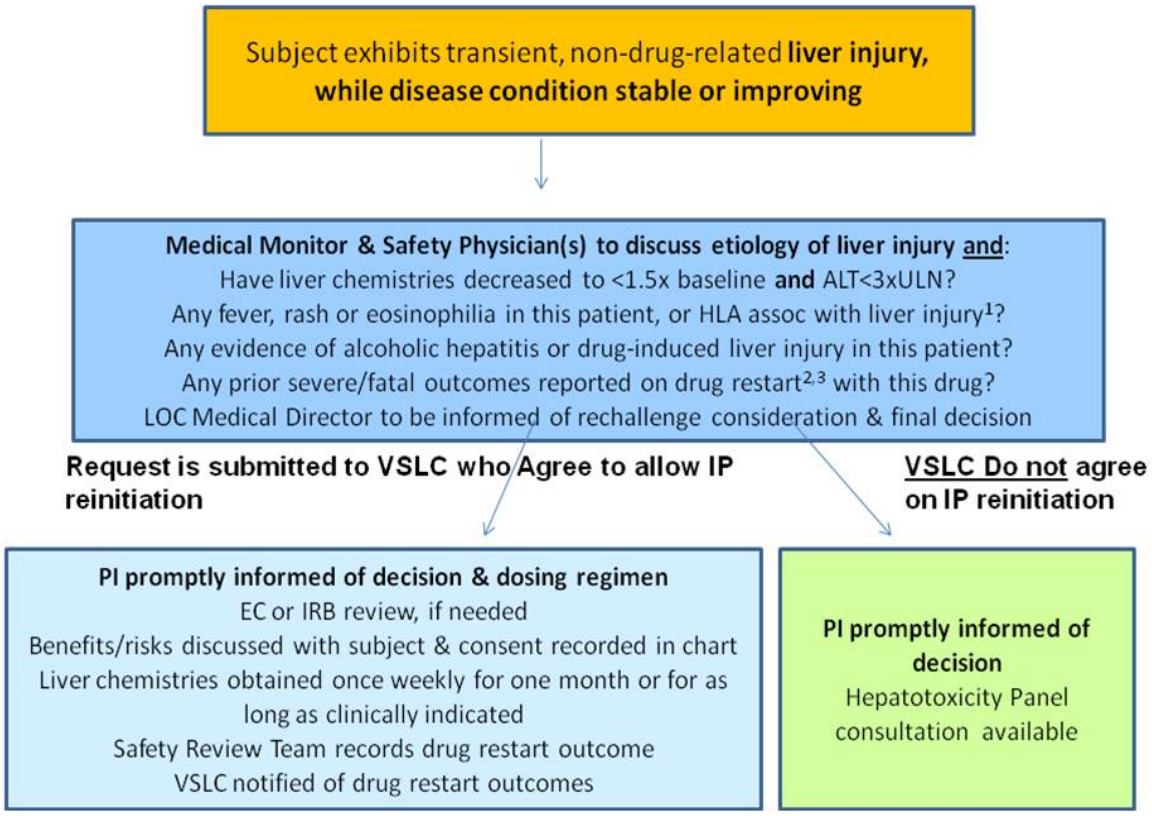
Liver Chemistry Stopping Criteria - Liver Stopping Event	
If baseline ALT ≤1.5x ULN	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥3xULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
If baseline ALT >1.5x ULN	
ALT-absolute	ALT ≥5x baseline OR >500 U/L (whichever occurs first)
ALT Increase	ALT ≥3x baseline but <5x baseline persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥3x baseline OR >300 U/L (whichever occurs first) **and** bilirubin ≥2xULN
Cannot Monitor	ALT ≥3x baseline but <5x baseline and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥3x baseline and 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 discontinue study intervention.
• Report the event to the Medical Monitor **within 24 hours**.
• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]**.**
• Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
• Perform liver event follow up assessments.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below).
• **Do not restart** participant with study intervention unless allowed per protocol and VSLC approval **is granted** (refer to Section 11.9.2).
• If restart is **not allowed or not granted**, permanently discontinue study intervention and may continue participant in the study for any protocol specified follow up assessments.
 	
MONITORING:
• Make every reasonable attempt to have participants return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments.
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline.
• A specialist or hepatology consultation is recommended.
	Make every attempt to carry out liver event follow-up assessments at the central laboratory as described below:
	• Viral hepatitis serology, including:
	  • Hepatitis A immunoglobulin M (IgM) 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.
	• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). The site must contact the Medical Monitor when this test is required.
	• Blood sample for pharmacokinetic (PK) analysis, obtained within 60 hours of last dose[4].
	• Serum CPK and lactate dehydrogenase (LDH).
	• Gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin
	• International normalized ratio (INR)
	• Fractionate bilirubin, if total bilirubin ≥1.5xULN.
	• Obtain complete blood count with

- Relevant physicians must review and agree on request for drug restart:
  - Safety Team Leader, VP, or Senior Safety Physician
  - Medicines Development Leader and Project Physician Leader.
- Hepatotoxicity Panel consultation is available.
- Justification for drug restart outlining the benefit and risk for this participant must be recorded by GSK's Global Clinical Safety and Pharmacovigilance (GCSP) Physician and sent to the VSLC Secretary.
  - VSLC must approve drug re-initiation and dosing regimen

Figure 4 VSLC process for drug restart approval or disapproval



1. 1. Andrade, 2009; 2. Papay, 2009; 3. Hunt, 2010

Medical Monitor, GCSP Physician and PI actions for Restart following VSLC decision

Medical Monitor and (Global Clinical Safety and Pharmacovigilance) GCSP Physician Actions

- Medical Monitor must notify PI of VSLC's restart decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Blood Pressure Abnormalities[1] ***Hypertension*** *(with the lowest reading taken after repeat testing during a visit)* *≥ 18 years of age*	140 to < 160 mmHg systolic OR 90 to < 100 mmHg diastolic	≥ 160 to < 180 mmHg systolic OR ≥ 100 to < 110 mmHg diastolic	≥ 180 mmHg systolic OR ≥ 110 mmHg diastolic	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
< 18 years of age	> 120/80 mmHg	≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)	≥99th percentile +5mmHg adjusted for age, height, and gender (systolic and/or diastolic)	Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) OR Hospitalization indicated
Hypotension	No symptoms	Symptoms corrected with oral fluid replacement	Symptoms AND IV fluids indicated	Shock requiring use of vasopressors or mechanical assistance to maintain blood pressure
Cardiac Ischemia or Infarction *Report only one*	NA NA	NA	New symptoms with ischemia (stable angina) OR New testing consistent with ischemia	Unstable angina OR Acute myocardial infarction
Heart Failure	No symptoms AND Laboratory or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Symptoms at rest or with minimal activity or exertion (e.g., hypoxemia) OR Intervention indicated (e.g., oxygen)	Life-threatening consequences OR Urgent intervention indicated (e.g., vasoactive medications, ventricular assist device, heart transplant)

- When central laboratory testing is not possible at a particular visit, tests for management of participant safety, including HIV-1 RNA may be performed at an appropriately authorised/accredited local laboratory (or other relevant clinical facility), if this can be done within local restrictions on physical distancing. The site should proactively inform PPD/the sponsor about such instances. Local laboratory results done as per routine follow-up, including HIV-1 RNA, may be used to inform safety and patient management decisions. Results should be retained in source records and added to the eCRF.
    - If labs are collected on site and cannot be processed (either via central lab shipping, or local labs), freeze (and maintain at correct temperature for later processing) those samples that are sent frozen. Please safely discard ambient samples per site standards.
- When on-site visits are reduced, it is important that the investigator continue collecting relevant clinical information, including AEs/SAEs, from the participant through alternative means, e.g. by telephone contact. The assessment should include inquiries to determine if the participant has been impacted by COVID-19. Other protocol assessments and procedures as specified in the Schedule of Activities should be completed where possible (e.g. answer questions, update concomitant medications, emphasize adherence, plan/schedule participants return for next scheduled visit). This information should be placed in source records and entered into the eCRF when next possible. If the eC-SSRS assessment is able to be completed as part of the remote telephone visit, participants can complete the eC-SSRS at home by providing them with the activation code and the phone number or URL. Where possible, the site should be in contact with the participant before and after the completion of the assessment to ensure proper follow-up of positive alerts and have plans in place for addressing any positive results, and referring for care as necessary. The HIV TSQ and SDM questionnaires may be completed over the phone.
- There may be cases where the current principal investigator (PI) of a site is indisposed for a period and may need to delegate parts of his/her duties temporarily, e.g. to a sub-investigator. Any such changes should be documented in the site's source records. Any permanent changes in PI should be communicated to the sponsor.
- There may also be circumstances where immediate actions are required by the sponsor and/or investigator, outside of what is contemplated in the protocol, in order to protect a study participant from immediate hazard. Any such measures will be carefully documented and conducted in accordance with the National Competent Authority (NCA)/IRB/IEC regulations.

11.14.2. Changes to Informed Consent

Informed consent should continue per normal procedure and as described in the main body of the protocol, to the extent possible. However, there may be circumstances where re-consent of participants is needed, and a physical signature on site is not possible. In these cases, alternative ways of obtaining such re-consent should be considered, such as

Objectives	Endpoints
To assess health related quality of life for participants treated with DTG/3TC FDC compared to CAR	Change from Baseline in health status using HIV treatment satisfaction questionnaire (HIV TSQ) at Weeks 24 and 48 (or Withdrawal from the study) and symptom distress module (SDM) at Weeks 24, 48 and every 24 weeks during the continuation phase (or Withdrawal from the study)

Overall Design:

This is a 52-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of switching from CAR to DTG/3TC FDC in adults living with HIV who are virologically suppressed and stable on CAR. The study will include a Screening Phase (up to 28 days), a Randomized Phase up to Week 52, and a Continuation Phase (post Week 52) (Section 1.2). The Continuation Phase is not applicable for participants in Sweden and Denmark. Approximately 490 adults living with HIV who are on a stable CAR will be randomized 1:1 to switch to DTG/3TC FDC once daily for up to 52 weeks, or to continue their CAR for 52 weeks. To control for treatment related factors that may impact study outcomes, randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]). For participants randomized to CAR, provisions will be in place, as needed and after discussion with the study team, to assist participants in obtaining CAR during the study.

The primary endpoint for the study is the virologic failure endpoint as per FDA Snapshot category at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last participant has had their Week 48 viral load assessed, including any retests. Participants randomized to DTG/3TC FDC will receive DTG/3TC FDC up to Week 52.

All participants in the DTG/3TC FDC arm who successfully complete up to 52 weeks of treatment will have the opportunity to continue receiving DTG/3TC FDC once daily in a Continuation Phase (See Section 4.3). The Continuation Phase is not applicable for participants in Sweden and Denmark.

CVW Sub-study: A sub-study of Virologic Response to Subsequent ART after Discontinuation from 208090 for Meeting CVW or Precautionary Virologic Withdrawal (PVW) Criteria will be conducted. Details are provided in Section 11.2.

Disclosure Statement: This is a parallel-group treatment study with two arms that is open-label.

Number of Participants: Assuming 20% screen failure rate, approximately 622 adult participants living with HIV will be screened to achieve approximately 490 randomized

Procedures	**Screening Visit[a]**	**Randomized Phase**							**Continuation Phase[c]**	**Withdrawal**	**Follow-up[d]**
		Baseline/ Day 1	**4**	**12**	**24**	**36**	**48[b]**	**52**	**Every 12 Weeks After Week 52**		
PBMCs[ff]		X			X		X			X[gg]	
Study Treatment											
IVRS/IWRS[hh]	X	X	X	X	X	X	X	X	X	X	X
Dispense IP		X	X	X	X	X	X	X	X		
IP accountability (pill counts)			X	X	X	X	X		X	X	

ART - antiretroviral therapy, BMI - body mass index, CDC - centers for disease control and prevention, DNA - deoxyribonucleic acid, ECG – electrocardiogram, eCRF - electronic case report form, HBV – hepatitis B virus, HCV – hepatitis C virus, INR - international normalized ratio, IP - investigational product

a. As soon as all Screening results are available, randomization may occur.
b. Participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (primary endpoint) must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later, occurring prior to Week 52.
c. All participants on the DTG/3TC FDC arm who complete through Week 52 will have the opportunity to enter the Continuation Phase. The Continuation Phase is not applicable for participants in Sweden and Denmark. For participants who will not continue past Week 52, do not dispense study intervention. Participants completing the Continuation Phase must return to the clinic for an End of Continuation Phase visit when transitioning to commercial supplies or to an alternate ART regimen, if appropriate. At this visit, conduct study assessments as specified for all Continuation Phase visits except for dispensing study intervention.
d. An in-clinic Follow-Up visit will be conducted 4 weeks after the last dose of study intervention for participants with the following conditions at the last on-study visit: ongoing AEs, serious adverse events (SAEs) regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant. However, the investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up
e. Inclusion/exclusion criteria will be assessed fully at the Screening visit. Changes between the Screening visit and the Day 1 visit should be considered to ensure eligibility, including review of additional assessments performed at Day 1. Genotypic resistance testing results if available MUST be provided to ViiV after screening and before randomization.
f. Full medical history will be conducted prior to randomization and include assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), psychiatric (e.g., depression), renal (e.g., nephrolithiasis, nephropathy, renal failure), and bone disorders.
g. Menopause history will include date of last menstrual period (collected at Day 1, Week 52 or withdrawal) and menopausal status (collected at Screening, Week 52 or withdrawal) based on the criteria in Section 11.4.1. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

4. STUDY DESIGN

4.1. Overall Design

This is a 52-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group study to assess the non-inferior antiviral activity and safety of switching from CAR to DTG/3TC FDC in adults living with HIV who are virologically suppressed and stable on CAR. The study will include a Screening Phase (up to 28 days), a Randomized Phase up to Week 52, and a Continuation Phase (post Week 52) (Section 1.2). The Continuation Phase is not applicable for participants in Sweden and Denmark. Approximately 490 adults living with HIV who are on a stable CAR will be randomized 1:1 to switch to DTG/3TC FDC once daily for up to 52 weeks, or to continue their CAR for 52 weeks. To control for treatment related factors that may impact study outcomes, randomization will be stratified by baseline third agent class (protease inhibitor [PI], integrase inhibitor [INI], or non-nucleoside reverse transcriptase inhibitor [NNRTI]). For participants randomized to CAR, provisions will be in place, as needed and after discussion with the study team, to assist participants in obtaining CAR during the study.

The primary endpoint for the study is the virologic failure endpoint as per FDA Snapshot category at Week 48 using the Intent-to-Treat Exposed (ITT-E) population. The Week 48 primary analysis will take place after the last participant has had their Week 48 viral load assessed, including any retests. Participants randomized to DTG/3TC FDC will receive DTG/3TC FDC up to Week 52.

All participants in the DTG/3TC FDC arm who successfully complete up to 52 weeks of treatment will have the opportunity to continue receiving DTG/3TC FDC once daily in a Continuation Phase (See Section 4.3). Participants in the CAR arm will complete the study at Week 52. The Continuation Phase is not applicable for participants in Sweden and Denmark.

No dose reductions, modifications, or changes in the frequency of any components of each regimen will be allowed during this study with the exception of a switch from a PI boosted with ritonavir to the same PI boosted with cobicistat and vice versa. A switch from lamivudine to emtricitabine and vice versa is also permitted. Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in the Schedule of Activities (Section 1.3), are essential and required for study conduct. If deviations are required for the management of immediate safety concerns, these should be communicated promptly to the study medical monitor.

An Independent Data Monitoring Committee (IDMC) will be instituted to ensure external objective medical and/or statistical review of efficacy to protect the ethical interests and well-being of participants and to protect the scientific validity of this study.

A sub-study of Virologic Response to Subsequent ART after Discontinuation from 208090 for Meeting CVW or PVW Criteria will be conducted. Details are provided in Section 11.2.

laboratory abnormality). The Follow-Up visit is not required for successful completion of the study.

4.4. Scientific Rationale for Study Design

The design of this study (1:1 randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study) is well established for confirming the non-inferiority of an investigational agent compared with an active ART standard-of-care regimen and generally is accepted by regulatory authorities as rigorous proof of antiviral activity. The primary endpoint, proportion of participants defined as virologic failures by the FDA Snapshot algorithm, is recommended in the FDA's 2015 guidance document for assessing efficacy in Switch Trials [CDER, 2015]. The key secondary endpoint, proportion of participants at Week 48 with plasma HIV-1 RNA<50 c/mL, is also a well-established surrogate endpoint for prognosis of HIV-1 infection and disease progression [CDER, 2015].

Several studies have demonstrated the value/feasibility of a switch study design, an approach that has been shown to generate valuable data supporting ARV combinations that allow dosing flexibility, reduced toxicity and/or drug interactions or a reduction in pill burden. A simplified ARV regimen may also contribute to increased medication adherence and reduced HIV transmission. A potential disadvantage of a switch study design is that effective, well-tolerated ART is discontinued at the time of switching to the simplified regimen [Carr, 2012].

Previous studies have shown the non-inferiority of a 2-drug regimen in maintaining virologic suppression when participants who were virologically suppressed on a 3-drug regimen were switched to a 2-drug regimen (See Section 2.2).

In this study, participants will be randomized 1:1 to switch to DTG/3TC FDC from CAR at Day 1 or stay on their CAR for up to 52 weeks. The primary endpoint will be evaluated at Week 48 using a 5% non-inferiority (NI) margin. The rationale for this decision is provided in Section 9.2.1. This study is evaluating the rate of Snapshot algorithm measured virologic failure in already suppressed participants to test the hypothesis that maintenance of the suppression of HIV-1 replication by DTG/3TC FDC will be non-inferior to that observed in the CAR arm of the study through Week 48.

This study will also evaluate the safety and tolerability of this 2-drug regimen in persons with a creatinine clearance of between 30 – 49 mL/min/1.73m^2. The DTG 50mg dose is approved for persons with a creatinine clearance of as low as 30 mL/min/1.73m^2. 3TC plasma concentrations area under the curve (AUC) are increased in participants with moderate to severe renal impairment due to decreased clearance, and the current label recommends a dose of 150 mg once a day for a creatinine clearance of between 30-49 mL/min/1.73m^2. However, several randomized controlled studies that have compared a total 3TC daily dose of 600 mg/day to 300 mg/day showed only small, statistically non-significant differences between the treatment arms in the frequency of AEs, drug-related AEs, SAEs, Grade 3/4 clinical and laboratory toxicities and withdrawals due to AEs [Eron, 1995; GlaxoWellcome Document Number UCR/95/003, 1995; GlaxoWellcome Document Number GIO/94/005, 1995]. Our study will allow

lamivudine AUC(0-∞). However, the bilayer tablet showed a modest increase in lamivudine Cmax compared to the single entity tablet, which is not considered to be clinically significant.

Baseline Assessments

At Day 1 and prior to randomization, any changes to the eligibility parameters must be assessed and any results required prior to randomization (e.g., Day 1 urine pregnancy test for women of childbearing potential) must be available and reviewed.

Other baseline information to be collected at Day 1 includes assessment of HIV risk factors and mode of transmission, general medical history and current medical conditions, and menopause history. Laboratory and health outcomes assessments will also be collected. Questionnaire/surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. Refer to Section 1.3 for a summary of all procedures at the Baseline (Day 1) visit.

8.1. Efficacy Assessments

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the Schedule of Activities (Section 1.3). Methods to be used may include but are not limited to the Abbott Realtime HIV-1 Assay lower limit of quantitation 40 c/mL. In some cases, (e.g., where the plasma HIV-1 RNA is below the lower limit of detection for a given assay) additional exploratory methods may be used to further characterize plasma HIV-1 RNA levels.

Lymphocyte Subsets

Lymphocyte subsets will be collected for assessment by flow cytometry (total lymphocyte counts, percentage, and absolute CD4+ and CD8+ lymphocyte counts, CD4+/CD8+ ratio) according to the Schedule of Activities (Section 1.3).

CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the Schedule of Activities (Section 1.3). HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (see Section 11.12). When assessing CDC stage at Screening/Baseline, consider only the latest available CD4 T-cell count, except when the participant had an active Stage 3 event in the 6 months prior to Screening. Indicators of clinical disease progression are defined as:

CDC Stage 1 at enrolment → Stage 3 event;

CDC Stage 2 at enrolment → Stage 3 event;

CDC Stage 3 at enrolment → New Stage 3 Event;

CDC Stage 1, 2 or 3 at enrolment → Death.

8.1.1. Primary Efficacy Endpoint

The primary endpoint will be the proportion of participants with virologic failure endpoint as per FDA snapshot category at week 48 for the ITT-E population. Virologic

investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behaviour. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

Assessment of treatment-emergent suicidality will be monitored during this study using the electronic version of the Columbia Suicidality Severity Rating Scale (eC-SSRS). The definitions of behavioural suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behaviour, 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 eC-SSRS is to be administered as a participant completed questionnaire specified in the SoA. The eC-SSRS will be conducted electronically by telephone or by computer/tablet connected to the internet.

Additionally, the investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (non-serious or SAE) eCRF form on any participant that experiences a possible suicidality-related AE while participating in this study. This 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 ViiV/GSK within 1 week of the investigator diagnosing a possible suicidality-related AE.

8.2.6. Pregnancy

Details of all pregnancies in female participants will be collected after the start of study intervention and ending at the final Follow-up visit. If a pregnancy is reported, the investigator should inform ViiV/GSK/PPD within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 11.4.3.

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child(ren). Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the participant has completed the study and considered by the investigator as possibly related to the study intervention must be reported promptly to ViiV/GSK (or designee).

GSK's central safety department will forward this information to the ART Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of

- urine phosphate, and
- serum creatinine.

Bone biomarkers (blood):

- bone-specific alkaline phosphatase,
- procollagen type 1 N-propeptide,
- type 1 collagen cross-linked C-telopeptide,
- osteocalcin

Inflammatory Biomarkers (blood):

- Interleukin-6 (IL-6)
- High-sensitivity C reactive protein (hs-CRP)
- D-dimer
- Soluble CD14 (sCD14)
- Soluble CD163 (sCD163)

HbA1c and insulin and glucose for HOMA-IR calculation

Other Biomarkers:

- Whole blood will be used for measurement of telomere length.

Since the intention is to utilize these biomarkers for research purposes and the clinical significance of these results is uncertain, the Sponsor will not be reporting real time results of these assessments to the investigator except for Cystatin C (Day 1 only) and HbA1c.

8.9. Health Economics and Outcomes Research

Health outcomes assessments will be conducted according to the Schedule of Activities (SoA) (Section 1.3). In the event of translations being unavailable, no such assessments will be conducted and the responses will be considered as missing in the final analyses. Assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments. Questionnaires will be administered on paper except the willingness to switch survey, which will be a verbal question.

The following health outcomes assessments will be utilized in this study:

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This study is designed to show that the antiviral effect of switching to a simplified two-drug regimen of DTG/3TC FDC once-daily is not inferior to continuation of their CAR at week 48 in ART-experienced participants living with HIV-1.

Non-inferiority will be concluded if the upper bound of a two-sided 95% confidence interval for the difference in virologic failure rates between the two treatment arms is smaller than 5%. If r_d is the virologic failure rate on DTG/3TC FDC and r_f is the virologic failure rate on the CAR regimen, then the hypotheses can be written as follows:

$$H_0: \ r_d - r_f \geq 5\% \qquad H_1: r_d - r_f < 5\%$$

9.2. Sample Size Determination

9.2.1. Sample Size Assumptions

The original sample size calculation required approximately 300 participants per arm (from a target of 857 screened participants) based on a true virologic failure rate of 2.25% per arm, a non-inferiority margin of 4%, and a 2.5% one-sided significance level to provide approximately 91% power to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL) at Week 48.

The COVID-19 pandemic of 2019/2020 occurred during screening, and enrolment. Because of the COVID-19 pandemic, there is potential impact on participant compliance with study visits, study drug adherence, and data quality, and then consequently the virologic failure rate could be higher than originally expected. With the increase of assumed true virologic failure rate, we propose to change non-inferiority margin from 4% to 5%. Assuming a virologic failure rate of 3%, a non-inferiority margin of 5%, and a 2.5% one-sided significance level, a sample size of 245 participants per arm would provide approximately 90% power to show non-inferiority for the proportion of participants with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL) at Week 48. Based on the sample size recalculation and both statistical and practical considerations due to COVID-19 pandemic, a decision was made to terminate the study enrolment. At the time of enrolment termination, approximately 445 participants were randomized and 53 were in screening. Assuming a 20% screen failure rate the final number of participants is expected to be approximately 490 (245 per arm).

Rationale for non-inferiority margin

According to the FDA's 2015 guidance document (Human Immunodeficiency Virus-1 Infection: Development of ART Drugs for Treatment, November 2015), the margin for switch trials is driven by the largest clinically tolerable virologic failure rate and could be from 4% to 6% depending on virologic failure rate. Per the FDA document, typical rates of virologic failure seen in switch studies range from 1 to 3 percent and a margin of 4%

MRHD	maximum recommended human dose
MSDS	Material Safety Data Sheet
NADES	Non-Acquired Immuno-Deficiency Syndrome (AIDS)-Defining Events
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed Case
OCT-2	Organic cation transporter
PBMC	Peripheral Blood Mononuclear Cell
PDVF	Protocol defined virologic failure
PI	Protease inhibitor
PK	Pharmacokinetic
PP	Per-protocol
PPD	Pharmaceutical Product Development
PSRAE	Possible suicidality-related adverse event
PVW	Precautionary virologic withdrawal
QTc	Corrected QT interval
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RBP	Retinol Binding Protein
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RPV	Rilpivirine, Edurant
RT	Reverse transcriptase
RTV	Ritonavir
SAE	Serious adverse event
SDM	Symptom Distress Module
SJS	Stevens-Johnson syndrome
SRM	Study Reference Manual
STR	Single tablet regimen
SVW	Suspected Virologic Withdrawal
TAF	Tenofovir alafenamide
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine, Truvada
TEN	Toxic epidermal necrolysis
TLOVR	Time To Loss Of Virologic Response
TSQ	Treatment Satisfaction Questionnaire
TRDF	Treatment Related Discontinuation = Failure
ULN	Upper limit of normal
VSLC	ViiV Safety and Labelling Committee
WBC	White blood cell
WOCBP	Women of childbearing potential
ZDV/3TC	Zidovudine/lamivudine, COMBIVIR

Since this sub-study is an observational study of participants who have withdrawn from the main study, the protocol-specified withdrawal and stopping criteria are not applicable.

11.2.4. Sub-study data Collection

For this study, participant data will be entered into eCRFs, transmitted electronically to GSK or designee and supplemented with demographic and clinical data provided from the 208090 study in a validated data system.

Management of clinical data will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data, e.g. removing errors and inconsistencies in the data.

Adverse events, SAEs and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSKDrug.

eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent at the end of the study in CD format to GSK to be retained. Each investigator will receive a copy of his or her site-specific data in the same format to maintain as the investigator copy. Participant initials will not be collected or transmitted to ViiV Healthcare/GSK according to ViiV Healthcare/GSK policy.

11.2.5. Statistical Considerations and Data Analysis

This is a descriptive study. No formal hypothesis will be tested. Where possible, frequency tables will be provided.

The endpoint assessing the proportion of participants with plasma HIV-1 RNA <50 copies/mL, 50-200 copies and >200 copies/mL at the end of 12 months will be based on an observed case analysis for this descriptive study.

Further details will be provided in the RAP.

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

11.3.1.6. Rash

Mild to moderate rash is an expected adverse reaction for DTG-containing ART. 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. No instances of serious skin reaction, including SJS, TEN and erythema multiforme, have been reported for DTG in clinical trials. For further characterisation of HSR and rash observed with DTG-containing ART, please see the current version of the IB and any IB supplements [GlaxoSmithKline Document Number RM2007/00683/11, GlaxoSmithKline Document Number 2017N352880_00, GlaxoSmithKline Document Number 2017N352880_01].

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

Participants may continue study intervention for an isolated Grade 2 rash. However, study intervention (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 participant 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.

Participants should permanently discontinue study intervention [and all other concurrent medication(s) suspected in the Investigators causality assessment] for an isolated Grade 3 or 4 rash, except where the aetiology of the rash has been definitively diagnosed as NOT attributable to study intervention (see below), and the participant should be withdrawn from the study. Participants should be treated as clinically appropriate and followed until resolution of the AE. Every effort should be made to collect as much information as possible about the evolution of the event and any relationship with potentially related medical events (e.g., viral infection) or start of concomitant medication.

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings, Section 11.10.

However, if the aetiology of the rash has been definitively diagnosed as being unrelated to study intervention and due to a specific medical event or a concomitant infection or a concomitant non-study medication, routine management should be performed and

Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

11.4.3. Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to ViiV/GSK/PPD within 2 weeks of learning of a participant's pregnancy.
- Participants will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to ViiV/GSK/PPD. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. GSK's central safety department will forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers and licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to ViiV/GSK/PPD as described in Appendix 8. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating will be withdrawn from the study.

11.8. Appendix 8: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

11.8.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.8.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to ViiV/GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to ViiV/GSK/PPD.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ViiV/GSK/PPD to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide ViiV/GSK with a copy of any post-mortem findings including histopathology.

	differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG 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 eCRF forms. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake eCRF.

CPK - creatine phosphokinase

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant 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) **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants 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)
4. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

- The Safety Review Team must record restart outcomes and the GCSP Physician must send these to the VSLC
    - All severe reactions (restart associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities with drug restart must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions:

- The PI must obtain Ethics Committee or Institutional Review Board approval of drug restart, as required.
- If drug re-initiation VSLC-approved, the participant must provide informed consent with a clear description of possible benefits and risks of drug administration including recurrent, more severe liver injury or possible death.
- The participant's informed consent must be recorded in the study chart, and the drug administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be followed ***once weekly for 'restart' cases*** for one month or for as long as clinically indicated following drug re-initiation. If participant exhibits protocol-defined liver chemistry elevations, study intervention should be discontinued as protocol specified.

VSLC and the IRB/IEC must be informed of the participant's outcome following drug restart.

Restart safety outcomes:

- 0 = no liver chemistry elevation
- 1 = recurrent liver chemistry elevation not meeting participant stopping criteria
- 2 = recurrent liver chemistry elevation meeting participant stopping criteria
- 3 = serious adverse event
- 4 = fatality

References

Andrade RJ, Robles M, Lucena MI. Rechallenge in drug-induced liver injury: the attractive hazard. Expert Opin Drug Saf. 2009; 8:709-714.

Hunt, CM. Mitochondrial and immunoallergic injury increase risk of positive drug rechallenge after drug-induced liver injury: A systematic review. Hepatol. 2010; 52:2216-2222.

Papay JI, Clines D, Rafi R, et al. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009; 54:84-90.

[1] Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C

Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hemorrhage (with significant acute blood loss)	NA	Symptoms AND No transfusion indicated	Symptoms AND Transfusion of ≤ 2 units packed RBCs indicated	Life-threatening hypotension OR Transfusion of > 2 units packed RBCs (for children, packed RBCs > 10 cc/kg) indicated
Prolonged PR Interval or AV Block *Report only one* *> 16 years of age*	PR interval 0.21 to < 0.25 seconds	PR interval ≥ 0.25 seconds OR Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
≤ 16 years of age	1st degree AV block (PR interval > normal for age and rate)	Type I 2nd degree AV block	Type II 2nd degree AV block OR Ventricular pause ≥ 3.0 seconds	Complete AV block
Prolonged QTc Interval[2]	0.45 to 0.47 seconds	> 0.47 to 0.50 seconds	> 0.50 seconds OR ≥ 0.06 seconds above baseline	Life-threatening consequences (e.g., Torsade de pointes, other associated serious ventricular dysrhythmia)
Thrombosis or Embolism *Report only one*	NA	Symptoms AND No intervention indicated	Symptoms AND Intervention indicated	Life-threatening embolic event (e.g., pulmonary embolism, thrombus)

[2] As per Bazett's formula

the investigator contacting the participant by telephone or video call and obtaining verbal consent, supplemented with email confirmation.

Any alternative informed consent procedure must be undertaken only after site IRB/Ethics Committee agreement and approval.

Any updated informed consent form or other participant-facing materials should be provided to participants by e-mail, mail or courier before re-consent is obtained. Any consent obtained this way should be documented in source records and confirmed by way of normal consent procedure at the earliest opportunity when participants attend their next on-site study visit.

The changes to the protocol, including COVID-19 related changes may be implemented before an ICF including COVID-19 related updates will be signed.

11.14.3. Direct-To-Patient (DTP) Shipment of Study IP

If a participant is unable to attend a study visit or to come to the site to pick-up investigational product (IP) due to site restrictions, or due to an inability to travel to the site (for personal precaution/sequestration, or government mandated travel restrictions, etc.), sites can consider DTP shipments of drug, from the site, to the participant, to ensure access to medicines. All other options, including alternative travel options for participants, should be considered before reverting to DTP shipments.

- If the study site is considering DTP shipment of IP, the site must first verify if DTP IP dispensing by investigators/hospital pharmacies is locally permitted and **whether it requires regulatory and/or local ethics pre-approval, or post-hoc notification.**
- The study participant should express his/her agreement for DTP shipment and the sharing of their personal information with any third-party couriers (as applicable), in accordance with local requirements. This agreement should be documented in source records.
- Enough IP to bridge to the next scheduled study visit can be supplied. For example, if the next visit is 12 weeks away, a 12-week supply can be dispensed via the IRT system

  NOTE: When the visit interval is only 4 weeks, then at least 8 weeks of IP can be provided to the participant
- Ensure local courier vendors, or vendors of hospital pharmacies, can ensure proper in-transit temperature monitoring, have enough shipper boxes and temperature loggers and can document storage conditions during IP transportation.
- Where temperature monitoring is not available, oral DTG/3TC FDC can be shipped at ambient temperatures with couriers that can provide shipper boxes capable of maintaining the shipment temperature storage requirements as described in the study guides. The risk of going outside of the excursion ranges