CLINICAL STUDY PROTOCOL

Primary Study Intervention(s)	GSK3515864 (dolutegravir/lamivudine, DTG/3TC)
Other Study Intervention(s)	NA
Study Identifier	219516
EU CT Number	2022-503137-66-00
Approval Date	09 Jul 2025
Title	A Phase 3b, multicenter, single-arm, open-label study evaluating the efficacy, safety, and tolerability of switching to DTG/3TC single tablet regimen administered once daily from a bictegravir/emtricitabine/tenofovir alafenamide single tablet regimen in people living with HIV of at least 50 years of age who are virologically suppressed
Compound Number/Name	GSK3515864 (dolutegravir/lamivudine, DTG/3TC)
Brief Title	Ph 3b, BIC/FTC/TAF to DTG/3TC FDC, 96 Week switch, efficacy, safety, and tolerability study in ART-experienced older adults living with HIV with virologic suppression
Sponsor (Excluding US)	ViiV Healthcare UK Limited, 980 Great West Road, Brentford, Middlesex TW8 9GS, United Kingdom
U.S. IND Sponsor	ViiV Healthcare Company, 410 Blackwell Street, Durham, NC 27701, USA
Sponsor signatory	Sherene Shakib Min, MD, MPH VP, Head of Global Clinical Development ViiV Healthcare

Medical monitor name and contact information can be found in the local study contact information document.

ADDITIONAL SPONSOR INFORMATION

In some countries, local law requires that the clinical trial sponsor is a local company legal entity. In these instances, the appropriate company to be identified as Sponsor must be agreed with the global ViiV Healthcare clinical team and signed off by the Senior Vice President, Head of Research & Development.

This study is sponsored by ViiV Healthcare. GSK and PPD are supporting ViiV Healthcare in the conduct of this study.

Based on TMF-14732712 Protocol v3.0.

Protocol Amendment 04 Investigator Agreement

- **To assume responsibility for the proper conduct of the study at this site.**
- **That I am aware of and will comply with GCP and all applicable regulatory requirements.**
- **That I will comply with the terms of the clinical study site agreement.**
- **To ensure that all persons assisting me with the study are adequately informed about the GSK/ViiV study intervention and other study-related duties and functions as described in the protocol.**
- **To cooperate with representative(s) of GSK/ViiV in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.**

Study identifier	219516
EU CT number	2022-503137-66-00
Approval date	09 Jul 2025

Title

Investigator name _____

Signature _____

Date of signature

(DD Month YYYY) _____

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
GSK Document Number	**Document**	**Approval Date**
TMF-21725476	Amendment 04	09 Jul 2025
TMF-19615487	Amendment 03	30 September 2024
TMF-17050843	Amendment 02	12 October 2023
TMF-16109599	Amendment 01	10 May 2023
TMF-15145377	Original Protocol	22 February 2023

Amendment 04 (09 Jul 2025)

Overall rationale for the current Amendment: The primary reason for Protocol Amendment 04 is to address regulatory requests from the European Medicines Agency to better differentiate between both study parts (i.e., the interventional “main study” and the observational sub-study) when referring to the sub-study that was added in Protocol Amendment 03.

LIST OF MAIN CHANGES IN THE PROTOCOL AND THEIR RATIONALE:

Section # and title	Description of change	Brief rationale
Header	Updated document type and version.	Administrative update (a new TMF number has been assigned).
Section 4.1 Section 7 Section 7.1.2.2	Specified “main study” when alluding to the original interventional study in reference to the observational sub-study.	To better clarify between the two study parts (i.e., the main study and the sub-study) as requested by the European Medicines Agency.
Section 7.1.2	Removed extra text from SVW definition that references prior HIV-1 RNA assessment: One assessment with HIV-1 RNA ≥200 c/mL “with an immediately prior HIV-1 RNA <50 c/mL” after Day 1. Corrected text: One assessment with HIV-1 RNA ≥200 c/mL after Day 1.	Typographical error corrected/removed to prevent confusion. The presence or absence of this text does not change the participant virologic management or study conduct given detailed information on participant management for SVW present in Section 7.1.2.1.
Section 10.14. Appendix 14. Protocol amendment history	Moved summary of changes associated with the previous protocol amendment 03 to this Appendix. Specified “main study” when alluding to the original interventional study in reference to the observational sub-study.	Administrative update per protocol template standards. To better clarify between the two study parts (i.e., the main study and the sub-study) as requested by the European Medicines Agency.

Section # and title	Description of change	Brief rationale
Section 10.15. Appendix 15 Section 10.15.1 Section 10.15.2; Table 18 Section 10.15.3; Table 19 Section 10.15.4	Specified “main study” when alluding to the original interventional study in reference to the observational sub-study (including within the sub-study title). Clarified language describing sub-study design. Added clarity around the definition of “baseline” and approximate local data collection timepoints.	To better clarify between the two study parts (i.e., the main study and the sub-study) as requested by the European Medicines Agency. To address feedback from the European Medicines Agency. Clarifying information for the sub-study.
Throughout document List of Abbreviations and Definitions of Terms	Minor administrative changes, typographical edits, and abbreviation alignment.	Clarifications, typographical updates, and adminsitrative edits.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

2DR	Two drug regimen
3DR	Three drug regimen
3TC	Lamivudine, EPIVIR
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B core Antibody
APR	Antiretroviral Pregnancy Registry
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
AxMP	Auxiliary medicinal product
BIC	Bictegravir
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
c/mL	Copies/milliliter
CD	Cluster of Differentiation
CDC	Centers for Disease Control and Prevention
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID	Coronavirus disease
CRF	Case Report Form
CRO	Contract research organization
CSR	Clinical Study Report
C-SSRS	Columbia Suicidality Severity Rating Scale
CI	Confidence interval
COBI	Cobicistat
CA	Competent authority
CONSORT	Consolidated Standards of Reporting Trials
CoEQ	Control of Eating Questionnaire
CPK	Creatine phosphokinase
CrCl	Creatinine clearance
CTFG	Clinical Trial Facilitation Group
CV	Cardiovascular
CVW	Confirmed Virologic Withdrawal
DAIDS	Division of Acquired Immune deficiency Syndrome
DDI	Drug Drug Interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DTG	Dolutegravir, TIVICAY
DTP	Direct-to-participant
DXA	Dual-X-absorptiometry
EATG	European AIDS Treatment Group
ECG	Electrocardiogram
eCRF	Electronic case report form
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
eDM	Electronic Data Management
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EATG	European AIDS Treatment Group
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination

FTC	Emtricitabine
GCP	Good Clinical Practice
GFR	Glomerular Filtration rate
GGT	Gamma-glutamyl transferase
HbA1c	Glycated hemoglobin
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hCG	Human chorionic gonadotropin
HDL	High density lipoprotein
HDPE	High density polyethylene
HIV	Human immunodeficiency virus
HIV TSQ	HIV treatment satisfaction questionnaire
HLA	Human leukocyte antigen
HRT	Hormone replacement therapy
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
ICH	International Council on Harmonization
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IgM	Immunoglobulin M
IMP	Investigational medicinal product
IN	Integrase
INSTI	Integrase strand transfer inhibitor
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
iSRC	Internal safety review committee
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IxRS	Interactive response system
LCCRC	Liverpool Combined Comorbidity Risk Calculator
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
MCH	Mean Corpuscular Hemoglobin
MCv	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
Mg	Milligram
Mg/dL	Milligram per deciliter
MRS	Menopause Rating Scale
MTCT	Mother to child transmission
NADEs	Non-Acquired Immune-Deficiency Syndrome (AIDS)-Defining Events
NRTI	Nucleoside reverse transcriptase inhibitor
NTD	Neural tube defect
OCT-2	Organic cation transporter
OTC	Over the counter
PBMC	Peripheral Blood Mononuclear Cell
PI	Principal Investigator
PK	Pharmacokinetic
PP	Per-protocol
PPD	Pharmaceutical Product Development
PRO	Patient Reported Outcome
PSRAE	Possible suicidality-related adverse event
PVW	Precautionary Virologic Withdrawal

QTc	Corrected QT interval
QTL	Quality tolerance limit
QOL	Quality of Life
RBC	Red blood cell
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT	Reverse transcriptase
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome–related coronavirus
SJS	Stevens-Johnson syndrome
SRM	Study Reference Manual
SoA	Schedule of activities
SOC	Standard of care
SVW	Suspected Virologic Withdrawal
TAF	Tenofovir alafenamide
TEN	Toxic epidermal necrolysis
TSQ	Treatment Satisfaction Questionnaire
TRDF	Treatment Related Discontinuation = Failure
ULN	Upper limit of normal
VAS	Visual Analog Scale
UK	United Kingdom
US	United States
VAT	Visceral adipose tissue
VSLC	ViiV Safety and Labelling Committee
WBC	White blood cell
WHOQOL	World Health Organization Quality of Life
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

Term	**Definition**
Adverse Drug Reaction (ADR)	An adverse event where a causal relationship between a medicinal product and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out. In the context of a clinical trial, an ADR can be serious or non-serious. Serious ADRs may be subject to expedited reporting if they are considered unexpected (see SUSAR definition). For marketed products, ADRs are subject to expedited reporting within the country where they are authorized
Auxiliary Medicinal Product (AxMP)	Medicinal products used in the context of a clinical trial but not as investigational medicinal products, such as medicinal products used for background treatment, challenge agents, rescue medication, or used to assess end-points in a clinical trial. Auxiliary medicinal products should not include concomitant medications, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial. Authorized AxMP = Medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product. Safety reporting with regard to auxiliary medicinal products shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC. Unauthorized AxMP = Medicinal product not authorized in accordance with Regulation (EC) No 726/2004. Safety reporting for unauthorized auxiliary medicinal products will follow the same processes and procedures as SUSAR safety reporting

Term	Definition
Background treatment	Type of medicinal product administered to each of the clinical trial participant, regardless of randomization group, to treat the indication that is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared with an active comparator or with placebo plus background treatment.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Challenge agent	A product given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed.
Comparator	Any product used as a reference (including placebo, marketed product, GSK or non-GSK) for an investigational product being tested in a clinical trial. This is any product that is being used to assess the safety, efficacy, or other measurable value against the test product (IMP).
Co-administered products	A product given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Direct-to-Participant Shipments	Shipping of Investigational Product, lab kits, devices, etc., to the participant's residence under secure and controlled conditions.
eDiary	Electronically registered participant data and automated data entries on, for example, a handheld mobile device, tablet or computer.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced
Intercurrent event	Event occurring after study intervention initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational medicinal product (IMP)	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Medicinal products used to assess end-points	A product given to the participant in a Clinical Trial as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.
Placebo	An inactive substance or treatment that looks the same as, and is given in the same way as, an active drug or intervention/treatment being studied.
Rescue medication	Medicines identified in the protocol as those that may be administered to the participants when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.
Standard of Care	Medicine(s) for a specific indication, or a component of the standard care for a particular medical indication, based on national and/or international consensus; there is no regulatory significance to this term. Products/regimens considered standard of care may differ country to country, depending on consensus in individual countries
Suspected Unexpected Serious Adverse Reaction (SUSAR)	In a clinical trial, a serious adverse reaction that is considered unexpected, i.e., the nature or severity of which is not consistent with the reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product). All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting.
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate

Term	Definition
	study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
Legally acceptable representative (LAR)	An individual, judicial or other body authorized under applicable law to consent on behalf of a prospective participant to the participant's participation in the clinical study. The terms legal representative or legally authorized representative are used in some settings.
Last Subject Last Visit (LSLV)	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Participant identifier	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study treatment (vaccine(s)/product(s)/control). Synonyn: subject.
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. In other words, Primary Completion Achieved is the date of the last contact with the participant when data has been collected/intervention done for the purpose of data collection for analysis of all primary endpoints. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures. This date may occur prior to the study end or be the same date as the study end milestone.
Remote visit	A visit conducted in the place other than the study site.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Study intervention	Term used throughout the clinical study to cover all types of investigational and non-investigational products including medical devices and vaccines intended to be administered to the study participants during the study conduct. Procedures conducted to manage participants or to collect data are excluded from the usage of this term. Note: "Study intervention" and "study treatment" are used interchangeably unless otherwise specified.
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.
Virtual visit	This term refers to study visits conducted using multimedia or technological platforms.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3b, multicenter, single-arm, open-label study evaluating the efficacy, safety, and tolerability of switching to DTG/3TC single tablet regimen administered once daily from a bictegravir/emtricitabine/tenofovir alafenamide single tablet regimen in people living with HIV of at least 50 years of age who are virologically suppressed

Brief Title: Ph 3b, BIC/FTC/TAF to DTG/3TC FDC, 96 Week switch, efficacy, safety, and tolerability study in ART-experienced older adults living with HIV with virologic suppression

Rationale: Refer to Section 2.1.

Objectives, Endpoints, and Estimands: Refer to Section 3.

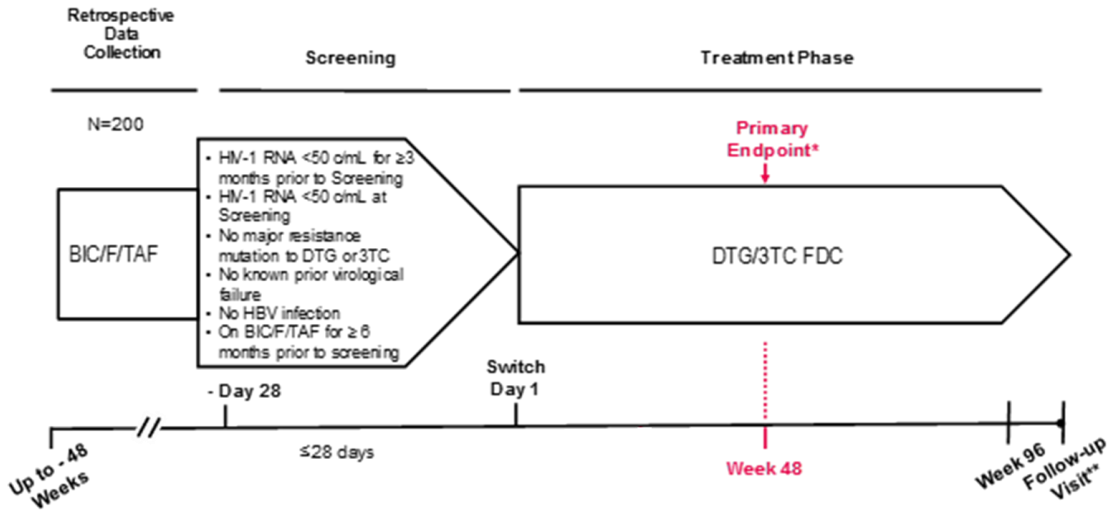
Overall Design: Refer to Section 4.1.

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview



* Primary Endpoint: participants with plasma HIV-1 RNA ≥50 copies/mL at week 48 (Snapshot algorithm)

** Follow-up Visit: to be conducted approximately 2-4 weeks after the last dose of study medication for participants who meet specific criteria. Refer to Section 4.4.1.

1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities

Procedure	Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent)		Treatment Phase[a, v] (DTG/3TC)								
	1 to 2 data collection time points at -48 Wks to Screening	Screening[b]	Day 1	Wk 4 ±6 days	Wk 12 ±6 days	Wk24 ±6 days	Wk48 ±6 days	Wk72 ±6 days	Wk96 ±6 days	Withdrawal [w]	Follow-Up Visit [x]
Written Informed Consent[c]		X									
Eligibility Verification (Inclusion/ Exclusion Criteria)		X	X								
Demography		X									
Medical History[d]		X									
Current medical conditions		X									
Medication History including Complete Prior ART history		X									
Cardiovascular risk assessment[d]		X	X			X	X		X		
Syphilis serology + reflex Rapid Plasma Reagin (RPR)		X	X								

Procedure	Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent)		Treatment Phase[a, v] (DTG/3TC)								
	1 to 2 data collection time points at -48 Wks to Screening	Screening[b]	Day 1	Wk 4 ±6 days	Wk 12 ±6 days	Wk24 ±6 days	Wk48 ±6 days	Wk72 ±6 days	Wk96 ±6 days	Withdrawal [w]	Follow-Up Visit [x]
Symptom Directed Physical Exam and Medical Assessment[e]		X	X	X	X	X	X	X	X	X	X
Weight, Height and BMI[f]	X	X	X	X	X	X	X	X	X	X	
Waist Circumference[f]			X			X	X		X	X	
Hip Circumference[f]			X			X	X		X	X	
Vital Signs (BP, HR)[g]	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[h]			X								
Retrospective Hematology (CD4, including CD4 Nadir, CD8, Platelets) Clinical Chemistry (Creatinine, eGFR and liver chemistry [ALT, AST, GGT, total and direct bilirubin]) as available	X										
CDC HIV-1 stage[i]		X	X								
HIV Associated Conditions			X	X	X	X	X	X	X	X	X

Procedure	Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent)		Treatment Phase[a, v] (DTG/3TC)								
	1 to 2 data collection time points at -48 Wks to Screening	Screening[b]	Day 1	Wk 4 ±6 days	Wk 12 ±6 days	Wk24 ±6 days	Wk48 ±6 days	Wk72 ±6 days	Wk96 ±6 days	Withdrawal [w]	Follow-Up Visit [x]
AEs, SAEs, Concomitant Medications[j]		X	X	X	X	X	X	X	X	X	X
Electronic Columbia Suicidality Severity Rating Scale (eC-SSRS)[k]		X	X		X	X	X		X	X	
Clinical chemistry		X	X	X	X	X	X	X	X	X	X
Hematology		X	X	X	X	X	X	X	X	X	X
Pregnancy Testing[l]		S	S/U	U	U	U	U	U	U	S	U
HIV-1 RNA quantitation and sample(s) for storage[m]		X	X	X	X	X	X	X	X	X	X
CD4+ cell count			X	X	X	X	X	X	X	X	X
CD8+ cell count			X			X	X		X	X	
Urinalysis[n]			X	X		X	X		X	X	
Fasting Labs: Glucose, Insulin, HbA1c, Cholesterol (Total, HDL and LDL) and Triglycerides[o]	X		X			X	X		X	X	

Procedure	Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent)		Treatment Phase[a, v] (DTG/3TC)								
	1 to 2 data collection time points at -48 Wks to Screening	Screening[b]	Day 1	Wk 4 ±6 days	Wk 12 ±6 days	Wk24 ±6 days	Wk48 ±6 days	Wk72 ±6 days	Wk96 ±6 days	Withdrawal [w]	Follow-Up Visit [x]
Hepatitis B (HBsAg), Anti-HBc, and Anti-HBsAG, Hepatitis C (anti-HCV Ab)		X									
PT/PTT/INR		X	X								
Whole Blood (Virology)[p]			X			X	X		X	X	
PBMCs[p]			X				X		X	X	
Renal, and bone biomarker analytes (blood and urine)[q]			X			X	X		X	X	
Liver Fibroscan[y]			X				X		X		
DXA Scan for Body Composition[r]			X				X		X		
HIV TSQs[s]			X			X			X	X	
HIV TSQc[s]							X				
Symptom Distress Module[s]			X			X	X		X	X	
WHOQOL-HIV BREF[s]			X			X	X		X	X	
Menopause Rating Scale (MRS) questionnaire [s]			X								

Procedure	Retrospective Data Collection while on BIC/FTC/TAF When available (post-participant's consent)		Treatment Phase[a, v] (DTG/3TC)								
	1 to 2 data collection time points at -48 Wks to Screening	Screening[b]	Day 1	Wk 4 ±6 days	Wk 12 ±6 days	Wk24 ±6 days	Wk48 ±6 days	Wk72 ±6 days	Wk96 ±6 days	Withdrawal [w]	Follow-Up Visit [x]
Bespoke Participant Questionnaires (HO & ImpSc)[s]			X			X	X		X		
Bespoke Provider Questionnaires (HO & ImpSc) [t]			X			X	X		X		
Participant Interviews (HO & ImpSc)[u]			X			X	X		X		
Provider Interviews (HO & ImpSc) [u]			X			X	X		X		
Control of Eating Questionnaire (CoEQ). See Section 8.3.3			X	X	X		X		X		
Actigraphy and Participant Health Self Reporting App[v]		X	X	X	X	X	X	X			
Dispense Study Treatment			X		X	X	X	X			
Study Treatment accountability				X	X	X	X	X	X	X	X

Note: BP – Blood pressure, HR – Heart Rate, BMI – Body Mass Index, HDL – High Density Lipoprotein, LDL – Low Density Lipoprotein, PT - Prothrombin Time, PTT - Partial Thromboplastin Time, INR - International normalized ratio, PBMC – peripheral blood mononuclear cell, RNA – Ribonucleic acid, HbA1c = Glycated hemoglobin, HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus, HIV-1 = human immunodeficiency virus type 1, HO – Health Outcome, ImpSc: Implementation Science.

a. The acceptable window around any visit, post Day 1 is ±6 days. Participant must come in no later than +6 days of the visit windows or participant will run out of drug supply.
b. Complete all Screening assessments within 28 days. Participants may begin the Treatment Phase as soon as all Screening assessments are complete. Participants may be rescreened once and will be assigned a new participant number. Collect gender identity and sex at birth/sex at time of study entry.
c. Refer to Section 10.1.3 for informed consent process. Enrolled participants should be re-consented using the latest approved version of the ICF, as applicable.
d. Collect full routine medical history plus (report at Baseline visit): Cardiovascular risk factors (assessments include smoking status and history, family history of cardiac events), recent [≤6 months] illicit drug use, intravenous drug use, gastrointestinal disease, metabolic, psychiatric, renal, bone, and neurologic disorders. At Screening, Day 1, Week 24, Week 48 and Week 96 visits assessments inclusive of smoking status, alcohol use and illicit drug use since the start of the study will be performed.
e. Physical exams should be conducted as part of normal routine clinical care. Medical assessments include any decisions the study staff must make for participants management and/or care of participant.
f. Height collected at Baseline Day 1 only. Recommended procedures to measure weight, waist and hip circumference can be found in Section 10.12.
g. Measure vital signs after about 5 minutes of rest in a semi-supine position.
h. A 12-lead ECG will be performed after resting in a semi-supine position for at least 5 minutes.
i. 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 6 months prior to Screening.
j. Only SAEs related to study participation or to a concomitantly administered ViiV Healthcare/GSK product will be collected between obtaining informed consent and administration of study treatment at Day 1
k. eC-SSRS will be completed at the beginning of the visit after administration of any other PROs, and prior to administration of study treatment. On Day 1, eC-SSRS is to be administered prior to the first dose.
l. Women of childbearing potential only. S=serum; U=urine. Pregnancy events will be captured starting at Day 1 following first dose of study treatment. Serum pregnancy test can substitute for urine pregnancy test if locally required but must be appropriately timed to confirm pregnancy status prior to enrolment and first dose of study treatment (as applicable). Where both serum and urine tests (S + U) are indicated for a given visit, proceed based on the result of the urine test, and review serum test result once available. If urine test is positive at Day 1, perform a serum test and do not administer study treatment. The frequency of pregnancy tests should be performed according to local requirements. Do not perform the assessment for participants already confirmed to be pregnant based on results of a prior test.
m. Plasma samples will be collected at each visit starting at Screening, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). These samples may also be used when needed such as when samples are lost, arrive at the laboratory unevaluable, or particularly for virologic resistance analyses when participants meet Suspected and Confirmed Virologic Withdrawal criteria. Plasma and serum samples may also be used for further post-hoc assessments of relevant cardio-metabolic, inflammation biomarkers or virology tests that may assist with the understanding of any study finding. Retain frozen; refer to lab manual for specific handling instructions.
n. A morning specimen is preferred. To assess biomarkers: urine albumin/creatinine ratio; urine protein/creatinine ratio; urine phosphate; beta-2-microglobulin; and retinol binding protein.
o. An overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable. Blood sample for insulin and HbA1c.
p. Whole blood/PBMC collection samples may be used for virologic analyses.
q. Blood sample for renal and bone biomarker assessments: **Renal:** CystatinC; Beta-2-Microglobulin; Retinol Binding Protein (RBP); **Bone:** bone specific alkaline phosphatase, procollagen type 1-N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D.
r. A +6 weeks window is allowed. Refer to Section 8.3.5 for full details. Pregnancy testing should be performed for women of childbearing potential, and results available, before the DXA scan; the radiation procedures will not go ahead without a confirmed negative pregnancy test. Repeat DXA scans will be avoided wherever possible, no more than 1 repeat is allowed.

s. All PROs are recommended to be administered before other assessments take place at each designated visit. PRO will be completed electronically by participants. For MRS : MRS questionnaire available at https://www.hormonebalance.org/files/MRS%20QOL%20questionnaire%20.pdf
t. Provider interviews will occur after the first participant at the site had completed the corresponding visit e.g. Week 24 interview conducted, after first participant at the site performed their Week 24 visit.
u. Participant and Provider qualitative interviews will only be conducted in the US, UK and Canada
v. Refer to Section 8.13 and SRM.
w. Refer to Section 7 of the protocol for additional information on performing withdrawal assessments.
x. A Safety Follow-Up visit will be conducted 2-4 weeks after the last dose of study intervention for participants who meet specific criteria as described in Section 4.4.1. Only the assessments necessary to evaluate the AE/SAE/laboratory abnormality should be collected.
y. The baseline fibroscan should be completed on Day 1; however, a +6 week window is permittable if necessary due to operational delays.

2. INTRODUCTION

As individuals living with HIV require lifelong therapy, a need for effective treatments with limited long-term toxicity remains. Two-drug regimens (2DRs) reduce the number of antiretroviral agents in a regimen and may reduce treatment-associated toxicity, drug-drug interactions, and costs. Current HIV treatment guidelines recommend the 2DR DTG/3TC as an initial treatment regimen based on results from the phase 3 GEMINI-1/GEMINI-2 studies [Cahn, 2022] and in switch settings in ART-experienced virologically suppressed people living with HIV based on the phase 3 SALSA and TANGO studies [Llibre, 2022; van Wyk, 2020; Osiyemi, 2022].

The 3DR BIC/FTC/TAF (Biktarvy) is also a recommended regimen for both ART initiation and as a switch regimen in ART-experienced virologically suppressed people living with HIV [Biktarvy, 2022].

The STR of two potent, well-characterized and well-tolerated ARVs, DTG plus 3TC, provides a 2-drug regimen that provides effective long-term antiviral suppression with the potential to reduce the risk of adverse reactions associated with ARV's.

2.1. Study rationale

Contemporary potent 3-drug ARV treatment has led to remarkable declines in morbidity and mortality in treated people living with HIV leading to longer life expectancy. This longer life expectancy has been accompanied by higher rates of non-acquired immune deficiency syndrome (non-AIDS)-defining events (NADEs) such as cardiovascular disease, liver disease, and cancer. These NADEs are now the leading causes of morbidity and mortality among treated people living with HIV. The etiologies of these NADEs are multi-factorial and may include chronic inflammation and immune activation, behavioral, and lifestyle-related factors, co-morbidities and the adverse effects of ART. In addition, as people living with HIV live longer, aging-associated co-morbidities are being seen with greater frequency, and this multi-morbidity often requires concomitant use of other medications. As ART needs to be taken lifelong, there is an unmet need for streamlined regimens that can minimize ART-related long-term toxicities and DDI while maintaining viral suppression. Even modest improvements in side effects have the potential to improve tolerability and increase adherence to lifelong treatment regimens. Living long-term with HIV and ART, even when clinically well-controlled, is associated with premature onset of chronic conditions such as heart and kidney disease, frailty, and neurocognitive impairments. This may represent premature or accelerated aging linked to HIV infection itself and pre-ART disease acute infection and set-points characteristics but may also potentially be linked to some long-term ART toxicity. Second generation INSTIs (DTG and BIC) as well as the NRTI TAF have been shown to be independently associated with weight gain with a potential additive effect of the association of a second generation INSTI and TAF [Kanters, 2022]. TAF has also been associated with an unfavorable lipid profile compared to TDF [Mallon, 2021] or DTG [Osiyemi, 2022]. Switching from the 3-drug regimen Biktarvy (BIC/FTC/TAF) to the 2-drug regimen, DTG/3TC FDC (Dovato) may therefore limit the worsening of the above metabolic parameters and improve the overall health especially in older adults living with HIV.

The 2-drug regimen, DTG/3TC FDC (Dovato) is approved in US, Canada, EU, UK, Japan, Australia and multiple other countries globally and is a preferred regimen in both ART-naïve and ART-experienced virologically suppressed people living with HIV, in international treatment guidelines.

219516 (**EYEWITNESS**: h**E**alth**Y** ag**E**ing **WIT**h dovato amo**N**g div**E**r**S**e population**S)** is designed to assess the maintenance of virological suppression of DTG/3TC FDC (Dovato) administered once daily over 96 Weeks post switch from Biktarvy (BIC/FTC/TAF) administered orally once daily in a diverse population of people living with HIV of at least 50 years of age. The study will also assess cardiometabolic health, liver and renal health, anthropometric measures and participants' reported health outcome measures over 96 weeks as well as testing some implementation strategies (See Section 8.13). The study will also assess the impact of switching from BIC/FTC/TAF to DTG/3TC with active comorbidity management on the overall health of study participants. To assess the overall health impact of switching from a 3-drug to a 2-drug regimen, an exploratory assessment to understand change in slopes from the BIC/FTC/TAF pre-switch period to the DTG/3TC post-switch period may be performed for limited parameters where sufficient data are available.

The study will enroll people living with HIV of at least 50 years of age with the following population demographic characteristics diversity targets: ≥30% women; ≥30% aged 65 or over and ≥30% participants identifying as Black race and ≥10% of Hispanic/Latinx ethnicity.

2.2. Background

Switching from BIC/FTC/TAF (Biktarvy) to DTG/3TC FDC (Dovato) 2-DR will reduce the number of ARV's to which a participant is chronically exposed and has the potential benefit of reducing potential long-term toxicity and decreasing the likelihood of DDIs. The present phase 3b study (219516) will evaluate efficacy, safety, and overall health including quality of life of people living with HIV of at least 50 years of age virologically suppressed on BIC/FTC/TAF switching to DTG/3TC through Week 96.

2.3. Benefit-risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of DTG/3TC can be found in the IBs and product labels.

Careful monitoring of events will be conducted using SAE reports and alerts for Grade 3 or 4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for people living with HIV, See Section 10.5). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of study treatment, and will be followed to resolution as per Sponsor's standard medical monitoring practices. Clinical Safety Data will be routinely reviewed in GSK/ViiV Safety Review Team meetings. This will include in-stream review of data from this clinical trial on a routine basis, review of aggregate data on a protocol and program basis when available, and review of competitor data from the literature.

The following section outlines the risk assessment and mitigation strategy for this protocol.

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [DTG and 3TC] Refer to IBs for additional information		
DTG: Hypersensitivity reaction (HSR) and rash	**DTG:** HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase 2b/3 clinical trials; episodes were generally mild to moderate in intensity.	• Participants with history of allergy/sensitivity to any of the study treatments are excluded. • Specific/detailed toxicity management guidance is provided for rash (Section 10.4.1.6). • The Participant ICF includes information on this risk and the actions Participants should take in the event of a HSR or associated signs and symptoms
DTG: Drug induced liver injury (DILI) and other clinically significant liver chemistry elevations **3TC**: Use in HBV co-infected participants and emergence of HBV variants resistant to 3TC	**DTG:** Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. Drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For Participants with HBV and/ HCV co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG-containing ART, along with inadequate therapy for HBV co-infected participants, likely contributed to significant elevations in liver chemistries. **3TC**: Current treatment guidelines [DHHS, 2024; EACS, 2022] do not recommend monotherapy with 3TC for participants with HBV infection, which is what participants randomized to DTG plus 3TC, would effectively be receiving. Emergence of HBV variants associated with resistance to 3TC has been reported in HIV-1-infected participants who have received 3TC-containing antiretroviral regimens in the presence of concurrent infection with HBV. Additionally, discontinuation of 3TC in HBV co-infected participants can result in severe exacerbations of hepatitis B.	• Exclusion criteria as described in Section 5.2 will prohibit participants with significant liver impairment based on screening liver chemistry including transaminases (ALT and AST) as well on prior medical history. Participants with a history of chronic liver disease will have additional confirmatory assessments to confirm suitability for entry into the study. • Participants negative for anti-HBs but positive for anti-HBc (negative HbsAg status) are excluded; • Participants positive for anti-HBc (negative HbsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded. • Participants with HCV co-infection at Screening are eligible only if: i. liver enzymes meet entry criteria; and ii. HCV disease is not anticipated to require on-study treatment with any agent(s) that have potential adverse DDIs with the study treatments; and

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		iii. HCV disease has undergone appropriate work-up and is not advanced or associated with cirrhosis (refer to Exclusion Criteria 4, 7 and 8). • The Investigator should consider any additional information (where available) to evaluate the eligibility of participants with HCV co-infection at Screening which may include, e.g., results from any liver biopsy, Fibroscan, ultrasound or other fibrosis evaluation (e.g. FIB-4 score), history of cirrhosis or other decompensated liver disease, and any prior treatment. • Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Appendix 7).
DTG: Psychiatric disorders	**DTG:** Psychiatric disorders including suicidal ideation and behaviors are common in people living with HIV. In clinical trials, the psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was generally similar or favorable compared with other antiretroviral therapy. An evaluation of aggregate data, including post-marketing data concluded that a causal association between DTG and depression, anxiety and suicidal behaviors could not be ruled out. These events occur primarily in patients with a prior history of psychiatric illness.	• Participants who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating. • The electronic Columbia Suicidality Severity Rating Scale (eC-SSRS) participant questionnaire will be performed at Screening to aid investigator assessing suicidality risk. The questionnaire will also be performed during the study as per the SoA. • Because of the elevated risk in people living with HIV, treatment-emergent assessment of suicidality will be monitored during this study through the end of the treatment Phase. Investigators are advised to consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior (see Section 8.3.8).
DTG: Risk of virologic failure/ Observed Resistance	Virologically suppressed participants switching from stable ART to DTG/3TC may experience virologic failure/breakthrough and development of resistance. **DTG**: Week 96 and Week 144 analyses for the Phase 3/3b clinical studies supported the efficacy findings from earlier	• Participants with any switch to a second line regimen due to previous virologic failure, and participants with evidence of pre-existing 3TC or INSTI major resistance mutation [Wensing, 2022], are excluded from this study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	analyses, and demonstrated robust maintenance of viral suppression with no finding of HIV-1 resistance in treatment-naïve participants and treatment experienced participants in the GEMINI and TANGO studies respectively. **3TC:** M184V/I is the common RT mutation that confers resistance to 3TC	• All available historic genotypic resistance testing results must be reviewed by ViiV Virology to ensure participants with exclusionary mutations are not enrolled. • Participants will have HIV-1 RNA measured at each study visit. Potential virologic failure will be closely monitored (see Section 7.1.2).
DTG: Theoretical serious drug interaction with dofetilide, pilsicainide and fampridine / dalfampridine	Co-administration of DTG with products with narrow therapeutic windows that are substrates of organic cation transporter 2 (OCT2), including but not limited to the antiarrhythmic agents dofetilide and pilsicainide (available in Japan) or the potassium channel blocker fampridine (also known as dalfampridine), may increase plasma concentrations, resulting in potentially life-threatening toxicity.	• The co-administration of DTG with dofetilide, pilsicainide or fampridine/dalfampridine is prohibited in the study (Section 6.10.2).
DTG and 3TC: Renal function	**DTG**: Mild elevations of creatinine have been observed with DTG which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate (GFR) or effective renal plasma flow. **3TC**: 3TC is eliminated by renal excretion and exposures increase in participants with renal dysfunction.	• Creatinine clearance is calculated in all participants prior to initiating therapy and renal function (creatinine clearance and serum phosphate) will be monitored at all subsequent study visits. • Participants with an estimated creatine clearance <30mL/min per 1.73 m2 using the refitted, race-neutral Chronic Kidney Disease Epidemiology Collaboration (CKD-EPIcr_R) method are excluded in this study. • Specific/detailed toxicity management guidance is provided for participants who develop a decline in renal function (Section 10.4.1.3).
DTG: Creatine Phosphokinase (CPK) elevations	Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.	• Specific detailed toxicity management guidance is provided for participants who develop Grade 3 to 4 CPK elevations (Section 10.4.1.8).
DTG: Neural tube defects (NTDs)	Although preliminary data (as of May 2018) from an ongoing birth surveillance study in Botswana suggested an association between NTDs and DTG exposure at the time of conception, updated results from this study, including over 9,000 pre-conception	• Women who are pregnant or breastfeeding or plan to become pregnant or breastfeed during the study are excluded. • Participants who are WOCBP should be counselled on the benefit-risk of contraceptive use, in order for the participant to make an

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	exposures to DTG at conception, now show no statistically significant difference in the incidence of NTDs between regimens with and without DTG. In data through March 2022, among women taking DTG at conception, 10 NTDs were identified among 9,460 exposures (0.11%; 95%CI 0.06%, 0.19%) compared with 25 NTDs among 23,664 exposures to non-DTG regimens at conception (0.11%; 95%CI 0.07%, 0.16%). This represents a prevalence difference (%) (95% CI) of 0.00 (-0.07, 0.10) [Zash, 2022].	informed decision on whether or not to use an effective or highly effective method of contraception. • ViiV Healthcare recommends that WOCBP use one of the acceptable effective or highly effective methods for avoiding pregnancy (see Section 10.9) in accordance with guidance outlined in Section 5.3.2. • WOCBP will be reminded re: pregnancy avoidance and adherence to contraception at every study visit. • Pregnancy status is monitored at every study visit for WOCBP. Pregnant participants who remain in the study do not need pregnancy testing for the duration of the pregnancy. • Participants who become pregnant during the study may remain in the study and continue to receive study treatment, provided that the conditions and requirements outlined in Section 8.4.6 have been met (which includes signing a pregnancy-specific ICF addendum). Pregnancy outcomes will be monitored. • Details regarding management of pregnant participants are found in Appendix 10.
Study Procedures		
Exposure to ionizing radiation from DXA scans	Participants will receive a whole body DXA scan at baseline, week 48 and week 96. A + 6 weeks window is allowed to perform the DXA scan at these visits. At these visits, the estimated per-visit radiation dose to a participant in the study is less than 0.1mSv. That would give a maximum dose per participant for the study of 0.3mSv. Naturally-occurring background radiation typically ranges from about 1.5 to 3.5 mSV per year. The total maximum radiation dose per participant in this study corresponds to a risk of fatal cancer	• All DXA scans will be performed by a qualified technician following standardized instructions. • Repeat DXA scans will be avoided wherever possible, only one repeat is allowed. • Pregnancy testing will be performed and results available before the DXA scans are conducted, and the radiation procedures will not go ahead without a confirmed negative test to avoid exposing the fetus to ionizing radiation. When the DXA scans are performed not on study visit day, but within the 6 weeks allowed window, a pregnancy urine test kit will be given to the participant in order to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	induction of about 1 in 13,000, generally considered to be 'low' to 'very low'.	be self-administered on scan day. A confirmed negative test needs to be reported to the site (e.g. women/DXA technician will give a telephone call to the site, to the investigator team) before the radiation procedure can go ahead. If the self-administered pregnancy test results ambiguous or positive, the pre-scheduled radiology procedure must be suspended, and a confirmatory serum pregnancy test should be mandated. This information will be recorded in the eCRF. • Women of reproductive potential must be using highly effective methods of contraception and a pregnancy test will be conducted at every visit.

2.3.2. Benefit assessment

International guidelines, including the 2022 International Antiretroviral Society–USA [Gandhi, 2022], Department of Health and Human Services [DHHS, 2024], and 2022 European AIDS Clinical Society [EACS, 2022] recommend the 2DR dolutegravir/lamivudine (DTG/3TC) as an initial treatment regimen based on results from the phase 3 GEMINI-1/GEMINI-2 studies [Cahn, 2019; Cahn, 2020; Cahn, 2022]. Dolutegravir/Lamivudine is also recommended in switch settings in these international guidelines, supported by 48-week results from the phase 3 SALSA and TANGO studies [Llibre, 2022; van Wyk, 2020]. In both studies proportion of participants with HIV-1 RNA ≥50 c/mL (primary endpoint, Snapshot algorithm) switching to single-tablet FDC DTG/3TC was non-inferior to continuing current antiretroviral regimen in virologically suppressed individuals. In TANGO, through Week 144 switching to DTG/3TC was non-inferior to continuing TAF-based 3- or 4-drug regimens, with <1% of participants in both groups having HIV-1 RNA ≥50 c/mL [Osiyemi, 2022]. In both studies, there were no confirmed virologic withdrawals (CVWs) observed in the DTG/3TC group. Safety profiles were also comparable between treatment groups [Llibre, 2022; van Wyk, 2020; Osiyemi, 2022]

Switching participants to a DTG/3TC regimen from a dual NRTI-based 3-drug regimen may increase tolerability, reduce the frequency of adverse events associated with NRTI-based regimens and/or drug-drug interactions. Study participants also may benefit from the medical tests and screening procedures performed as part of this study.

2.3.3. Overall benefit-risk conclusion

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with DTG/3TC are justified by the anticipated benefits that may be afforded to study participants switching to this 2-drug regimen.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Table 2 Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary	
To evaluate the maintenance of virologic suppression of DTG/3TC at Week 48 post-switch from BIC/FTC/TAF	Participants with plasma HIV-1 RNA ≥50 copies/mL (Snapshot algorithm) at Week 48.
Secondary	
To evaluate the antiviral activity, immunologic effects, and incidence of disease progression (HIV-associated conditions, AIDS and death) of DTG/3TC over time	Participants with plasma HIV-1 RNA ≥50 copies/mL (Snapshot algorithm) at 24 and 96 weeks. Participants with plasma HIV-1 RNA <50 copies/mL (Snapshot algorithm) at 24, 48 and 96 weeks. Absolute values and changes from baseline in CD4+ cells count and CD4:CD8 ratio at 24, 48 and 96 weeks. Occurrence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48 and 96.
To assess viral resistance in participants experiencing protocol-defined virologic failure over time	Occurrence of viral resistance in participants meeting confirmed virologic withdrawal criterion over time.
To evaluate the safety and tolerability of DTG/3TC over time	Occurrence of DTG/3TC-non-Serious Adverse drug-related reactions, all SAEs and proportion of participants who discontinue treatment due to AEs.

Objective(s)	Endpoint(s)
Exploratory	
To evaluate the efficacy and immunologic response of DTG/3TC by participant characteristics subgroups (e.g., demographic factors, Baseline CD4, CD4 nadir) and pre-specified target population (≥65 years old, women, non-white race, CV risk, comedication) over time	Participants with plasma HIV-1 RNA <50 copies/mL (Snapshot algorithm) at 24, 48 and 96 weeks by subgroups and pre-defined target population. Absolute values and changes from baseline in CD4+ cells count and CD4:CD8 ratio at 24, 48 and 96 weeks by subgroups and pre-defined target population. Occurrence of disease progression (HIV-associated conditions, AIDS, and death) through Weeks 24, 48 and 96 by subgroups and pre-defined target population.
To evaluate further safety and tolerability parameters of DTG/3TC over time	Incidence and severity of AEs and laboratory abnormalities over time through Week 96.
To evaluate renal (in urine and blood) and bone (in blood) biomarkers over time	Change from Baseline (Day 1) in renal and bone biomarkers at Weeks 48 and 96. Changes from baseline in estimated glomerular filtration rate (Creatinine and Cystatin C CKD-EPI uncorrected for Race) and urinary protein/creatinine at 48 and 96 weeks.
To evaluate insulin resistance over time	Change from Baseline (Day 1) in fasting insulin, fasting glucose, HbA1c and HOMA-IR at Weeks 48 and 96.
To evaluate liver health (including fibrosis and steatosis) over time	Change from baseline in AST, ALT, GGT levels and liver fibroscan score at Weeks 48 and 96.
To evaluate cardiovascular risk over time	Change from Baseline in Framingham and DAD cardiovascular risk scores at Weeks 48 and 96. Change from Baseline in systolic and diastolic blood pressure at Week 24, 48 and 96.

Objective(s)	Endpoint(s)
To evaluate fasting lipids over time	Change from baseline in total, HDL and LDL cholesterol, triglycerides and TC/HDL ratio at 24, 48 and 96 weeks.
To evaluate weight and body morphology evolution over time	Absolute weight and BMI change and proportion of participants with weight change >5% and >10% from baseline at 24, 48 and 96 weeks. Change from baseline in total and regional (trunk and limbs) fat and lean (fat-free) mass by DXA at 48 and 96 weeks in a subset of participant performing DXA scans. Change from Baseline in Waist to Height and Waist to Hip ratio at Weeks 24, 48 and 96
To evaluate control of appetite over time using the Control of Eating Questionnaire (CoEQ) respectively	Change from baseline in CoEQ score at Weeks 24, 48, and 96.
To evaluate baseline menopausal symptoms among women participants	Baseline score using the Menopause rating scale (MRS) health-related quality of life (QoL) questionnaire.
To assess participant reported treatment satisfaction	Change from baseline in HIVTSQs and HIVTSQc total treatment satisfaction score and individual responses at 24, 48 and 96 weeks.
To assess bother from HIV-related symptoms	Change from baseline in bothersome symptoms using the Symptom Distress Module at 24, 48 and 96 weeks.
To assess health-related quality of life	Change from baseline in health-related quality of life using the WHOQOL-HIV BREF at 24, 48 and 96 weeks.

Objective(s)	Endpoint(s)
To evaluate participants' motivations for switching to DTG/3TC within a clinical trial and their treatment aspirations of less medicine	At baseline, ask participants the reasons for switching to DTG/3TC using a ViiV developed questionnaire. At weeks 24, 48 and 96, repeat select questions to assess if baseline aspirations are being met. Qualitative interviews* will also be conducted to further understand participants motivations at baseline and weeks 24, 48 and 96.
To evaluate investigators' motivations for switching participants to DTG/3TC within a clinical trial and assess the ease of switch	At baseline, ask investigators the reasons for switching participants to DTG/3TC using a ViiV developed questionnaire. At weeks 24, 48 and 96, assess the ease of switch and experience of the use of DTG/3TC. Qualitative interviews* will also be conducted to further understand investigator motivations and experience at baseline and weeks 24, 48 and 96.
To explore Pre-switch (≥24 weeks post-BIC/FTC/TAF initiation and up to -48 weeks to Day 1) and Week 24, 48 and Week 96 post-Switch slopes of the following endpoints where sufficient data available	Weight and BMI based on available data collected retrospectively in the pre-switch period. Lipids (total, HDL and LDL cholesterol, triglycerides) based on available data collected retrospectively in the pre-switch period. Liver Chemistry (ALT, AST) based on available data collected retrospectively in the pre-switch period. Blood Hematology (CD4, CD8 and Platelet counts) and Clinical Chemistry (Fasting glucose, HbA1c, insulin and Creatinine) based on available data collected retrospectively in the pre-switch period.
To evaluate the acceptability, uptake and utility of the Liverpool Combined Co-Morbidity Risk Calculator in clinical practice in countries where the tool is implemented	Summary data of provider questionnaires at Week 24, Week 48 and Week 96. Thematic output of provider (support staff, nurses, and physicians) qualitative interviews* at Week 24, Week 48 and Week 96.

Objective(s)	Endpoint(s)
To evaluate the acceptability, uptake and utility of participant leaflet among participants and providers.	Summary data of participant and provider questionnaires. Participant questionnaire - Day 1, week 24, 48. Provider questionnaire - - Day 1, week 24, 48. Thematic output of patient and provider qualitative interviews*. Participant qualitative interviews* - Day 1, week 24, 48. Provider qualitative interviews* - Day 1, week 24, 48.
To evaluate the uptake, acceptability, utility, persistence and adherence of Actigraphy and self-reporting of behaviors (participant watch and App). To explore sleep quality, physical activity and health behaviors (alcohol intake, mood, water intake, stress level as collected via Actigraphy and the study App.	Summary data of Participant Survey: Day 1, Week 24, 48 and 96. Thematic output of Participant qualitative interviews*: Day 1, Week 24, 48, 96. Descriptive statistics of endpoints related to sleep quality, physical activity and health behaviors (alcohol intake, mood, water intake, stress levels).

Footnote: * Participant and Provider qualitative interviews will only be conducted in the US, UK and Canada.

3.1. Primary Estimands

The primary efficacy estimand aims to evaluate virologic failure with DTG/3TC at Week 48 post-switch from BIC/FTC/TAF in virologically suppressed people living with HIV of at least 50 years of age.

Virological Failure

Population	People living with HIV of at least 50 years of age who are virologically suppressed on Biktarvy (BIC/FTC/TAF).
Treatment	DTG/3TC FDC (Dovato) administered once daily over 48 Weeks post switch from Biktarvy (BIC/FTC/TAF) administered orally once daily

Intercurrent Events	Study treatment discontinuation due to lack of efficacy or other reasons that impact the viral load outcome: Composite strategy. *Rationale*: The presence of missing data due to lack of efficacy or discontinuation for other reasons on the primary endpoint is adequately accounted for in the Snapshot Algorithm which frames the outcome around these events. Please see SAP for full details.
Endpoint	Participants with virologic failure (plasma HIV-1 RNA ≥50 c/mL as per Snapshot algorithm at 48 weeks).
Summary measures	Number and percentage of participants with virologic failure (plasma HIV-1 RNA ≥50 c/mL as per Snapshot algorithm at 48 weeks), within group 95% confidence interval using Exact (e.g., Clopper-Pearson) methodology.

3.2. Key Secondary Estimands

The key secondary efficacy estimand is to evaluate virological suppression with DTG/3TC at Week 48 post-switch from BIC/FTC/TAF in virologically suppressed people living with HIV of at least 50 years of age. Key Safety estimands include drug-related AEs, SAEs, and AEs leading to discontinuation over time through Week 96.

Virological Suppression

Population	People living with HIV of at least 50 years of age whose virus is virologically suppressed on Biktarvy (BIC/FTC/TAF).
Treatment	DTG/3TC FDC (Dovato) administered once daily over 48 Weeks post switch from Biktarvy (BIC/FTC/TAF) administered orally once daily
Intercurrent Events	Study treatment discontinuation due to lack of efficacy or other reasons that impact the viral load outcome: Composite strategy. *Rationale*: The presence of missing data due to lack of efficacy or discontinuation for other reasons on the primary endpoint is adequately accounted for in the Snapshot Algorithm which frames the outcome around these events. Please see SAP for full details.

Endpoint	Participants with virologic suppression (plasma HIV-1 RNA <50 c/mL as per Snapshot algorithm at 48 weeks).
Summary measures	Number and percentage of participants with virologic suppression (plasma HIV-1 RNA <50 c/mL as per Snapshot algorithm at 48 weeks), within group 95% confidence interval using Wilson-Score methodology.

3.2.1. Safety Estimands

Population	People living with HIV of at least 50 years of age whose virus is virologically suppressed on Biktarvy (BIC/FTC/TAF).
Treatment	DTG/3TC FDC (Dovato) administered once daily over 48 Weeks post switch from Biktarvy (BIC/FTC/TAF) administered orally once daily
Intercurrent Events	• Treatment discontinuation due to any reason: treatment policy strategy • Prohibited medication use: treatment policy strategy *Rationale*: Safety data will be monitored throughout the study after the start of treatment. There is interest in evaluating and reporting safety events regardless of whether participants have completed treatment course or not and regardless of the use of prohibited medication. All safety data will be included up to the end of follow-up regardless of the occurrence of these intercurrent events.
Endpoint	• Occurrence and severity of drug-related AEs over time through Week 96 • Occurrence of SAEs over time through Week 96 • Participants who discontinue treatment due to AEs over time through Week 96.
Summary measures	Frequency and percentage of participants

4. STUDY DESIGN

4.1. Overall design

219516 (EYEWITNESS) is a Phase 3b, multicenter, single-arm, open-label study evaluating the efficacy, safety, and tolerability of switching to DTG/3TC FDC

administered once daily from a BIC/FTC/TAF FDC in people living with HIV of at least 50 years of age who are virologically suppressed.

Table 3 Study phases, duration and treatment arms

Phase Title	Duration	Study Visits	Description
Retrospective Data Collection	≥24 weeks post-BIC/FTC/TAF initiation and up to -48 weeks prior to screening	After collecting consent for study participation.	1 to 2 data points during the -48 Weeks to Screening Time point while on BIC/FTC/TAF as available
Screening	Up to 28 days	One or more, as required	Details about the study and procedures will be explained through the informed consent process. Participants will have various screening procedures to determine eligibility. Participants who meet all the eligibility criteria can be enrolled.
Switch Treatment Phase (DTG/3TC)	Up to Week 96	Day 1 Weeks 4, 12, 24, 48, 72, 96	At the enrolment visit (Day 1), all eligible participants will switch from BIC/FTC/TAF to DTG/3TC FDC once daily. At Week 96, all on-going participants will switch to locally available Dovato or local standard of care per investigators' discretion and participant's choice.
Safety Follow-Up Visit	Conduct approximately 2 to 4 weeks after the last dose of study intervention.	Post-Day 1	Required only if the participant has ongoing AEs, SAEs, or clinically significant lab abnormalities (i.e., considered AEs or potentially harmful to the participant), or if the participant discontinues the study due to virologic concerns (e.g., baseline viral resistance, virologic withdrawal criteria, lack of efficacy). See Section 4.4.1 for details.

Assuming a 20% screen failure rate, approximately 250 HIV-1 infected adult participants will be screened to achieve approximately 200 enrolled participants. Participants are planned to be enrolled from but not limited to the following countries: United States, United Kingdom, Austria, France, Belgium, Netherlands, Spain, Italy, Portugal, Canada, and Germany.

A goal of this study is to enroll populations that are traditionally underrepresented in clinical studies, including:

- ≥ 30% Women
- ≥ 30% aged 65 or over
- ≥30% participants identifying as black race
- ≥10% of Hispanic/Latinx ethnicity

The above diversity targets also aim at enrolling a population with a greater proportion having a ≥10% cardiovascular risk as assessed by Framingham risk score, a higher use of comedication and more comorbidities to enable subgroups analyses by these factors.

An Internal Safety Review Committee (iSRC) will be implemented to review in-stream study efficacy and safety data if specified threshold for ad hoc iSRC review is met, as described in the iSRC Charter. Refer to Section 8.3.9.

Participants who withdraw from the main study may be eligible to participate in an optional, observational sub-study describing virologic response to post-study/subsequent ART. Details are provided in Section 10.15.

4.2. Scientific rationale for study design

The primary endpoint, of participants with virologic failure (plasma HIV-1 RNA ≥50 c/mL as per Snapshot algorithm at 48 weeks) is the clinically relevant endpoint to assess durability of virologic suppression in switch studies; it also is the widely accepted and recognized endpoint by regulatory authorities for assessing the efficacy in virologically suppressed people living with HIV. Additionally, as people living with HIV of at least 50 years of age meeting the study entry criteria and the study demographics diversity targets will limit the study enrollment; a single-arm design will enable to recruit the study in a timely manner and provide important efficacy, safety and overall health data on DTG/3TC in this under-represented population more rapidly.

4.2.1. People Living with HIV community input into design

Feedback on the protocol design was provided by volunteer representatives from the European AIDS Treatment Group (EATG). Updates were made to the protocol in light of the feedback including to ensure that appropriate person-centered language was used, making the use of contraception for women of childbearing potential as a recommendation rather than a requirement, as well as including that the concept of ‘undetectable equals untransmittable’ (U=U) should be discussed with participants.

4.3. Justification for dose

The 2-drug regimen, DTG/3TC FDC (Dovato) containing DTG (50 mg) and 3TC (300 mg), is approved in US, Canada, EU, UK, Japan, Australia and multiple other countries globally and is a preferred regimen in both ART-naïve and ART-experienced virologically suppressed people living with HIV, in international treatment guidelines.

For a description of pharmacological properties and data, refer to the most current Investigator Brochure for DTG/3TC and current product labeling.

4.4. End-of-study definition

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

- Completed all periods of the study up to and including Week 96 of the Treatment Phase (defined as transitioning off study to commercially accessible product, or to alternative local standard-of-care ART).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the study globally.

4.4.1. Safety Follow-up visit

A Safety-Follow Up visit should be performed per the guidance below, to assess the clinical status of participants after discontinuing study treatment. Results from the prior on-study visit should be available and reviewed by the Investigator prior to conducting the Safety Follow-Up visit.

A Safety Follow-up visit may occur approximately 2-4 weeks after the last dose of study intervention and is only required for:

- Participants with ongoing AEs, SAEs regardless of attributability, and any clinically significant laboratory abnormalities (i.e., AEs or potentially harmful to the participant). However, the Investigator, in consultation with the Medical Monitor where necessary, should continue to follow up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Assessments to be performed should reflect any ongoing complaints or clinical concerns, as applicable (e.g., blood draw to follow a laboratory abnormality). The visit may be conducted by telephone if a blood draw is not required.
- Participants that discontinued due to virologic concerns (e.g., baseline viral resistance, virologic withdrawal criteria, lack of efficacy). Assessments to be performed should reflect any ongoing complaints or clinical concerns, as applicable; in addition, a plasma HIV-1 RNA sample should be obtained. The visit should be performed in-person as a blood draw is required.

The Safety Follow-up visit is not required in order for a participant to be considered to have successfully completed the study, with respect to the study completer definition in Section 4.4.

Refer to Section 6.8 for further guidance on continued access to study treatment after the end of the study and managing the transition to commercially accessible product.

5. STUDY POPULATION

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

- Able to understand and comply with protocol requirements, instructions, and restrictions;
- Understand the long-term commitment to the study and likely to complete the study as planned;
- Be considered an appropriate candidate for participation in an investigative clinical trial with oral medications (e.g., acute major organ disease, or planned long-term work assignments out of the country, etc.).

The following are study specific eligibility criteria unless stated otherwise. In addition to these criteria, Investigators must exercise clinical discretion regarding selection of appropriate study participants, taking into consideration any local treatment practices or guidelines and GCP. All participants must be considered appropriate candidates for antiretroviral therapy in accordance with local treatment guidelines.

To assess any potential impact on participant eligibility with regard to safety, the investigator must refer to the IB and any supplements thereto, approved product labels, and/or local prescribing information for detailed information regarding warnings, precautions, contraindications, AEs, drug interactions, and other significant data pertaining to the study treatments.

Laboratory results from the central laboratory services provided by this trial will be used to assess eligibility, a single repeat to determine eligibility is allowed with the exception of a Screening plasma HIV-1 ≥50 c/mL. In exceptional circumstances only, if a repeat lab is required because a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor for determination of participant eligibility. A repeat central lab will be submitted concurrently or at the next planned visit.

Source documentation to verify entry criteria must be reviewed by the Principal Investigator or designee prior to enrolment. Source documents from other medical facilities must be located/received during the 28-day screening phase and under no circumstances may a participant be enrolled in the absence of supporting source documentation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

AGE
1. Age ≥50 years at the time of obtaining informed consent.
SEX AT BIRTH
2. Male or female. Female participant is eligible to participate if she is not pregnant (as confirmed by a negative serum hCG test at Screening and a negative urine hCG test at Enrolment) and not lactating. Further guidance and recommendations around use of contraception can be found in Section 5.3.2
PARTICIPANT KEY CHARACTERISTICS
3. Adults Living with HIV-1 with documented plasma HIV-1 RNA <50 c/mL within 3 months prior to Screening. 4. Must have been on uninterrupted ART for ≥1 year (except for brief periods [less than 30 days] where all ART was stopped due to tolerability and/or safety concerns) 5. Must be on uninterrupted BIC/FTC/TAF for at least 6 months prior to Screening 6. Plasma HIV-1 RNA <50 c/mL at Screening 7. No known prior regimen switches due to documented virologic failure (defined as a confirmed plasma HIV 1 RNA ≥200 c/mL) 8. Participants with unknown full treatment/clinical history beyond 5 years prior to Screening may be eligible upon discussion and agreement with the medical monitor.
INFORMED CONSENT
9. Participant is capable of giving written informed consent as described in 10.1.3, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. Eligible participants must sign a written Informed Consent Form before any protocol-specified assessments are conducted. Enrolment of participants who are unable to provide direct informed consent is optional and will be based on local legal/regulatory requirements and site feasibility to conduct protocol procedures.
COUNTRY SPECIFIC REQUIREMENTS
10. Participants enrolled in France must be affiliated to, or a beneficiary of, a social security category.

5.2. Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Women who are pregnant or breastfeeding or plan to become pregnant or breastfeed during the study.
2. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], EXCEPT cutaneous Kaposi's sarcoma not requiring systemic therapy. Historical or current CD4 cell counts less than 200 cells/mm^3 are NOT exclusionary.
3. Signs and symptoms which, in the opinion of the Investigator, are suggestive of active SARS-CoV-2 infection within 14 days prior to enrolment.
4. Participants with severe hepatic impairment (Class C) as determined by Child-Pugh classification
5. Evidence of hepatitis B virus (HBV) infection based on the results of testing at Screening for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs) and HBV DNA as follows: • Participants positive for HBsAg are excluded; • Participants negative for anti-HBs but positive for anti-HBc (negative HBsAg status), whether negative or positive for HBV DNA, are excluded; • Participants positive for anti-HBc (negative HBsAg status) and positive for anti-HBs (past and/or current evidence) are immune to HBV and are not excluded.
6. Participants with HCV co-infection at Screening are eligible only if: • Liver enzymes meet entry criteria; and • HCV disease is not anticipated to require on-study treatment with any agent(s) that have potential adverse DDIs with the study treatment; and • HCV disease has undergone appropriate work-up and is not advanced or associated with cirrhosis (refer to Exclusion Criterion 4, 7 and 8). The Investigator should consider any additional information (where available) to evaluate the eligibility of participants with HCV co-infection at Screening which may include, e.g., results from any liver biopsy, Fibroscan, ultrasound or other fibrosis evaluation (e.g. FIB-4 score), history of cirrhosis or other decompensated liver disease, and any prior treatment.
7. Unstable liver disease (as defined by any of the following: presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice or cirrhosis), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment)
8. History of liver cirrhosis with or without hepatitis viral co-infection.

9. Untreated syphilis infection (positive rapid plasma reagin [RPR] at Screening without clear documentation of treatment). Participants who are at least 7 days post completed treatment are eligible.
10. History or presence of allergy or intolerance to the study treatment or their components or drugs of their class or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
11. Ongoing malignancy other than cutaneous Kaposi's sarcoma, basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia.
12. Participants who in the investigator's judgment, poses a significant suicidality risk. Participant's history of suicidal behavior and/or suicidal ideation should be considered when evaluating for suicide risk.

EXCLUSIONARY TREATMENTS PRIOR TO SCREENING OR DAY 1

13. Treatment with an HIV-1 immunotherapeutic vaccine within 90 days of Screening.
14. Treatment with any of the following agents within 28 days of Screening
    - radiation therapy
    - cytotoxic chemotherapeutic agents
    - any systemic immune suppressant
15. Exposure to an experimental drug or experimental vaccine within either 28 days, 5 half-lives of the test agent, or twice the duration of the biological effect of the test agent, whichever is longer, prior to the first dose of IP.
16. Use of any regimen consisting of single ART or dual ART not recommended in treatment guidelines.
17. Any known history of switch to another regimen, defined as change of a single drug or multiple drugs simultaneously, due to virologic failure to therapy (defined as a confirmed plasma HIV 1 RNA ≥200 c/mL
18. Participants receiving any protocol-defined prohibited medication and who are unwilling or unable to switch to an alternate medication (See Section 6.10.2 for details on prohibited medications and non-drug therapies)

LABORATORY VALUES OR CLINICAL ASSESSMENTS AT SCREENING

19. Any evidence of any major 3TC resistance associated mutations (M184V/I and/or K65R and/or MDR) or presence of any major INSTI resistance associated mutation [Wensing, 2022] in any available prior resistance genotype assay test result. All available historical resistance reports with HIV-1 reverse transcriptase or integrase genotypic data ***must*** be provided to ViiV after screening and before enrollment for review by ViiV Virology. Refer to the Section 8.10 for more information.
20. Any verified Grade 4 laboratory abnormality with the exception of Grade 4 lipid abnormalities.
21. Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN) *or* ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin).

22.	Participant has estimated creatine clearance <30mL/min per 1.73 m^2 using the refitted, race-neutral Chronic Kidney Disease Epidemiology Collaboration (CKD-EPIcr_R) method.
OTHER	
23.	Participants who are currently participating in or anticipate to be selected for any other interventional study.

5.3. Lifestyle considerations

5.3.1. Sexual health

All participants participating in the study should be counselled on safer sex practices including the use and benefit/risk of preventative measures (*e.g.* male condom) and on the risk of HIV transmission to an uninfected partner. It is recommended that the Investigator inform participants of the principle of 'undetectable equals untransmittable' (U=U) which asserts that individuals who achieve and maintain an undetectable viral load by taking ART as prescribed have effectively no risk of sexually transmitting the virus to others [DHHS, 2024].

5.3.2. Pregnancy and Contraception

ViiV Healthcare recommends that:

- All participants of childbearing potential should be counselled on the benefit-risk of contraceptive use, in order for the participant to make an informed decision on whether or not to use an effective or highly effective method of contraception.
- ViiV Healthcare recommends that participants of childbearing potential use an effective or highly effective method of contraception (see Appendix 9) prior to starting study treatment, throughout the study, for a least 7 days after discontinuation of DTG/3TC. The chosen method of acceptable contraception, or the participant's decision not to use contraception, should be recorded in the participant's medical notes and study records.
- Participants of childbearing potential should be counselled prior to enrolment, at every study visit, and on exit from the study, on the importance of avoiding pregnancy, safer sexual practices, the proper use of their chosen method of effective or highly effective contraception, and the potential risks associated with fetal exposure to study treatment, if pregnancy were to occur. These discussions should be documented in the participant's medical notes and study records.
- Where a method of contraception is being initiated, it is recommended that it is started prior to starting study treatment. The period the contraceptive method should be used prior to starting study treatment should be in accordance with the contraceptive product label (where applicable) but not shorter than 7 days prior to starting study treatment. Where this is not feasible, the participant should be

counselled on pregnancy avoidance before their contraceptive method becomes fully effective (e.g., use of condoms in addition to their hormonal contraceptive method).

- Prior to enrolment, the Investigator is responsible for review of any current contraceptive use, medical history, menstrual history, and recent sexual activity, to be reviewed in conjunction with pregnancy test results, to decrease the risk of inclusion of an individual with an early undetected pregnancy.
- Where reproductive status (defined in Appendix 9) is in doubt it is recommended that postmenopausal status is confirmed with blood FSH and estradiol levels. It is recommended that females on hormone replacement therapy (HRT) whose menopausal status is in doubt use an effective or highly effective method of contraception compatible with their HRT whilst continuing HRT during the study.
- Upon discontinuation of study treatment, ViiV Healthcare recommends that participants continue to use an effective or highly effective method of contraception for at least 7 days after discontinuation of DTG/3TC.
- Participants who are found to be pregnant after enrolment will not be treated as a protocol deviation, and may request continuation of study treatment, subject to the conditions and requirements outlined in Section 8.4.6.
- For further information on managing pregnancy, refer to Section 8.4.6 and Appendix 9.

5.4. Screen failures

Screen failures are defined as participants who consent to participate in the clinical trial but are never subsequently randomized/enrolled. In order to ensure transparent reporting of screen failure participants meets the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and responds to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events (Section 8.4.5)

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

Laboratory results provided from central laboratory services will be used to assess eligibility. In exceptional circumstances only, if a central lab result cannot be generated, local labs can be reviewed and approved by the Medical Monitor, for consideration of participant eligibility, except for plasma HIV-1 RNA.

Source documentation to verify entry criteria must be reviewed by the Principal Investigator or designee prior to enrollment. Source documents from other medical facilities must be located/retrieved during the screening period. Under no circumstances may a participant be enrolled in the absence of source documentation including prior qualifying viral load data (as outlined in the Inclusion Criteria).

5.5. Criteria for temporarily delaying administration of study treatment

Delaying screening window beyond 28 days is not allowed. Participant will be classified as a screen failure and require rescreening.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

The definition of study treatment is provided in the table of definitions.

6.1. Study treatment administered

Table 4 Study Treatment Administered

Treatment Name	DTG/3TC FDC Tablet
Treatment Description	One tablet once daily orally with or without food
Type	Drug
Dose Formulation	Film-coated tablet
Unit Dose Strength(s)	50 mg/300 mg
Dosage Level(s)	50 mg/300 mg
Route of Administration	Oral
Use	Experimental (IMP)
Investigational Medicinal Product (IMP)	DTG/3TC FDC Tablet
Sourcing	Provided centrally by the Sponsor
Packaging and Labeling	Study Treatment will be made available to study sites centrally through the Clinical Supply Chain team at GSK. Study treatment will be provided in high-density polyethylene bottles. Each bottle will be labelled as required per country requirement
Current/Former Name(s) or Alias(es)	GSK3515864 Dovato

6.2. Preparation, handling, storage, and accountability

- **The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment.**
- **Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply, prepare, or administer study treatment**.
- **All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.**
- **The investigator** is **responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).**
- **Further guidance and information for the final disposition of unused study treatment are provided in the pharmacy manual**.

6.3. Assignment to study treatment

Informed consent must be obtained prior to any study procedures, including any screening assessment. Study treatment assignment will be facilitated by an interactive response system (IxRS). Following confirmation of fulfilment of study eligibility criteria, study site personnel will be required to contact the IxRS to register participants.

Assignment of study treatment at Day 1 is non-randomized in this open-label single arm study.

6.4. Blinding

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

6.5. Study treatment compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

As participants will self-administer oral study treatment at home, compliance will be assessed at each study visit by direct questioning, counting returned tablets, and documented in the source documents and eCRF. Deviations from the prescribed dosage regimen should be recorded. Treatment start and stop dates also will be recorded in the CRF.

Additionally, a record of the number of DTG/3TC tablets dispensed to and taken by each participant must be maintained and reconciled with study treatment and compliance records.

6.6. Dose Justification

DTG/3TC FDC will be dosed once daily as per label.

6.7. Dose reductions, modification or changes in frequency

No dose adjustments are permitted in this study.

6.8. Continued access to study treatment after the end of the study

Upon completion of the Week 96 visit, participants are expected to exit the study and transition to commercially accessible DTG/3TC or another suitable local standard-of-care ART regimen.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether ViiV Healthcare is or is not providing specific post-study treatment.

The planned transition to commercially accessible DTG/3TC or alternative ART for individual participants post-study should be done in consultation with the Sponsor (or CRO designee), and the Medical Monitor, as appropriate.

Refer to Section 4.4.1 for information around completion of a Safety Follow-up visit prior to study exit.

6.9. Treatment of overdose

For this open-label study, any tablet intake exceeding the daily number of tablets for DTG/3TC will be considered an overdose (see current product labeling) [Dovato, 2023]. ViiV does not recommend specific treatment for an overdose of DTG/3TC.

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 8.4). 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:

1) contact the Medical Monitor immediately

2) closely monitor the participant for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until DTG/3TC can no longer be detected systemically (for at least 2 days).

3) obtain a plasma sample for pharmacokinetic (PK) analysis within 60 hours from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis)

4) document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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.

6.10. Prior and concomitant therapy

- Concomitant medications (prescription and non-prescription) should be administered only as medically necessary during the study.
- Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician.
- Participants should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, including multivitamins and dietary supplements, because of the potential drug-drug interactions between such treatments and the study intervention. The investigator should evaluate any potential drug-drug interactions at every visit, including reviewing the most current version of the US and/or local prescribing information for approved ViiV Healthcare medicines, especially if any new concomitant medications are reported by participants.
- All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.
- Because non-HIV vaccines may cause a temporary increase in the level of HIV-1 plasma RNA, it is highly recommended that a vaccine, if necessary, be given during or immediately after a scheduled visit after all laboratory tests have been drawn and only when scheduled visits are ≥4 weeks apart. This approach will minimize the risk of non-specific increases in the level of plasma HIV-1 RNA at the next scheduled assessment.

6.10.1. Permitted medications and non-drug therapies

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

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

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

6.10.2. Prohibited medications and non-drug therapies

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

- HIV immunotherapeutic vaccines are not permitted at any time during the study.
- Other experimental agents, antiretroviral drugs not otherwise specified in the protocol, cytotoxic chemotherapy, or radiation therapy may not be administered (see Section 5.2).
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the pharmacy manual). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis [James, 2009].
- Chronic use of systemic (oral or parenteral) glucocorticoids must be avoided due to immunosuppressive effect; however, short treatment courses (e.g., 14 days or less) of oral prednisone/ prednisolone/methylprednisolone are allowed. Topical, inhaled or intranasal use of glucocorticoids will be allowed.

6.10.2.1. Prohibited Medications for Participants Receiving DTG/3TC

For participants receiving DTG/3TC, the following medications could significantly decrease the levels of DTG and/or 3TC due to enzyme induction and therefore must not be administered concurrently:

- carbamazepine
- oxcarbazepine
- phenobarbital
- phenytoin
- rifabutin
- rifampicin / Rifampin
- rifapentine
- St. John’s wort (*Hypericum perforatum*)

Dofetilide, pilsicainide, and fampridine/dalfampridine are prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide/pilsicainide and fampridine/dalfampridine concentrations and potential for toxicity.

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

For information on concurrent therapies and interactions suspected to be relevant to other antiretroviral therapy in the regimen, please consult the local prescribing information.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants permanently discontinuing study treatment prior to the Week 96 visit are considered to be withdrawn from the study treatment and study.

Participants withdrawn from the main study due to virologic concerns (e.g., baseline viral resistance, virologic withdrawal criteria, lack of efficacy) will have the option to participate in an observational sub-study describing subsequent ART regimens up to 6 months post-withdrawal. Participants withdrawn for any other reason, if impacted by virologic-management related concerns during participation in the main study, may also be considered to participate in the sub-study. See Appendix 15 for details on the sub-study.

A participant may withdraw consent and discontinue participation in this study at any time at his/her own request. The investigator may also, at his or her discretion, discontinue the participant from participating in this study at any time (e.g., safety, behavioral or administrative reasons). Participants may have a temporary interruption to their study treatment for management of toxicities. Withdrawn participants will not be replaced.

Please refer to Appendix 13 for study management information during the COVID-19 pandemic.

7.1. Discontinuation of study treatment

All decisions regarding treatment interruption, resumption, or substitution should be discussed with the Medical Monitor in advance.

Participants may have a temporary interruption to their study treatment for management of toxicities. Such interruption of study treatment does not require withdrawal from the study. However, consultation with the Medical Monitor is required. No toxicity-related dose reductions of study treatment will be allowed. Study treatment should be restarted as soon as medically appropriate; in general, for oral dosing, this should be no longer than 4

weeks after discontinuation (unless Grade 3 or 4 toxicities persist). Refer to Section 10.4 for further details on toxicity management.

Participants permanently discontinuing study treatment prior to the Week 96 visit are considered to be withdrawn from the study treatment and study.

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

- Adverse event / Serious adverse event.
- Protocol deviation.
- Participant lost to follow-up.
- Participant or Investigator non-compliance.
- Termination of the study by the Sponsor.
- At the request of the participant, Investigator, GSK or ViiV Healthcare.
- The participant requires concurrent prohibited medications during the course of the study. The participant may remain in the study if in the opinion of the Investigator and the medical monitor; such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the participant.

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

- Virologic withdrawal criteria as specified in Section 7.1.2 are met.
- Participant requires dose reduction or regimen substitution with non-study ART.
- Grade 4 clinical AE considered causally related to study treatment. Section 10.4.1.
- Liver toxicity where stopping criteria are met and no compelling alternate cause is identified. Section 7.1.1.
- Renal toxicity where criteria are met and no compelling alternate cause is identified. Section 10.4.1.3.
- Allergic reaction or Rash criteria as described in Section 10.4.1.5 and Section 10.4.1.6 are met and no compelling alternate cause is identified
- Participant withdrew consent

The primary reason for premature discontinuation of the study treatment will be documented in the eCRF.

7.1.1. Liver chemistry stopping criteria

7.1.1.1. Liver chemistry monitoring criteria

A liver monitoring event is an occurrence of predefined liver chemistry changes 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.

Liver monitoring event criteria are defined as any of the following:

- **Baseline ALT ≤1.5x ULN**: ALT ≥5x ULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity.
- **Baseline ALT >1.5x ULN**: ALT ≥3x baseline and <5x baseline and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity

Actions to be taken by the Investigator:

- **Notify the Medical Monitor within 24 hours of learning of the abnormality to discuss participant safety.**
- Participant can continue to receive study treatment unless otherwise indicated by the Medical Monitor.
- Participant must return every 2 weeks for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution or stabilization (ALT <5 × ULN on 2 consecutive evaluations).
- If at any time participant meets the liver chemistry stopping criteria, proceed as described below (Table 5).

Asymptomatic liver enzyme elevations

For asymptomatic participants who have ALT≥3XULN, following discussions with Medical Monitor, ALT and other specific lab tests can be repeated in an unscheduled visit. This may include liver panel tests included in study protocol, even though participant did not meet any liver monitoring or liver stopping criteria above.

7.1.1.2. Liver chemistry stopping criteria

Discontinuation of study treatment for abnormal liver tests is required by the Investigator when a participant meets 1 of the conditions outlined in the table of Liver Stopping Criteria (Table 5) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

Table 5 Liver chemistry stopping criteria

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.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment 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).

When any of the liver chemistry stopping criteria is met, do the following:

- **Immediately stop further study treatment administration, do not** administer another dose until approval is received from the ViiV Safety and Labelling Committee.
- Report the event to the Medical Monitor within 24 hours of learning its occurrence.
- Complete the liver event eCRF and SAE eCRF, where applicable.
- Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
- Perform liver event follow-up assessments (described in Section 10.7), and monitor the participant until liver chemistries resolve, stabilize, or return to Baseline values as described below.
- Make every reasonable attempt to have participants return to clinic within 24 hours for repeat liver chemistries, liver event follow-up assessments, and close monitoring.
- A specialist or hepatology consultation is recommended.
- Monitor participants twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within Baseline values.

Further details on required actions and follow-up laboratory assessments following a Liver Stopping Event is included in Section 10.7.

If participant meets liver chemistry stopping criteria, **do not** restart study treatment unless:

a. ViiV Healthcare Safety and Labelling Committee (VSLC) approval is granted;
b. IEC and/or IRB approval is obtained, if required; and
c. Separate consent for study treatment restart is signed by the participant.

7.1.1.3. Study Treatment Restart After Liver Stopping Criteria Are Met

Study treatment restart after liver chemistry stopping criteria are met is allowed in this study. If the participant meets liver chemistry stopping criteria, do not restart the participant with study treatment unless:

- **ViiV Safety and Labelling Committee (VSLC) approval is granted**
- **Ethics and/or IRB approval is obtained, if required, and**
- **Separate consent for intervention restart is signed by the participant**

NOTE: If study treatment was interrupted for suspected treatment-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and reconsented before resumption of dosing.

Refer to Section 10.7 Liver Safety: Suggested Actions and Follow-up Assessments and Refer to Section 10.8 Study treatment Restart Guidelines for details on the restart/rechallenge process.

If VSLC approval to restart the participant with study treatment is not granted, then the participant must permanently discontinue study treatment and may continue in the study for protocol-specified follow-up assessments.

7.1.2. Virologic Criteria for Participant Management and Viral Resistance Testing

For the purposes of clinical management in this study, **suspected virologic withdrawal (SVW)** and **confirmed virologic withdrawal (CVW)** criteria are defined here, wherein the virologic withdrawal criteria are based on the HIV-1 RNA cut-off of 200 c/mL.

Suspected Virologic Withdrawal criteria

- one assessment with HIV-1 RNA ≥200 c/mL after Day 1

Confirmed Virologic Withdrawal criteria

- two consecutive assessments with HIV-1 RNA ≥200 c/mL after Day 1

Plasma HIV-1 RNA viral load results determined by the central laboratory only will be used to assess protocol-defined virologic management and withdrawal criteria in the study. Local laboratory HIV-1 RNA viral load results, and any other supportive testing, may be obtained at the discretion of the Investigator to inform participant clinical management and safety decisions. Local laboratory HIV-1 RNA viral load results obtained during enrollment in study 219516 at the discretion of the Investigator should be retained in source records and documented in the eCRF.

7.1.2.1. Managing Participants Meeting Suspected Virologic Withdrawal (SVW) Criteria

Participants with HIV-1 RNA plasma levels ≥200 c/mL at any visit after Day 1 meet SVW criteria ("virologic management" criteria) and must have plasma HIV-1 RNA levels re-assessed. Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as meeting SVW criteria ("virologic management" criteria), the Investigator should query the participant regarding intercurrent illness, recent immunization, concomitant medications/supplements, or interruption of therapy.

All cases meeting SVW criteria ("virologic management" criteria) must be confirmed by a second measurement performed at least 2 weeks but not more than 4 weeks after the date of the original sample, unless delay is necessary to meet the requirements of confirmatory HIV-1 RNA testing as outlined below.

The following guidelines should be followed for scheduling confirmatory HIV-1 RNA testing in an effort to avoid false-positive results:

- Confirmatory testing should be scheduled 2 to 4 weeks following resolution of any intercurrent illness, during which time the participant should receive full doses of all study treatment.
- Confirmatory testing should be scheduled 2 to 4 weeks following any immunization, during which time the participant should receive full doses of study treatment.
- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2 to 4 weeks following resumption of full doses of study treatment.

The participant should have received full doses of study treatment for at least 2 weeks at the time confirmatory plasma HIV-1 RNA is done. Sites should contact the Medical Monitor to discuss individual participants, whenever necessary.

7.1.2.2. Managing Participants Meeting Confirmed Virologic Withdrawal (CVW) Criteria

Once a participant has been confirmed as meeting CVW criteria, a 'plasma for storage' sample from the SVW visit will be sent as soon as possible for resistance testing and the result made known to the Investigator if and when available. A whole blood or PBMC sample from the Day 1 visit will also be sent for baseline proviral DNA testing. Plasma samples for storage will be obtained at scheduled and unscheduled visits including the time of a CVW criteria (see Schedule of activities (SoA).

Participants may continue to receive study intervention at the discretion of the investigator until results of resistance testing are available or up to 30 days at which time the participant must be discontinued from the study intervention. If genotype data cannot be generated, the participant must also be discontinued from the study intervention.

If a participant is prematurely discontinued from participation in the study, the Investigator must make every effort to perform the Withdrawal visit evaluations outlined in the SoA. These data will be recorded, as they comprise an essential evaluation that needs to be done before discharging any participant from the study.

Refer to Section 4.4.1. for details on the Safety Follow-up visit.

Selection of the post-study ART regimen will be recorded in the eCRF.

Participants who withdraw from the main study may be eligible to participate in an optional, observational sub-study describing virologic response to post-study/subsequent ART. Details are provided in Section 10.15.

7.1.2.3. HIV-1 RNA Blips

HIV-1 RNA 'blips' (transient increases in HIV-1 RNA ≥50 c/mL and <200 c/mL) are not usually associated with subsequent virologic failure [DHHS, 2024]. Although the implications of persistent HIV-1 RNA levels between the lower level of detection and <200 c/mL are unclear, the risk of emerging resistance is believed to be relatively low. Participants with HIV-1 RNA 'blips' are not considered SVWs and do not require a change in therapy.

Participants who have a HIV-1 RNA ≥50 c/mL and <200 c/mL at the key analysis timepoints (Weeks 48 and 96 visits) must return to the clinic as soon as possible (but no later than 4 weeks after the date of the visit) for a repeat HIV-1 RNA test such that the result falls within the same analysis window.

In order to better characterize HIV-1 RNA 'blips,' if there is a known reason / explanation for the blip (e.g., immunization, allergies, etc.), the central study team should be notified of the reason and case context.

If the Investigator has concerns regarding persistent low-level viremia (HIV-1 RNA ≥50 c/mL and <200 c/mL), the Medical Monitor should be contacted to discuss participant management. Following discussion with the Medical Monitor, additional viral load testing may be performed between visits to determine the appropriate participant disposition for the next scheduled visit.

7.1.3. Temporary discontinuation

Any interruption in therapy (scheduling conflicts, life circumstances, etc.) during any oral dosing period that is greater than 7 consecutive days must be discussed with the Medical Monitor prior to resumption of therapy. The Medical Monitor must be contacted upon site staff becoming aware of resumption in therapy, if therapy was resumed without prior approval.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of discontinuing from the study, if possible, an early discontinuation withdrawal visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued from the study treatment and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

The primary reason for participant discontinuation/ withdrawal from the study will be documented in the eCRF.

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.7.5).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, study treatment distribution and monitoring may be implemented by the sponsor or the investigator, as per local health authority/ethics requirements.
- The maximum amount of blood collected from each participant over the duration of the study (96 weeks), will not exceed 550 mL, excluding repeat or unscheduled samples.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Administrative and general/baseline procedures

8.1.1. Collection of demographic data

Record demographic data such as year of birth, sex at birth, sex at time of study entry, gender identity, race, and ethnicity in the participant's eCRF.

Collection of sex, gender, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, to determine if the trial participants are truly representative of the impacted population, and to enable evaluation of study outcomes by demographic subgroups.

Retrospective data while on BIC/FTC/TAF (includes weight, BMI, vital signs, laboratory, disease and safety parameters) will be collected 48 weeks prior to Screening after obtaining the participant's consent for study participation.

8.1.2. Medical history

Obtain the participant's past medical history, family history, social history, medication history, targeted history on cardiovascular risk (smoking history, family and personal history) and HIV-associated conditions by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study treatment in the eCRF.

8.1.3. Screening Assessments

All participants will complete the Screening period approximately 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 enrollment.

All information about the participant's current and any past regimen through at least 5 years prior to screening as per entry criterion # 8, must be available for review by the Principal Investigator or designee. Source documents from other medical facilities must be located/received during the 28 day screening period and under no circumstances may the participant be enrolled 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 and eCRF. When available, all historical resistance testing reports with genotypic data **must** be provided to ViiV after screening and before enrollment 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. **If a participant is identified as having been mistakenly screened/enrolled with exclusionary resistance, the participant will be withdrawn.**

Severe hepatic impairment is exclusionary and will be assessed by Child-Pugh grading at screening (see Section 10.11).

CrCl is calculated at Screening, and participants with a CrCl <30 mL/min per 1.73 m^2 via refitted, race-neutral CKD-EPIcr_R method are excluded due to requirements for dose reduction of 3TC in participants with renal dysfunction.

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

Participants with chronic active hepatitis B are excluded. Evidence of HBV infection is based on the results of testing at Screening for HBsAg. Participants who are negative for HBsAg should also be tested for anti-HBc, anti-HBs (HBsAb), and HBV DNA and excluded according to the algorithm defined in the SRM.

8.1.4. Baseline Assessments

At Day 1, any changes to the eligibility parameters must be assessed and any results required prior to Baseline (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 general medical history and current medical conditions. Laboratory and health outcomes assessments will also be assessed. Questionnaire/surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. eC-SSRS will be completed at the beginning of the visit after administration of any other PROs, and prior to administration of study treatment.

8.2. Efficacy assessments

Planned time points for all efficacy assessments are provided in the SoA.

Plasma HIV-1 RNA

Plasma for quantitative HIV-1 RNA will be collected according to the SoA (Section 1.3). Methods to be used may include but are not limited to the Roche 6800 platform HIV-1 Assay lower limit of quantitation 20 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) according to the SoA (Section 1.3).

CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the SoA (Section 1.3). HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (see Section 10.6). When assessing CDC stage at screening consider only the latest available CD4 T-cell count, including CD4 T-cell count at screening. If a Stage 3-defining opportunistic illness has been diagnosed up to screening, then the stage is 3 regardless of CD4 T-cell count test results.

For Baseline CDC classification at Day 1 use latest CD4 T-cell count, including CD4 T-cell count at baseline. If a Stage 3-defining opportunistic illness has been diagnosed between screening and Day 1, then the Stage is 3 regardless of CD4 T-cell count test results.

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.

8.2.1. Primary Efficacy Endpoint

The primary endpoint will be participants with virologic failure endpoint (plasma HIV-1 RNA ≥50 c/mL) as per snapshot category at Week 48 for the FAS.

8.2.2. Secondary Efficacy Endpoints

- Participants with plasma HIV-1 RNA ≥50 c/mL (snapshot) at Week 24 and Week 96 for the FAS
- Participants with plasma HIV-1 RNA <50 c/mL (snapshot) at Week 24, Week 48 and Week 96 for the FAS
- Absolute values and changes from Baseline in CD4+ cells count and CD4+:CD8+ cell counts ratio at Week 24, Week 48, and Week 96
- Occurrence of disease progression (HIV-associated conditions, AIDS and death) through Week 24, Week 48 and Week 96

8.2.3. Exploratory Efficacy Endpoints

- Participants with plasma HIV-1 RNA <50 c/mL (snapshot) at 24, 48, and 96 weeks by subgroups (e.g., demographic factors, Baseline CD4, CD4 nadir) and pre-specified target population (≥65 years old, women, non-white race, CV risk, comedication) and pre-defined target population
- Absolute values and changes from Baseline in CD4+ cell count and CD4+:CD8+ cell counts ratio at 24, 48, and 96 weeks by subgroups (e.g., by age, gender, Baseline CD4+) and pre-defined target population
- Occurrence of disease progression (HIV associated conditions, AIDS and death) through 24, 48, and 96 weeks by subgroups (e.g., by age, gender, Baseline CD4+) and pre-defined target population

8.3. Safety assessments

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

8.3.1. Physical examination/history directed physical examination

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

8.3.2. Vital signs

Vital signs will be assessed at each visit in semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure. Weight, hip and waist circumference, and BMI will also be collected. Height will be collected at Baseline visit only. Procedures to be followed for blood pressure, weight, waist and hip circumference assessments are provided in Section 10.12.

8.3.3. Dietary Assessment

Control of Eating Questionnaire (CoEQ) will be completed by participant at time points specified in SoA.

Control of Eating Questionnaire: The CoEQ comprises 21-items that are designed to assess the severity and type of food cravings an individual experiences over the previous 7 days. The CoEQ has been used in clinical trials as a multi-dimensional measure of appetite, craving and mood regulation [Dalton, 2015].

8.3.4. Electrocardiograms

A baseline pre-dose 12-lead ECG will be performed in a semi-supine position after 5 minutes of rest on Day 1, for possible use as a reference during the study (i.e., in evaluation of any pertinent cardiovascular event).

8.3.5. Dual-X-absorptiometry (DXA)

Whole-body DXA will be performed at baseline, 48, and 96 weeks. A + 6 weeks window is allowed to perform the DXA in these visits. An appropriate estimate of the per-visit radiation dose to a participant in this study is less than 0.1mSv, which is a conservative estimate and likely to be about a factor of 10 higher than reality. That would give a maximum dose for the study of 0.3mSv, corresponding to a risk of fatal cancer induction of about 1 in 13 000, generally considered to be ‘low’ to ‘very low.’ Repeat DXA scans will be avoided wherever possible.

Pregnancy testing should be performed for woman of childbearing potential, and results available, before the DXA scan; the radiation procedures will not go ahead without a confirmed negative test to avoid exposing the fetus to ionizing radiation. Sites will make effort to prioritize DXA scan on the study visit date, however when this is not possible and the DXA scan is performed within the 6 weeks allowed window, a pregnancy urine test kit will be given to the participant in order to be self-administered on DXA scan day. A confirmed negative test needs to be reported to the site (e.g., women/ DXA technician will give a telephone call to the site, to the investigator team) before the radiation procedure can go ahead. If the pregnancy test results are ambiguous or positive, the pre-scheduled radiology procedure must be suspended, and a confirmatory serum pregnancy test should be mandated. This information will be recorded in the eCRF. If any participant doesn’t meet criteria at baseline for the DXA scans required per protocol – i.e., participants with a BMI ≥40 kg/m^2- she/he will be excluded from the DXA scan measurements.

For sites with more than 1 DXA Scanner, every effort will be made to use the same scanner for the duration of the study.

Scans be performed by the same qualified technician at each site, and standardized instructions will be followed. There will be cross-site calibration and longitudinal calibration of scanners, using a standardized Instrument Quality Control programme, including phantom scans. Scan images be transmitted to, and read by, a Central Imaging Vendor who will also train site personnel performing scans on the procedures required for this study and work with study sites on the longitudinal and cross-site calibration of scanners.

Dual energy X-ray absorptiometry will be used to measure total and regional (trunk and extremities) fat and fat-free mass at baseline, week 48 and week 96.

The following data will be obtained:

Body Composition: Upper limb fat:% and gr; Lower limb fat:% and gr; Trunk fat:% and gr; Total fat:% and gr; Upper limb lean Mass:% and gr; Lower limb lean Mass:% and gr; trunk lean mass:% and gr; Total lean mass:% and gr.

Estimation of the VAT with DXA will be also assessed.

DXA does not directly discriminate visceral from subcutaneous fat as it is a 2-dimensional imaging technique, but we have developed a score to calculate DXA-estimated VAT volume (Dr. Silvana Di Gregorio's personal communication). In preliminary studies, DXA-estimated VAT volume was strongly correlated with MRI-measured VAT volume ($r = 0.902$, $P < 0.0001$) and CT-measured VAT area ($r = 0.83$, $P < 0.0001$), although DXA tended to underestimate VAT mass at low VAT levels and overestimate it at high VAT levels.

8.3.6. Clinical safety laboratory tests

- Regular monitoring of hematology, blood chemistry, urinalysis and fasting glucose and lipids will be performed.
- See Section 10.2 for the list of clinical laboratory tests to be performed in accordance with lab manual and the SoA (Section 1.3).
- All protocol required laboratory assessments must be performed by central laboratory services, apart from in exceptional circumstances during screening as noted in Section 5.4. Laboratory requisition forms must be completed and samples must be clearly labelled with the participant number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the central laboratory and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the central laboratory.
- Refer to the lab manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws. Labs will be graded automatically by the central lab according to the DAIDS toxicity scales (See Section 10.5)

- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant 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 should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - In the absence of a diagnosis, abnormal laboratory findings assessments or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Section 10.3.1 and Section 10.3.2).
    - If clinically significant 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.
    - 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., AE, SAE or dose modification) the results must be recorded in the eCRF. Local laboratory services may be used to verify pending laboratory parameters only after consultation and agreement with the study team.

8.3.7. Pregnancy testing

- Women of childbearing potential (WOCBP) must have a serum (Screening) and urine (Day 1) pregnancy test performed before the administration of any dose of study treatment. At Day 1, a serum pregnancy test should also be performed. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study treatment may only be administered if the pregnancy test is negative.
- WOCBP must have a negative pregnancy test at Screening, and at Enrolment. Pregnancy testing will also be conducted as per the SoA and at any time during the trial when pregnancy is suspected. Where both serum and urine tests (S + U) are indicated for a given visit, proceed based on the result of the urine test, and review serum test result once available.
- Additionally, the Medical Monitor may request that a urine pregnancy test be performed in the event of a treatment interruption greater than 7 days.
- Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.
- If pregnancy is confirmed, a discussion with the pregnant study participant assessing the benefit/risk assessment of continuing in the study will be undertaken. If, after this

discussion, the participant would like to continue in the study, this will be allowed, provided the pregnant participant signs the pregnancy-specific ICF addendum.

- Pregnant participants who remain in the study do not need pregnancy testing during the study, for the duration of their pregnancy.

Imaging procedures in women of reproductive age

- Pregnancy testing should be performed and results available before the DXA scan; the radiation procedures will not go ahead without a confirmed negative test.

8.3.8. Suicidal ideation and behavior risk monitoring

All sites should have a plan in place for managing possible risks for suicide-related events.

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidal ideation or behavior. In addition, there have been some reports of depression, suicidal ideation and behavior (particularly in participants with a pre-existing history of depression or psychiatric illness) in some participants being treated with INSTIs, including DTG.

Therefore, it is appropriate to monitor and closely observe participants prospectively before and during treatment for suicidal ideation and/or behavior, or any other unusual changes in behavior. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.
It is recommended that the Investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behavior.

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 behavioral suicidal events used in this scale are based on those used in the Columbia Suicide History Form [Posner, 2007]. Questions are asked on suicidal behavior, suicidal ideation, and intensity of ideation. Screening 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.

The Investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the Adverse Event (non-serious or Serious Adverse Events) eCRF form on any participant that experiences a possible suicidality-related adverse event 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 behavior, 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 Healthcare/GSK within one week of the Investigator diagnosing a possible suicidality-related adverse event.

8.3.9. Safety Monitoring and iSRC

- Participant safety will be continuously monitored by the Medical Monitor, designated Safety Lead (or delegate) and the internal safety review committee (iSRC) throughout the study. Pertinent findings and conclusions are shared with the product's SRT for review of the overall benefit-risk profile of the product.
- This study will utilize an iSRC to ensure the safety of the participants. The iSRC will review accumulated data for agreement of next steps if the threshold for ad hoc iSRC review is met, as described in the iSRC Charter. Further reviews may occur as determined by the iSRC.
- The iSRC charter will describe the required data review and documentation of the recommendation of the iSRC to continue, amend, pause or stop the study.

8.4. Adverse Events (AEs), serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information, see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up all AEs OR AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment or study (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

Please refer to Section 10.13 for study management information during restriction related to COVID-19 pandemic.

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

- All AEs and SAEs will be collected from the start of study treatment until the last study follow-up visit at the time points specified in the SoA.
- SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a

ViiV Healthcare/GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study.

- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.
- All SAEs will be recorded and reported to ViiV/GSK immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- A post study AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.
- Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor, please refer to Table 7 in Section 8.4.9 for appropriate Sponsor contact.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to ViiV/GSK are provided in Section 10.3.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Appropriate questions include:

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

8.4.3. 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 resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.

8.4.4. Specific Toxicity/ Adverse Event Management

Please refer to the Section 10.4.1 Toxicity management.

8.4.5. Regulatory reporting requirements for SAEs

- Prompt notification by the investigator to ViiV/GSK (or designee) of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met. See Section 8.4.1 for reporting timeframes.
- ViiV has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. ViiV will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.
- Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and ViiV/GSK policy and are forwarded to investigators as necessary.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.7.3.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 6 Timeframes for submitting SAE, pregnancy and other events reports to GSK

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Timeframe**	**Documents**	**Timeframe**	**Documents to be Updated**
All SAEs	24 hours	SAE eCRF [a]	24 hours	SAE eCRF [a]
Possible Suicidality Related Adverse Event (SAE)	SAE eCRF [a] 24 hours	SAE eCRF [a]	SAE eCRF [a] 24 hours	SAE eCRF [a]
	PSRAE eCRF 1 week	PSRAE eCRF	PSRAE eCRF 1 week	PSRAE eCRF
Possible Suicidality Related Adverse Event (AE)	1 week	AE eCRF	1 week	AE eCRF
		PSRAE eCRF		PSRAE eCRF
Pregnancy	24 hours	Pregnancy Initial Notification Form	24 hours	Pregnancy Follow-up Form
ALT ≥8×ULN	24 hours [b]	SAE eCRF [a]		SAE eCRF [a]

	Initial Reports		Follow-up Information on a Previous Report	
		Liver Event eCRF [c]		Liver Event eCRF [c]
		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]
ALT≥3×ULN and bilirubin≥2×ULN (>35% direct) (or ALT≥3×ULN)	24 hours [b]	SAE eCRF [a]	24 hours	SAE eCRF [a]
		Liver Event eCRF [c]		Liver Event eCRF [c]
		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]
ALT≥5×ULN that persists ≥2 weeks	24 hours [b]	SAE eCRF [a]	24 hours	SAE eCRF [a]
		Liver Event eCRF [c]		Liver Event eCRF [c]
		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]
ALT ≥3×ULN (if baseline ALT is <ULN) or ALT ≥3 fold increase from baseline value with appearance or worsening of symptoms of hepatitis or hypersensitivity	24 hours [b]	SAE eCRF [a]	24 hours	SAE eCRF [a]
		Liver Event eCRF [c]		Liver Event eCRF [c]
		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]		Liver Imaging and/or Liver Biopsy eCRFs, if applicable [c]

a. See Section 10.3.6 Reporting of SAE to ViiV Healthcare/GSK/PPD. If the electronic system (eCRF) is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
b. The Medical Monitor must be contacted at onset of liver chemistry elevations to discuss participant safety.
c. Liver event documents (i.e., "Liver Event eCRF" and updates, "Liver Imaging eCRF" and/or "Liver Biopsy eCRF", as applicable) should be completed as soon as possible.

8.4.6. Pregnancy

8.4.6.1. Collection of pregnancy information

- The Investigator will collect pregnancy information on any female participant who becomes pregnant whilst participating in this study. Details of all pregnancies in female participants will be collected after the start of study treatment and until the last study visit.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor (or CRO designee) within 24 hours of learning of the pregnancy. Refer to Section 8.4.9 for reporting procedures.

- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor (or CRO designee). See Section 8.4.9 for reporting timeframes.
- In case of pregnancy, the participant must be informed that personal information of the neonate (such as date of birth, sex, birth weight, any birth defects and HIV status) will be collected as part of safety follow-up. Consent for collection of personal information on the neonate may be obtained from the participant and/or their partner as per local regulations.
- Information about the pregnancy and pregnancy outcomes will be forwarded by the Sponsor to the Antiretroviral Pregnancy Registry (APR). This international registry is jointly sponsored by manufacturers or licensees of ARV products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com.
- The Investigator is also encouraged to report all pregnancies directly to the APR as soon as the pregnancy is identified. Pregnancies can be reported directly to the APR using the case report forms and contact details found at http://www.apregistry.com.
- While pregnancy itself is not considered 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 will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor (or CRO designee) as described in Section 8.4.3. 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.

8.4.6.2. Continuation of study treatment

Any female participant who becomes pregnant whilst participating in the study may request continuation of study treatment, if permitted according to local regulations and provided the below conditions are met.

Prior to continuation of study treatment following pregnancy, the following must occur:

- The sponsor and the relevant IRB/IEC give written approval.
- The participant gives signed informed consent using the pregnancy-specific study ICF addendum.
- The Investigator agrees to monitor the outcome of the pregnancy and the status of the participant and her offspring.

Further information and guidance around managing pregnancy, as well as pregnancy-specific assessments and procedures, can be found in Section 10.3.7.7, Appendix 9 and Appendix 10.

8.4.7. CV and death events

For any CV events whether or not they are considered SAEs and all deaths, specific CV and Death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV 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 CV section of the eCRF within 1 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 1 week of when the death is reported.

8.4.8. Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 10.6) 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 10.3.2), 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.

If either of the above conditions is met, then record the DRE on the SAE page rather than the HIV-Associated Conditions eCRF page and report promptly (Section 8.4.5) to ViiV Healthcare/GSK.

8.4.9. Contact information for reporting SAEs, pregnancies and study holding rules

Refer also to Section 10.3.7.7 ('Reporting of SAEs and pregnancies')

Table 7 Contact information for reporting SAEs, pregnancies and study holding rules

• **The primary mechanism for reporting of safety events to the Sponsor (or CRO designee) will be the electronic data collection tool (eCRF).** • **For any questions and follow-up on safety events, refer to the online study site portal for a current list of CRO and Sponsor study team contacts (including back-up contacts).**	
For questions regarding SAEs and pregnancy during the study	Contact study Medical Monitor or designated back-up
For instances where a participant meets a protocol-defined holding/stopping rule	If a holding/stopping rule is met, the Investigator must immediately inform the study Medical Monitor or designated back-up within 24 hours
For reporting of SAEs and pregnancy during the study – if the eCRF is not available	Contact the PPD PVG Safety Hotline, available 24/24 hours and 7/7 days: North America Phone: +1-800-201-8725 Fax: +1-888-488-9697 Latin America Phone: +55 11 4504 4801 Fax: +55 11 3958 0983 EMEA / APAC Phone: +44 122 337 4240 Fax: +44 122 337 4102
For reporting of SAEs, and pregnancy related to any ViiV Healthcare/GSK product – after the study has ended	Complete the SAE or pregnancy paper reporting form and send to GSK: Email: OAX37649@gsk.com Fax: +44 (0) 20 8754 7822 If paper forms are not available, the Investigator should provide a full written report to include the Investigator's assessment of causality (for SAEs) and the Investigator's signature, and forward to the email address/fax number as per the above.

8.4.10. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician, caregiver, and family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.5. Pharmacokinetics

PK is not evaluated in this study.

8.6. Pharmacodynamics

PD is 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 and bone biomarker assessments. Samples will be collected according to the schedule described in the SoA and as detailed in laboratory manual provided separately to sites. In addition to measurements of serum creatinine, estimated GFR, and urinary excretion of albumin, protein, creatinine and phosphate, additional renal and bone biomarkers include:

Renal biomarkers:

- Cystatin C (blood)
- Retinol Binding Protein (RBP, blood/urine)
- Beta-2-Microglobulin (B2M, blood/urine)

Bone biomarkers:

- Bone specific alkaline phosphatase
- Procollagen type 1 N-propeptide
- Type 1 collagen cross-linked C-telopeptide
- Osteocalcin
- 25 hydroxy-Vitamin D

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 25 hydroxy-vitamin D.

- Storage samples (plasma, serum, whole blood and PBMCs) will be collected to perform further post-hoc assessments of relevant cardio-metabolic, inflammation biomarkers or virology tests that may assist with the understanding of any study finding. These samples will be batch tested taking into account sample stability limits required for any specific biomarkers testing.

- Fasting Insulin, fasting glucose, HbA1c, and HOMA-IR

GSK may store samples for up to 20 years or as per the country local regulation after the end of the study to achieve study objectives. Additionally, with participants' consent, samples may be used for further research by GSK or others such as universities or other companies to contribute to the understanding of HIV or other diseases, the development of related or new treatments, or research methods.

8.9. Immunogenicity assessments

Not applicable.

8.10. Viral Resistance

Whole venous blood samples will be obtained from each participant to provide "plasma for storage samples" according to the Schedule of Activities in Section 1.3 (for potential viral resistance analyses). Participants meeting CVW criteria will have baseline whole blood and/or PBMC samples tested for proviral DNA genotype, and plasma samples tested for HIV-1 PR, RT and IN genotype and phenotype from samples collected at the time of meeting SVW criteria.

Details concerning the handling, labeling and shipping of these samples will be supplied separately in the laboratory manual.

A secondary endpoint of the study will be the incidence of observed resistance to DTG or 3TC for participants meeting virologic withdrawal criterion.

8.11. HIV-1 Exploratory Analysis

Additional exploratory analyses may include HIV-1 resistance testing on Baseline whole blood or PBMC samples, or virologic analysis on stored plasma samples from other relevant time points. Analyses may also include but are not limited to additional viral resistance testing for linkage and minority species composition, other HIV-1 RNA quantitation methods, measurement of viral replicative capacity, and/or for biomarkers that may reflect HIV-1 disease progression. HIV-1 resistance will also be determined on the last on-treatment isolates from all participants who have HIV-1 RNA ≥400 c/mL regardless of confirmatory HIV-1 RNA

8.12. Value Evidence and Outcomes

Patient reported outcomes (PROs) and insights will be assessed with a combination of existing PRO instruments and bespoke survey questions developed internally by ViiV Healthcare, for which no corresponding validated tool is available in the literature. Similarly, provider insights are also captured using bespoke survey questions developed internally by ViiV Healthcare, where no validated instrument exists. All surveys are self-completed.

Each instrument provides distinct outcomes and insights as described in this section below, and Table 2 of Section 3– 'Objectives and Endpoints'.

A subset of participants and providers in the US, Canada and the UK, can choose to take part in-depth qualitative interviews which will gather a deeper understanding of the implementation strategies and their overall experience throughout the study.

Health outcomes assessments will be conducted according to the SoA Table. Assessments are recommended to be administered via an ePRO format.

The following PROs will be administered:

- The **HIVTSQ status version (HIVTSQs)**: The HIVTSQ was designed to measure satisfaction with HIV medication including 10 items and underwent two stages of psychometric validation [Woodcock 2001, Woodcock 2006]. All items comprising the Total score, can also be reported and interpreted individually. The HIVTSQ status version (HIVTSQs) is assessing patients' satisfaction with their current treatment with a Total score ranging from 0 to 66. Higher scores indicate a greater level of satisfaction with HIV treatment. Individual items scores range from 0 to 6 (0=very dissatisfied, 6=very satisfied).
- The **HIVTSQ change version (HIVTSQc)** was developed to overcome ceiling effects associated with HIVTSQs. The HIVTSQc is assessing the change in patients' satisfaction between their previous and their current treatment within the same group. The Total score for HIVTSQc ranges from -33 to 33. Higher scores indicate a greater improvement in satisfaction with treatment; lower scores indicate a greater deterioration in satisfaction with treatment; a score of 0 represents no change. Individual items scores range from -3 to 3 (-3= much less satisfied now, 3= much more satisfied now).
- The **WHOQOL-HIV BREF** is an instrument developed by the World Health Organization and modified from the original WHOQOL-HIV version [O'Connell, 2012; O'Connell 2003]. The abbreviated version is a 31-item measure assessing the overall quality of life of people living with HIV.
- 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].

- The **"participant reasons for switch**" questionnaire will be administered at baseline to understand the participants motivations for switching to DTG/3TC within a clinical trial along with their treatment aspirations of less medicine. Select questions will be repeated at week 48 and 96 to evaluate if their treatment aspirations have been met. This questionnaire has been developed internally by ViiV Healthcare. For a subset of participants in the US, UK and Canada, in-depth qualitative interviews will be conducted.
- The **"investigator reasons for switch**" questionnaire will be administered at baseline to understand the investigator motivations for switching participants to DTG/3TC within a clinical trial along with their experience of switching. Select questions will be repeated at week 48 and 96 to evaluate their treatment experience. This questionnaire has been developed internally by ViiV Healthcare. For a subset of investigators in the US, UK and Canada, in-depth qualitative interviews will be conducted.

8.13. Implementation Science Interventions and assessments

In this study, 3 implementation strategies will be tested. The use of each strategy is optional.

- **Strategy 1: Participant leaflet**

  A leaflet will be developed to support participant understanding regarding Dovato. This can be used to support initial discussions post recruitment between the participant and the provider (e.g., physicians, support staff, nurses) and at any future timepoint in the study as the need arises. It will also be an ongoing reference resource for participants. The material will be available as both a hard copy resource and a digital material on the HCP and participant portals.

  The material will be optional to use and will be evaluated through (i) participant questionnaires and qualitative interviews (day 1, week 24 and week 48) and (ii) provider questionnaires and qualitative interviews (day 1, week 24 and week 48). Participant and provider qualitative interviews will only be conducted in the US, UK and Canada.

- **Strategy 2: Liverpool Combined Comorbidity Risk Calculator**

  The Liverpool Combined Comorbidity Risk Calculator (LCCRC) is an HCP facing digital web-based resource that clinics can use to help assess co-morbidity risks for participants. The LCCRC digitizes several freely available, commonly used, established risk calculators* within a single website. The intent is to help support the clinical encounter by simplifying access to the calculators and allowing one-time data entry, to facilitate easier co-morbidity risk factor and risk of disease assessments. The output of each tool is presented independently of the others i.e., they are stand-alone assessments. This is intended to support conversations between participants and providers, but results will not be documented in the eCRF. The

LCCRC will be made available in the US, UK, Mexico and Canada where it is not considered a medical device. It will not be available to sites in the EU.

The tool will be evaluated using provider questionnaires and qualitative interviews (physicians, support staff, nurses) (week 24, 48 and 96). Provider qualitative interviews will only be conducted in the US, UK and Canada.

The tool will be available to all HCPs in the US, Canada, Mexico and the UK on the HCP portal and will be optional to use. Other providers, nurses, and other clinical staff can all access and use the tool on an as needed basis.

*The Liverpool Combined Comorbidities Risk Calculator Tool includes the following risk calculators:

- CHA2DS2-VASC Score for Atrial Fibrillation

- Child-Turcotte-Pugh (CTP) for Chronic Liver Disease and Cirrhosis

- Framingham Risk Score for Cardiovascular Disease (10 year)

- FRAX Risk Score for Osteoporosis Fracture (10 year)

- HAS-BLED Score for Major Bleeding Risk

- MDRD Glomerular Filtration Rate Equation

- **Strategy 3: Participant activity monitoring Watch and App (blinded to participants and investigators)**

  Actigraphy (wearable watch for participants) and health behavior assessments - Digital Biomarkers measured with Participant Wearable Watch and App self reporting of behaviors: Actigraphy is a non-invasive method of measuring activity and rest cycles. The intensity of daily activities can be measured continuously over time using motion-based devices, such as accelerometers. Actigraphy has been used as a tool to assess daily activity of participants and sleep quality in over 1200 clinical trials globally and referenced in ~20 000 scientific publications.

  In this study, participants in selected countries will be invited to participate in Actigraphy and self reporting of behaviors via an App. Participation to either or both Actigraphy and App are optional.

  Actigraphy assessments using a wrist-worn medical-grade watch (medical device; FDA 510(k) cleared, and CE marked for intended use) will be conducted as a means of objectively measuring changes in the physical activity and sleep patterns from a baseline measurement taken prior to enrolment up to 14 days after the Week 72 visit. Actigraphy data will not be used for participant clinical management or monitoring

and will only be used for exploratory analyses at specified timepoints (i.e. not part of the study intervention).

Participants who opt into the actigraphy component of the study (i.e., sign actigraphy optional component of the ICF) will be asked to wear the watch for 14 days during the screening phase, and then for 14 days post each clinic visit up to and including Week 72. Participants other health behaviors (i.e., alcohol intake, mood, water intake, stress level) will be assessed using PROs that will be self-documented through an associated App on the participant's own mobile device for participants who opt into this App (i.e., sign health behavior App optional component of the ICF). Participants will be asked to document these health behaviors for 14 days during the screening phase, and after each subsequent clinic visit. Actigraphy and App data collection will conclude 14 days after the week 72 visit.

Actigraphy data will complement PRO data to provide a better understanding of overall co-morbidity status and health behaviors. It will provide a means to measure objectively how the participants function in their daily lives and provide a means to objectively assess sleep quality. As an exploratory endpoint, this study will aim to explore the application of actigraphy by:

• Assessing objective, quantitative measures of physical activity

• Evaluating change from baseline and change over time of actigraphy measures.

• Evaluating how actigraphy measures relate to participants reported measures of symptoms and other efficacy assessments.

• The data collected may also be used to conduct exploratory further analyses of physical activity and sleep

Sleep and exercise digital biomarkers will be collected through the watch. Digital biomarker data will not be visible to the participant or the provider.

Uptake, persistence, adherence, utility and acceptability of wearing the watch and logging the daily behaviors will be evaluated using participant questionnaires (Day 1, Week 24, Week 48 and Week 96) and participant qualitative interviews (Day 1, Week 24, Week 48 and Week 96). Participant qualitative interviews will only be conducted in the US, UK and Canada.

Further details regarding actigraphy, including training for the participant and storage and transmission of data to and from the study site, is included in the relevant study user manual and ICF.

Exploratory Endpoint Analysis will be fully described in the SAP.

Implementation Outcome	**Measurement Method(s) (e.g., observations, surveys, routinely collected data)**	**Level of Measurement (i.e., individual participant, individual service provider, health service facility (e.g., hospital))**	**Measurement Time point(s)**
Participant acceptability, uptake and utility of participant leaflet	Participant surveys Participant qualitative interviews*	Participants	Participant surveys: Day 1, week 24, week 48 Participant qualitative interviews*: Day 1, week 24, Week 48
Provider acceptability, uptake and utility of participant-provider participant leaflet	Provider (support staff, nurses, and physicians) surveys. Provider qualitative interviews* (support staff, nurses, and physicians)	Providers	Provider survey: Day 1, week 24, week 48 Provider qualitative interviews*: Day 1, Week 24, 48
Acceptability, uptake and utility of the Liverpool Co-Morbidity Risk Calculator	Provider (support staff, nurses, and physicians) surveys. Provider qualitative interviews* (support staff, nurses, and physicians) Website monitored metrics: Number of users in a given time period (day, week, month, quarter etc.) Geographical location of users Calculators selected	Providers	Week 24, 48 and 96
Uptake, acceptability, utility, persistence and adherence (participant watch [Actigraph] and app). Sleep quality Physical Activity Health Behaviors	Participant surveys. Participant qualitative interviews* App entry data (persistence, and adherence) Actigraphy data (persistence, adherence, uptake) Actigraphy data -Total Sleep Time -Sleep efficiency -Wake after sleep onset)	Participant	Participant Survey: Day 1, Week 24, 48 and 96 Participant qualitative interviews*: Day 1, Week 24, 48 and 96 Actigraphy and app data: Summary from 14 day screening period, and each 14 day period of watch wearing after each study visit.

Implementation Outcome	Measurement Method(s) (e.g., observations, surveys, routinely collected data)	Level of Measurement (i.e., individual participant, individual service provider, health service facility (e.g., hospital))	Measurement Time point(s)
	Actigraphy data -Moderate to vigorous activity -Non-sedentary time -Step Count) Self reported via app -EtOH (alcohol) Intake -Water Intake -Mood -Stress Level		

Footnotes:

* Participant and Provider qualitative interviews will only be conducted in the US, UK and Canada.

9. STATISTICAL CONSIDERATIONS

The SAP will be finalized prior to database lock for the primary analysis and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1. Statistical hypotheses

No formal hypotheses testing will be performed.

9.1.1. Multiplicity Adjustment

As there is no type 1 error, adjustment for multiplicity is not applicable. Multiple subgroups will be analyzed in order to understand the treatment effect in different populations, particularly in those populations that are underrepresented. Subgroup summaries, particularly in under-represented populations, are exploratory and should be interpreted with caution.

9.2. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	All participants who were screened for eligibility.	Study Population
Enrolled	All participants who entered the study (who were enrolled or received study treatment or underwent a post screening study procedure). Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Met eligibility but not treated) are excluded from the Enrolled analysis set as they did not enter the study.	Study Population
Assigned	All participants who were assigned to study treatment in the study.	Study Population
Full Analysis Set (FAS)	All assigned participants who received at least one dose of study treatment.	Efficacy / Safety
Full Analysis Set Staff Study Participants (FASS)	All staff participants at sites that complete any Implementation Science endpoint assessment.	Implementation Science
Confirmed Virologic Withdrawal (CVW)	All participants in the FAS who met Confirmed Virologic Withdrawal (CVW) criteria defined as: two consecutive assessments with HIV-1 RNA ≥200 c/mL after Day 1.	Efficacy

9.3. Statistical analyses

9.3.1. General considerations/definitions

Summary statistics for continuous parameters will include mean, median, standard deviation, minimum, maximum, and geometric mean and %CV where data are log-transformed. The 25th and 75th percentile will be reported where applicable. Categorical parameters will be summarized by number and percentage of participants, with confidence intervals generated using Wilson-Score or Exact (e.g., Clopper-Pearson) methodology.

All efficacy analyses will be performed on the Full Analysis Set. All safety analyses will be performed on the Safety Analysis Set.

Further details of statistical analyses will be provided in the SAP.

9.3.2. Primary Estimand(s) analysis

The primary estimand is described in Section 3.1.

The primary endpoint of virologic failure (plasma HIV-1 RNA ≥50 c/mL as per Snapshot algorithm at 48 weeks) will be analyzed based on the Full Analysis Set (FAS), (i.e., all participants who received at least 1 dose of DTG/3TC).

9.3.2.1. Definition of endpoints

The primary endpoint is virologic failure (plasma HIV-1 RNA ≥50 c/mL as per Snapshot algorithm) at 48 weeks.

9.3.2.2. Main Analytical Approach

The number and percentage of participants with HIV-1 RNA ≥50 c/mL per Snapshot algorithm will be summarized at Week 48 including 95% Clopper-Pearson exact confidence intervals.

9.3.3. Safety estimand analyses

Safety estimands are described in Section 3.2.1.

The endpoints include:

- Occurrence and severity of AEs over time through Week 96
- Occurrence and severity of drug-related AEs over time through Week 96
- Occurrence of SAEs over time through Week 96
- Participants who discontinue treatment due to AEs over time through Week 96.
- Occurrence of laboratory abnormalities over time including through Week 96

9.3.4. Other analysis

9.3.4.1. Secondary Analyses

The key secondary estimand is described in Section 3.2.1.

The key secondary endpoint is virologic suppression (plasma HIV-1 RNA <50 c/mL as per Snapshot algorithm at 48 weeks). Due to the low expected number of events for the primary endpoint; exploratory subgroup analyses, including those in under-represented populations, will be conducted on this key secondary endpoint.

Details of secondary estimand and secondary/exploratory endpoint analyzes will be provided in the SAP.

9.3.4.2. Exploratory Analyses

Regression slope modelling where, rather than using a single baseline value, changes in slopes pre vs post treatment switch may be estimated for clinically relevant endpoints where there is sufficient data available to augment traditional change from baseline summaries.

DTG/3TC has been extensively studied in sponsored and non-sponsored studies in adult studies. Bayesian Dynamic Borrowing techniques or meta-analysis techniques may be

explored to provide population estimates using a prior distribution of appropriate data in trials identified through a systematic literature review. The analysis will be considered exploratory, and details of the prior distribution and analysis approach will be documented in a technical appendix to the study analysis plan.

The statistical analysis plan will provide a detailed description of the planned analyzes for other endpoints.

9.4. Interim analyses

The primary analysis will be completed after the last participant evaluable completes the Week 48 visit or prematurely discontinues from the study. Further, additional analyses may be performed to support regulatory activities, business planning, publications or other purposes. The final analysis is conducted after all participants complete 96 weeks (EOS) of follow-up or prematurely discontinue the study.

Additional details regarding the sequence of planned analyses will be provided in the statistical analysis plan which will be finalized prior to database lock.

In addition, adhoc review of data by the iSRC may occur if the review threshold is met. Full details of the analyses to be performed will be provided in the iSRC Charter. These reviews will be conducted on instream data and will not be considered formal study interim analyses.

9.5. Sample size determination

Assuming a 20% screen failure rate, approximately 250 HIV-1 infected adult participants will be screened to achieve approximately 200 enrolled participants. This sample size will allow for a reasonable number of subjects to estimate the effects of switching to DTG/3TC from BIC/F/TAF in important under-represented populations. For virological failure, we observed a rate of <1% in our prior studies, in this more diverse and older study population we assume a VF rate of 1%. Using a 2-sided 95% test for one-proportion with an estimated sample size of 200 we have 95% confidence that the true population VF rate is no more than 4.2% with 90% power. The estimated two-sided 95% confidence interval using Clopper-Pearson exact methodology assuming a sample size of 200 participants for our assumed virological failure rate of 1% is 0.1% to 3.6% (width = 3.4%).

Based on our observed virological suppression rate of 93%, using a two-sided 95% test for one-proportion with an estimated sample size of 200 we have 95% confidence that the true population VS rate is at least 86% with 90% power. The estimated two-sided 95% confidence interval using Wilson (Score) method assuming a sample size of 200 participants for our observed virological suppression rate of 93% is 88.6% to 95.8% (width = 7.2%).

9.5.1. Sample Size Sensitivity for Subgroups

For a sample size of 200 enrolled participants, and a virological suppression rate of 93%, the confidence interval width for VS in these under-represented populations can be estimated using a using the Wilson-Score method. The study is not powered with respect to these subgroups, hence an estimation approach only is taken. The table below provides estimates of CI widths for the population split of 30% (women, aged 65 and over), 40% (identifying as non-white), 50% (cardiovascular risk >10%), 60% (white, 1 non-ART concomitant medication), and 70% (men, aged below 65).

Table 8 Summary of confidence intervals widths for varying subgroup sizes

Effect size	Total sample	Subgroup proportion	Subgroup sample	CI of effect	CI width
VS 93%	200	30%	60	(83.64, 97.19)	13.5
	200	40%	80	(85.22, 96.84)	11.6
	200	50%	100	(86.25, 96.57)	10.3
	200	60%	120	(86.98, 96.35)	9.4
	200	70%	140	(87.53, 96.18)	8.6

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1. Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g. advertisements, participant's facing materials) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed consent process

- The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (where applicable), local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant.
- By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed, and agreed with GSK/ViiV.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.
- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional further research. The Investigator or authorized designee will explain to each participant the objectives of the further research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.
- In case of unexpected pregnancy, participant must be informed that personal information such as date of birth, sex, birth weight, and birth defects (if any) of the baby will be collected as part of safety follow-up. Consent for the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

To recruit the required number of participants, historical and current data has been evaluated to determine the most suitable countries and investigator sites to enroll the study population. Consideration has also been given to demographic diversity targets.

Recruitment planning and enrolment will be the responsibility of PPD and overseen by GSK/ViiV Healthcare.

A number of strategies may be used to identify and recruit study participants, including but not limited to use of study leaflets, advertisements, and information materials. Any participant-facing materials will be locally approved in accordance with any IRB/IEC requirements.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- GSK/ViiV Healthcare will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant, that their data will be used as described in the informed consent.
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK/ViiV Healthcare and/or trusted third parties working on behalf of GSK/ViiV Healthcare and/or institutions working with GSK/ViiV Healthcare for the purposes of this study are contractually bound to protect participant coded data. GSK/ViiV Healthcare will protect participant coded data and will only share it as described in the ICF.
- GSK/ViiV Healthcare has a global, internal policy that requires all GSK/ViiV Healthcare staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

- A Safety Review Team (SRT) is in place for each ViiV Healthcare product. It comprises of a global cross-functional team responsible for the ongoing assessment

of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

- Participant safety will also be monitored by the Sponsor's internal safety review committee (iSRC), as defined in the iSRC Charter and Section 8.3.9.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or ViiV Healthcare Clinical Study Register in compliance with applicable regulations/ViiV Healthcare policy. ViiV Healthcare will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, ViiV Healthcare will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. ViiV Healthcare will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the layperson summary of results with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- ViiV Healthcare will provide the investigator with the enrollment codes and participant-level line listings for their site only after completion of the full statistical analysis.
- ViiV Healthcare intends to make anonymized participant-level data from this study available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve participant care. This helps ensure the data provided by study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of eCRFs will be provided in study-specific eCRF completion guidelines.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL Plan or equivalent document to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, involvement of central reading mechanism) methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan or equivalent document.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for a minimum period of 15 years from the issue of the final CSR/ equivalent summary, or in accordance with Applicable Law, whichever is longer. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. In the event of a conflict between this Protocol and the fully executed clinical study agreement, the protocol shall prevail with respect to records retention.

10.1.9. Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in Investigator Source Data Agreement.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the

study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Source data are shared with third parties contracted by ViiV/GSK for external assessment or adjudication (e.g., expert reader for DXA scans). Participant names or any information which would make the participant identifiable or is not essential for the external assessment or adjudication will be redacted by the investigator sites prior to transfer. Details of the participant information redaction strategy are provided in the relevant third party manuals and/or study plans. These source data will be used by the third party solely for the purpose indicated within this protocol.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

Study/Site Termination

GSK/ViiV Healthcare or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK/ViiV Healthcare. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor’s procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or temporary suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

GSK/ViiV Healthcare seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 9 will be performed by the central laboratory and local laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. Local Laboratory results may be obtained at the clinical discretion of the Investigator to inform participant clinical management and safety. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table below includes lab parameters to be assessed as per the SoA. In addition to the protocol-specified laboratory assessments the study Medical Monitor, in collaboration with the site investigator, may request additional central laboratory assessments be performed to support safety profiling and case management of individual study participants.

Table 9 Safety Laboratory Assessments

Hematology			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
Clinical Chemistry			
BUN	Potassium	AST	Total bilirubin[a]
Creatinine	Chloride	ALT	Albumin
Glucose[c]	Total CO_2	Alkaline phosphatase	Creatine phosphokinase
Sodium	Lipase	Phosphate	Creatinine clearance[b]
Calcium	Gamma-glutamyl Transferase (GGT)	Protein	Cystatin-C
Fasting Lipid Panel[d]			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Other Tests			

Plasma HIV-1 RNA[e]
CD4+ and CD8+ cell counts [CD4/CD8 ratio][f]
Peripheral Blood Mononuclear Cells (PBMCs): Day 1, Week 48, Week 96 and Withdrawal only
Hepatitis B (HbsAg), anti-HBc, anti-HbsAg, and hepatitis C antibody (Screening)
Syphilis serology + Reflex Rapid Plasma Reagin (RPR) (Screening and Baseline)
Prothrombin Time (PT)/International Normalized Ratio (INR)/ Partial Thromboplastin Time (PTT)
Pregnancy test for women of childbearing potential[g]
Urinalysis, urine albumin/creatinine ratio, and urine protein/creatinine ratio, urine phosphate
Follicle stimulating hormone (FSH) and estradiol (only for instances when postmenopausal status is questionable)
Renal biomarkers including Cystatin-C (blood), Retinol Binding Protein (RBP, blood/urine); and Beta 2 Microglobulin (B2M, blood/urine)[h]
Bone biomarkers including: Bone-specific alkaline phosphatase, procollagen type 1 N-propeptide, type 1 collagen cross-linked C-telopeptide, osteocalcin, 25 hydroxy-Vitamin D[h]
HbA1c, Insulin, HOMA-IR

MCV = mean corpuscular volume, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO2 = carbon dioxide, HDL = high density lipoprotein, LDL = low density lipoprotein, HbsAg= hepatitis B virus surface antigen, PT/INR = prothrombin time/international normalized ratio.

a) Direct bilirubin will be reflexively performed for all total bilirubin values >1.5 × ULN.
b) Glomerular filtration rate (GFR) will be estimated by the central laboratory using the refitted, race-neutral Chronic Kidney Disease Epidemiology Collaboration (CKD-EPIcr_R) method [Delgado,2022]. In addition, GFR will be estimated by the central laboratory using the refitted, race-neutral CKD-EPI-cystatin C [Delgado, 2022] at day 1 and when indicated by renal toxicity criteria.
c) For fasting glucose assessments, an overnight fast is preferred; however, a minimum of a 6-hour fast is acceptable for participants with afternoon appointments.
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 viral resistance data.
f) CD8+ cells will only be reported at Baseline, Day 1, Weeks 24, 48 and 96.
g) Urine pregnancy test/ serum pregnancy test will be performed according to the SoA (Section 1.3).
h) 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 25 hydroxy-Vitamin D.

Equations for determination of eGFR

Refitted, race-neutral CKD-EPIcr_R method equation:

$$eGFR_{cr} = 142 \times \min(SCr/k,1)^{\alpha} \times \max(SCr/k,1)^{-1.200} \times 0.9938^{age} \times 1.012 \text{ [if female]}$$

where SCr is standardized serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.241 for females and -0.302 for males, min indicates the minimum of SCr/k or 1, max indicates the maximum of SCr/k or 1.

Refitted, race-neutral CKD-EPI-cystatin C equation:

$$eGFR = 133 \times \min(Scys/0.8, 1)^{-0.499} \times \max(Scys/0.8, 1)^{-1.328} \times 0.996^{Age} \times 0.932 \text{ [if female]}$$

Abbreviations / Units:
eGFR (estimated glomerular filtration rate) = mL/min/1.73 m2
Scys (standardized serum cystatin C) = mg/l
min = indicates the minimum of Scys/0.8 or 1

max = indicates the maximum of Scys/0.8 or 1

The addresses of the clinical laboratories in charge of human biological sample testing are provided in a separate document ('List of clinical laboratories used for human biological sample analysis') and stored in TMF at the time of the protocol finalization.

10.3. Appendix 3: AEs and SAEs: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1. 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 treatment, whether or not considered related to the study treatment.
- 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 treatment.

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 condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment 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.
- Events that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).
- "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

Events Meeting the AE Definition
from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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, admission for routine examination.). • 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. Pre-existing diseases will be recorded in the medical history section of the eCRF. • Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline. • Diseases Related Events or outcomes listed in the CDC Classification System for HIV-1 Infections (Appendix 6) will not be recorded as an AE or SAE unless 1 or more of the conditions outlined in Section 8.4.8 are met.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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 admitted (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**

	fulfills 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 baseline is not considered an AE.**
d.	**Results in persistent or significant 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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.**
e.	**Is a congenital anomaly/birth defect in the offspring of a study participant**
f.	**Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy)**
g.	**Other situations:** • Possible Hy's Law case: ALT ≥ 3x ULN AND total bilirubin ≥ 2x ULN (>35% direct bilirubin) or INR >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Solicited events

Definition of solicited event
• Solicited AEs are predefined local and systemic events for which the participant is specifically questioned.

10.3.4. Unsolicited AE

Unsolicited AE Definition
• An unsolicited AE is an AE that was not solicited using a participant diary and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. Definition of CV events

CV Event 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

10.3.6. Definition of Treatment Emergent Adverse Event (TEAE)

TEAE Definition
• A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.7. Recording, assessment and follow-up of AEs, SAEs, and pregnancies

10.3.7.1. 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 reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the required eCRF / paper form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- 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.

10.3.7.2. Assessment of intensity

Every AE and SAE reported during the clinical trial should be evaluated by the investigator and graded in the eCRF according to the DAIDS toxicity scales accessed via the link below:
https://rsc.niaid.nih.gov/sites/default/files/daidsgradingcorrectedv21.pdf **(See** Appendix 5**).**

Note: Grade 4 DAIDS toxicity grades for laboratory parameters that are asymptomatic would not necessarily be considered SAEs, a clinical correlation would be necessary.

Where a DAIDS toxicity scale is not available for a particular event or parameter, the investigator should make an assessment of intensity using the following categories cited in the DAIDS AE grading document as shown below:

Table 10 DAIDS AE intensity grading for non-specified AEs

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical AE NOT identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated	Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

AE = Adverse event; DAIDS = Division of Acquired Immunodeficiency Syndrome.

Note: An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE.

10.3.7.3. Assessment of causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.
- 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.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- The Investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. 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 the Sponsor.
- The Investigator may change their 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.

10.3.7.4. Assessment of outcomes

The Investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.7.5. Follow-up of AEs, SAEs, pregnancies or any other events of interest

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor 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 the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

After the initial AE/SAE/pregnancy or any other event of interest, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Other nonserious AEs must be followed until the last study visit or until the participant is lost to follow-up.

Follow-up during the study

AEs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until the last study visit.

If a participant dies during their participation in the study or during a recognized follow-up period, ViiV Healthcare/GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to ViiV Healthcare/GSK using the paper or electronic pregnancy follow-up report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the Investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the Investigator to be reasonably related to the study treatment, to ViiV Healthcare/GSK as described in the Section 10.3.7.7.

10.3.7.6. Updating of SAE and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the Investigator. The updated report should be sent to the study contact for reporting SAEs (refer to Section 8.4.3).

10.3.7.7. Reporting of SAEs and pregnancies

SAE Reporting to the Sponsor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any ViiV Healthcare/GSK product that is not part of the study design they will report these events to the Sponsor or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.9

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor.

- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Section 8.4.9

10.4. Appendix 4: Toxicity Management

Adverse events that occur during the trial should be evaluated by the investigator and graded according to the DAIDS toxicity scales (see Appendix Section 10.5). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 8.3.

Study treatment may be interrupted at the discretion of the investigator and according to the severity of the AE. If one or more ART medication is held due to toxicity or AEs, all ART medications should be held to reduce the risk of development of resistance taking into account the length of the planned interruptions and the PK half-life of each ART of the regimen, in order to minimize the risk of development of resistance.

No toxicity-related dose reductions of study treatment will be allowed. Study treatment should be restarted as soon as medically appropriate; in general, this should be no longer than 4 weeks after interruption (unless Grade 3 or 4 toxicities persist). Decisions regarding sequential reintroduction of study treatment or temporary interruption of one but not all drugs within the ART regimen should be made with the understanding that these changes may result in incomplete viral suppression and selection of resistant virus. Guidance is provided below on participant management and study treatment interruptions based on the severity of the AE for specific toxicities. All changes in study treatment must be accurately recorded in the participant's eCRF.

Grade 1 or Grade 2 Toxicity/Adverse Event

Participants who develop a Grade 1 or Grade 2 AE or toxicity may continue study treatment at the discretion of the investigator. Participants who choose to withdraw from the study due to a Grade 1 or 2 AE should have study withdrawal and follow-up evaluations completed.

Grade 3 Toxicity/Adverse Event

Participants who develop a Grade 3 AE or toxicity should be managed as follows:

If the investigator has compelling evidence that the Grade 3 AE or toxicity has not been caused by study treatment, dosing may continue after discussion with the medical monitor.

Participants who develop a Grade 3 AE or toxicity that the investigator considers related or possibly related to the study treatment should have study treatment withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, study treatment may be restarted.

Should the same Grade 3 AE recur within 28 days in the same participant, study treatment should be permanently discontinued and the participant withdrawn from study.

Participants experiencing Grade 3 AEs requiring permanent discontinuation of study treatment should be followed weekly until resolution of the AE and have withdrawal

study evaluations completed. A Follow-up visit should be performed approximately 2-4 weeks after the last dose of study treatment.

Participants who develop a new asymptomatic Grade 3 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue study treatment if the investigator has compelling evidence that the toxicity is not related to study treatment.

Exceptions are noted for liver chemistry stopping criteria (Section 7.1.1.2), rash (Appendix Section 10.4.1.6), and lipid abnormalities (Appendix Section 10.4.1.7).

Grade 4 Toxicity/Adverse Event

Participants who develop a Grade 4 AE or toxicity should have study treatment discontinued. However, if the investigator has compelling evidence that the AE is not causally related to the study treatment, dosing may continue after discussion with and assent from the medical monitor. Participants should be rechecked each week until the AE returns to Grade 2.

Participants experiencing Grade 4 AEs requiring permanent discontinuation of study treatment should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and follow-up study evaluations as noted above.

Participants with asymptomatic Grade 4 laboratory abnormalities should be investigated for all potential non-drug related causes, and, following discussion with the medical monitor, may continue therapy if the investigator has compelling evidence that the toxicity is not related to study treatment. Exceptions are noted for lipid abnormalities in Section 10.4.1.7. An in-clinic Follow-Up visit will be conducted approximately 2-4 weeks after the last dose of study medication for participants with ongoing AEs, and SAEs and also any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant, at the last on-study visit. Isolated Grade 4 lipid abnormalities do not require withdrawal of IP.

10.4.1. Specific Toxicities/Adverse Event Management

General guidelines for the management of specific toxicities that are considered to be related or possibly related to study treatment are provided below.

Participants who permanently discontinue study treatment for reasons of toxicity should be followed weekly until resolution of the AE and encouraged to complete the withdrawal and Follow-up study evaluations (see Section 7).

10.4.1.1. Liver Chemistry Stopping and Follow-up Criteria

Liver chemistry threshold stopping criteria have been designed to assure participant safety and to evaluate liver event etiology during administration of study treatment and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 7.1.1.

10.4.1.2. Restarting Study treatment

Refer to Section 10.8 for details on drug restart following transient resolving liver events not related to study treatment.

10.4.1.3. 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 and urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI cystatin C method (using the refitted, race-neutral Chronic Kidney Disease Epidemiology Collaboration method [Delgado, 2022]) 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 refitted, race-neutral CKD-EPIcr_R method) of <30 mL/min/1.73m2 must return for a confirmatory assessment within 2 weeks [Delgado, 2022]. A urinalysis and urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the refitted, race-neutral CKD-EPI cystatin C method [Delgado, 2022] should be done at this confirmatory visit. If an estimated GFR of <30 mL/min is confirmed, then IP should be withheld and the investigator should contact the medical monitor to discuss the rationale for restarting study treatment (if appropriate). Consideration for confounding factors (e.g. other medications, dehydration, concurrent conditions) should be taken into account, and a nephrology consult may be obtained. If study treatment is reinitiated, it should have been withheld for no more than 4 weeks. If study treatment is not reinitiated the participant must be withdrawn.

10.4.1.4. 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.

10.4.1.5. Allergic reaction

Participants may continue study treatment 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.

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

10.4.1.6. 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 characterization of HSR and rash observed with DTG-containing ART, please see the current version of the DTG IB [GSK Document Number RPS-CLIN-044825].

Participants with an isolated Grade 1 rash may continue study treatment 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 treatment for an isolated Grade 2 rash. However, study treatment (and all other concurrent medication(s) suspected in the Investigators causality assessment) should be permanently discontinued for any Grade ≥2 rash that is associated with an increase in ALT. The 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 treatment (and all other concurrent medication(s) suspected in the Investigators causality assessment) for an isolated Grade 3 or 4 rash, except where the etiology of the rash has been definitively diagnosed as NOT attributable to study treatment (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, Appendix Section 10.5).

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

documentation of the diagnosis provided. In this situation, the study treatment should be continued.

10.4.1.7. Hypertriglyceridemia/Hypercholesterolemia

Samples for lipid measurements must be obtained in a fasted state according to the Schedule of Activities (Section 1.3). Participants who experience asymptomatic triglyceride or cholesterol elevations may continue to receive study treatment.

10.4.1.8. Creatine Phosphokinase (CPK) Elevation

A Grade 3 or higher elevation in CPK should result in a repeat assessment within 2 to 4 weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of drugs known to cause increase of CPK (such as statins), physical activity or exercise preceding the CPK evaluation should be obtained. Grade 4 elevations in CPK should have a repeat assessment after the participant has abstained from exercise for >24 hours. For persistent Grade 4 CPK elevations that are considered possibly or probably related to the study treatment, study treatment should be discontinued and the participant withdrawn from the study.

10.5. Appendix 5: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, July 2017

VERSION 2.1, July 2017

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Estimating Severity Grade for Parameters Not Identified in the Grading Table
The functional table below should be used to grade the severity of an AE that is not specifically identified in the grading table. In addition, all deaths related to an AE are to be classified as grade 5

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Clinical adverse event **NOT** identified elsewhere in the grading table	Mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Severe symptoms causing inability to perform usual social & functional activities with intervention or hospitalization indicated	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death

Major Clinical Conditions Cardiovascular

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arrhythmia (by ECG or physical examination) *Specify type, if applicable*	No symptoms AND No intervention indicated	No symptoms AND Non-urgent intervention indicated	Non-life-threatening symptoms AND Non-urgent intervention indicated	Life-threatening arrhythmia OR Urgent intervention indicated

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	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)

[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

Dermatologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Alopecia (scalp only)	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	NA	NA
Bruising	Localized to one area	Localized to more than one area	Generalized	NA
Cellulitis	NA	Non-parenteral treatment indicated (e.g., oral antibiotics, antifungals, antivirals)	IV treatment indicated (e.g., IV antibiotics, antifungals, antivirals)	Life-threatening consequences (e.g., sepsis, tissue necrosis)
Hyperpigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Hypopigmentation	Slight or localized causing no or minimal interference with usual social & functional activities	Marked or generalized causing greater than minimal interference with usual social & functional activities	NA	NA
Petechiae	Localized to one area	Localized to more than one area	Generalized	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pruritus[3] (without skin lesions)	Itching causing no or minimal interference with usual social & functional activities	Itching causing greater than minimal interference with usual social & functional activities	Itching causing inability to perform usual social & functional activities	NA
Rash *Specify type, if applicable*	Localized rash	Diffuse rash OR Target lesions	Diffuse rash AND Vesicles or limited number of bullae or superficial ulcerations of mucous membrane limited to one site	Extensive or generalized bullous lesions OR Ulceration of mucous membrane involving two or more distinct mucosal sites OR Stevens-Johnson syndrome OR Toxic epidermal necrolysis

[3] For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23 in source DAIDS Table).

Endocrine and Metabolic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Diabetes Mellitus	Controlled without medication	Controlled with medication OR Modification of current medication regimen	Uncontrolled despite treatment modification OR Hospitalization for immediate glucose control indicated	Life-threatening consequences (e.g., ketoacidosis, hyperosmolar non-ketotic coma, end organ failure)
Gynecomastia	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing pain with greater than minimal interference with usual social & functional activities	Disfiguring changes AND Symptoms requiring intervention or causing inability to perform usual social & functional activities	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hyperthyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid suppression therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., thyroid storm)
Hypothyroidism	No symptoms AND Abnormal laboratory value	Symptoms causing greater than minimal interference with usual social & functional activities OR Thyroid replacement therapy indicated	Symptoms causing inability to perform usual social & functional activities OR Uncontrolled despite treatment modification	Life-threatening consequences (e.g., myxedema coma)
Lipoatrophy[4]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA
Lipohypertrophy[5]	Detectable by study participant, caregiver, or physician AND Causing no or minimal interference with usual social & functional activities	Obvious on visual inspection AND Causing greater than minimal interference with usual social & functional activities	Disfiguring changes	NA

[4] Definition: A disorder characterized by fat loss in the face, extremities, and buttocks.

[5] Definition: A disorder characterized by abnormal fat accumulation on the back of the neck, breasts, and abdomen

Gastrointestinal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhea *≥ 1 year of age*	Transient or intermittent episodes of unformed stools OR Increase of ≤ 3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR Increase of 4 to 6 stools over baseline per 24-hour period	Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences (e.g., hypotensive shock)
< 1 year of age	Liquid stools (more unformed than usual) but usual number of stools	Liquid stools with increased number of stools OR Mild dehydration	Liquid stools with moderate dehydration	Life-threatening consequences (e.g., liquid stools resulting in severe dehydration,

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-
Dysphagia or Odynophagia *Report only one and specify location*	Symptoms but able to eat usual diet	Symptoms causing altered dietary intake with no intervention indicated	Symptoms causing severely altered dietary intake with intervention indicated	Life-threatening reduction in oral intake
Gastrointestinal Bleeding	Not requiring intervention other than iron supplement	Endoscopic intervention indicated	Transfusion indicated	Life-threatening consequences (e.g., hypotensive shock)
Mucositis or Stomatitis *Report only one and specify location*	Mucosal erythema	Patchy pseudomembranes or ulcerations	Confluent pseudomembranes or ulcerations OR Mucosal bleeding with minor trauma	Life-threatening consequences (e.g., aspiration, choking) OR Tissue necrosis OR Diffuse spontaneous
Nausea	Transient (< 24 hours) or intermittent AND No or minimal interference with oral intake	Persistent nausea resulting in decreased oral intake for 24 to 48 hours	Persistent nausea resulting in minimal oral intake for > 48 hours OR Rehydration indicated (e.g., IV fluids)	Life-threatening consequences (e.g., hypotensive shock)
Pancreatitis	NA	Symptoms with hospitalization not indicated	Symptoms with hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, hemorrhage, sepsis)
Perforation (colon or rectum)	NA	NA	Intervention indicated	Life-threatening consequences
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR	Symptoms causing inability to perform usual social & functional activities OR Operative	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-
Vomiting	Transient or intermittent AND No or minimal interference with oral intake	Frequent episodes with no or mild dehydration	Persistent vomiting resulting in orthostatic hypotension OR Aggressive rehydration indicated (e.g.,	Life-threatening consequences (e.g., hypotensive shock)

Musculoskeletal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Arthralgia	Joint pain causing no or minimal interference with usual social & functional activities	Joint pain causing greater than minimal interference with usual social & functional activities	Joint pain causing inability to perform usual social & functional activities	Disabling joint pain causing inability to perform basic self-care functions
Arthritis	Stiffness or joint swelling causing no or minimal interference with usual social & functional activities	Stiffness or joint swelling causing greater than minimal interference with usual social & functional activities	Stiffness or joint swelling causing inability to perform usual social & functional activities	Disabling joint stiffness or swelling causing inability to perform basic self-care functions
Myalgia (generalized)	Muscle pain causing no or minimal interference with usual social & functional activities	Muscle pain causing greater than minimal interference with usual social & functional activities	Muscle pain causing inability to perform usual social & functional activities	Disabling muscle pain causing inability to perform basic self-care functions
Osteonecrosis	NA	No symptoms but with radiographic findings AND No operative intervention indicated	Bone pain with radiographic findings OR Operative intervention indicated	Disabling bone pain with radiographic findings causing inability to perform basic self-care functions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Osteopenia[6] *≥ 30 years of age*	BMD t-score -2.5 to -1	NA	NA	NA
< 30 years of age	BMD z-score -2 to -1	NA	NA	NA
Osteoporosis[6] *≥ 30 years of age*	NA	BMD t-score < -2.5	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences
< 30 years of age	NA	BMD z-score < -2	Pathologic fracture (e.g., compression fracture causing loss of vertebral height)	Pathologic fracture causing life-threatening consequences

[6] BMD t and z scores can be found in: Kanis JA on behalf of the World Health Organization Scientific Group (2007). Assessment of osteoporosis at the primary health-care level. Technical Report. World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield, UK. 2007: Printed by the University of Sheffield

Neurologic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute CNS Ischemia	NA	NA	Transient ischemic attack	Cerebral vascular accident (e.g., stroke with neurological deficit)
Altered Mental Status (for Dementia, see *Cognitive, Behavioral, or Attentional Disturbance* below)	Changes causing no or minimal interference with usual social & functional activities	Mild lethargy or somnolence causing greater than minimal interference with usual social & functional activities	Confusion, memory impairment, lethargy, or somnolence causing inability to perform usual social & functional activities	Delirium OR Obtundation OR Coma

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Ataxia	Symptoms causing no or minimal interference with usual social & functional activities OR No symptoms with ataxia detected on examination	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Disabling symptoms causing inability to perform basic self-care functions
Cognitive, Behavioral, or Attentional Disturbance (includes dementia and attention deficit disorder) *Specify type, if applicable*	Disability causing no or minimal interference with usual social & functional activities OR Specialized resources not indicated	Disability causing greater than minimal interference with usual social & functional activities OR Specialized resources on part-time basis indicated	Disability causing inability to perform usual social & functional activities OR Specialized resources on a full- time basis indicated	Disability causing inability to perform basic self-care functions OR Institutionalization indicated
Developmental Delay *< 18 years of age* *Specify type, if applicable*	Mild developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for	Moderate developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Severe developmental delay, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting	Developmental regression, either motor or cognitive, as determined by comparison with a developmental screening tool appropriate for the setting
Headache	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Symptoms causing inability to perform basic self-care functions OR Hospitalization indicated OR Headache with significant impairment of alertness or other neurologic function

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
< 18 years of age (includes new or pre-existing febrile seizures)	Seizure lasting < 5 minutes with < 24 hours postictal state	Seizure lasting 5 to < 20 minutes with < 24 hours postictal state	Seizure lasting ≥ 20 minutes OR > 24 hours postictal state	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)
Pre-existing Seizure	NA	Increased frequency from previous level of control without change in seizure character	Change in seizure character either in duration or quality (e.g., severity or focality)	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory epilepsy)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Syncope	Near syncope without loss of consciousness (e.g., pre-syncope)	Loss of consciousness with no intervention indicated	Loss of consciousness AND Hospitalization or intervention required	NA

Pregnancy, Puerperium, and Perinatal

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal death occurring at ≥ 20 weeks gestation	NA
Preterm Birth (report using mother's participant ID)	Live birth at 34 to < 37 weeks gestational age	Live birth at 28 to < 34 weeks gestational age	Live birth at 24 to < 28 weeks gestational age	Live birth at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[7] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA

[7] Definition: A pregnancy loss occurring at < 20 weeks gestational age

Psychiatric

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early causing no or minimal interference with usual social & functional activities	Moderate difficulty falling asleep, staying asleep, or waking up early causing more than minimal interference with usual social & functional activities	Severe difficulty falling asleep, staying asleep, or waking up early causing inability to perform usual social & functional activities requiring intervention or hospitalization	NA
Psychiatric Disorders (includes anxiety, depression, mania, and psychosis) *Specify disorder*	Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities	Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities	Symptoms with hospitalization indicated OR Behavior causing inability to perform usual social & functional activities	Threatens harm to self or others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions
Suicidal Ideation or Attempt *Report only one*	Preoccupied with thoughts of death AND No wish to kill oneself	Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent	Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated	Suicide attempted

Respiratory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Bronchospasm	Forced expiratory volume in 1 second or peak flow reduced to ≥ 70 to < 80% OR Mild symptoms with intervention not indicated	Forced expiratory volume in 1 second or peak flow 50 to < 70% OR Symptoms with intervention indicated OR Symptoms causing greater than minimal interference with usual social & functional activities	Forced expiratory volume in 1 second or peak flow 25 to < 50% OR Symptoms causing inability to perform usual social & functional activities	Forced expiratory volume in 1 second or peak flow < 25% OR Life-threatening respiratory or hemodynamic compromise OR Intubation
Dyspnea or Respiratory Distress *Report only one*	Dyspnea on exertion with no or minimal interference with usual social & functional activities OR Wheezing OR Minimal increase in respiratory rate for age	Dyspnea on exertion causing greater than minimal interference with usual social & functional activities OR Nasal flaring OR Intercostal retractions OR Pulse oximetry 90 to < 95%	Dyspnea at rest causing inability to perform usual social & functional activities OR Pulse oximetry < 90%	Respiratory failure with ventilator support indicated (e.g., CPAP, BPAP, intubation)

Sensory

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Hearing Loss *≥ 12 years of age*	NA	Hearing aid or intervention not indicated	Hearing aid or intervention indicated	Profound bilateral hearing loss (> 80 dB at 2 kHz and above) OR Non-serviceable hearing (i.e., >50 dB audiogram and <50% speech discrimination)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 12 years of age (based on a 1, 2, 3, 4, 6 and 8 kHz audiogram)	> 20 dB hearing loss at ≤ 4 kHz	> 20 dB hearing loss at > 4 kHz	> 20 dB hearing loss at ≥ 3 kHz in one ear with additional speech language related services indicated (where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	Audiologic indication for cochlear implant and additional speech- language related services indicated (where available)
Tinnitus	Symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated	Symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated	Symptoms causing inability to perform usual social & functional activities	NA
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medical intervention indicated	Posterior or pan- uveitis OR Operative intervention indicated	Disabling visual loss in affected eye(s)
Vertigo	Vertigo causing no or minimal interference with usual social & functional activities	Vertigo causing greater than minimal interference with usual social & functional activities	Vertigo causing inability to perform usual social & functional activities	Disabling vertigo causing inability to perform basic self-care functions
Visual Changes (assessed from baseline)	Visual changes causing no or minimal interference with usual social & functional activities	Visual changes causing greater than minimal interference with usual social & functional activities	Visual changes causing inability to perform usual social & functional activities	Disabling visual loss in affected eye(s)

Systemic

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acute Allergic Reaction	Localized urticaria (wheals) with no medical intervention indicated	Localized urticaria with intervention indicated OR Mild angioedema with no intervention indicated	Generalized urticaria OR Angioedema with intervention indicated OR Symptoms of mild bronchospasm	Acute anaphylaxis OR Life-threatening bronchospasm OR Laryngeal edema
Chills	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cytokine Release Syndrome[8]	Mild signs and symptoms AND Therapy (i.e., antibody infusion) interruption not indicated	Therapy (i.e., antibody infusion) interruption indicated AND Responds promptly to symptomatic treatment OR Prophylactic medications indicated for ≤ 24 hours	Prolonged severe signs and symptoms OR Recurrence of symptoms following initial improvement	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Fatigue or Malaise *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	Incapacitating symptoms of fatigue or malaise causing inability to perform basic self-care functions
Fever (non-axillary temperatures only)	38.0 to < 38.6°C or 100.4 to < 101.5°F	≥ 38.6 to < 39.3°C or ≥ 101.5 to < 102.7°F	≥ 39.3 to < 40.0°C or ≥ 102.7 to < 104.0°F	≥ 40.0°C or ≥ 104.0°F

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Pain[9] (not associated with study agent injections and not specified elsewhere) *Specify location*	Pain causing no or minimal interference with usual social & functional activities	Pain causing greater than minimal interference with usual social & functional activities	Pain causing inability to perform usual social & functional activities	Disabling pain causing inability to perform basic self-care functions OR Hospitalization indicated
Serum Sickness 10	Mild signs and symptoms	Moderate signs and symptoms AND Intervention indicated (e.g., antihistamines)	Severe signs and symptoms AND Higher level intervention indicated (e.g., steroids or IV fluids)	Life-threatening consequences (e.g., requiring pressor or ventilator support)
Underweight[11] *> 5 to 19 years of age*	WHO BMI z-score < -1 to -2	WHO BMI z-score < -2 to -3	WHO BMI z-score < -3	WHO BMI z-score < -3 with life-threatening consequences
2 to 5 years of age	WHO BMI z-score < -1 to -2	WHO Weight-for- height z-score < -2 to -3	WHO Weight-for-height z-score < -3	WHO Weight-for-height z-score < -3 with life-threatening consequences
< 2 years of age	WHO BMI z-score < -1 to -2	WHO Weight-for- length z-score < -2 to -3	WHO Weight-for-length z-score < -3	WHO Weight-for-length z-score < -3 with life-threatening consequences
Unintentional Weight Loss (excludes postpartum weight loss)	NA	5 to < 9% loss in body weight from baseline	≥ 9 to < 20% loss in body weight from baseline	≥ 20% loss in body weight from baseline OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)

[8] Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.

[9] For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23 in source DAIDS Table).

[10] Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea

[11] WHO reference tables may be accessed by clicking the desired age range or by accessing the following URLs:
http://www.who.int/growthref/who2007_bmi_for_age/en/ for participants > 5 to 19 years of age and
http://www.who.int/childgrowth/standards/chart_catalogue/en/ for those ≤ 5 years of age.

Urinary

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Urinary Tract Obstruction	NA	Signs or symptoms of urinary tract obstruction without hydronephrosis or renal dysfunction	Signs or symptoms of urinary tract obstruction with hydronephrosis or renal dysfunction	Obstruction causing life-threatening consequences

Site Reactions to Injections and Infusions

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Injection Site Pain or Tenderness *Report only one*	Pain or tenderness causing no or minimal limitation of use of limb	Pain or tenderness causing greater than minimal limitation of use of limb	Pain or tenderness causing inability to perform usual social & functional activities	Pain or tenderness causing inability to perform basic self-care function OR Hospitalization indicated
Injection Site Erythema or Redness[12] *Report only one* *> 15 years of age*	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 15 years of age	≤ 2.5 cm in diameter	> 2.5 cm in diameter with < 50% surface area of the extremity segment involved (e.g., upper arm or thigh)	≥ 50% surface area of the extremity segment involved (e.g., upper arm or thigh) OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage	Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)
Injection Site Induration or Swelling *Report only one* *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*	Same as for **Injection Site Erythema or Redness,** *> 15 years of age*
≤ 15 years of age	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*	Same as for **Injection Site Erythema or Redness,** *≤ 15 years of age*
Injection Site Pruritus	Itching localized to the injection site that is relieved spontaneously or in < 48 hours of treatment	Itching beyond the injection site that is not generalized OR Itching localized to the injection site requiring ≥ 48 hours treatment	Generalized itching causing inability to perform usual social & functional activities	NA

[12] Injection Site Erythema or Redness should be evaluated and graded using the greatest single diameter or measured surface area.

Laboratory Values*
Chemistries

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Acidosis	NA	pH ≥ 7.3 to < LLN	pH < 7.3 without life-threatening consequences	pH < 7.3 with life-threatening consequences
Albumin, Low (g/dL; *g/L*)	3.0 to < LLN *30 to < LLN*	≥ 2.0 to < 3.0 *≥ 20 to < 30*	< 2.0 *< 20*	NA
Alkaline Phosphatase, High	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Alkalosis	NA	pH > ULN to ≤ 7.5	pH > 7.5 without life-threatening consequences	pH > 7.5 with life-threatening consequences
ALT or SGPT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Amylase (Pancreatic) or Amylase (Total), High *Report only one*	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
AST or SGOT, High *Report only one*	1.25 to < 2.5 x ULN	2.5 to < 5.0 x ULN	5.0 to < 10.0 x ULN	≥ 10.0 x ULN
Bicarbonate, Low (mEq/L; *mmol/L*)	16.0 to < LLN *16.0 to < LLN*	11.0 to < 16.0 *11.0 to < 16.0*	8.0 to < 11.0 *8.0 to < 11.0*	< 8.0 *< 8.0*
Bilirubin[13], High *> 28 days of age*	NA	NA	> ULN with other signs and symptoms of hepatotoxicity.	> ULN with life-threatening consequences (e.g., signs and symptoms of liver failure)
≤ 28 days of age	ULN to ≤ 1 mg/dL	> 1 to ≤ 1.5 mg/dL	> 1.5 to ≤ 2 mg/dL	> 2 mg/dL

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin, High *> 28 days of age*	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN with other signs and symptoms of hepatotoxicity.	≥ 5.0 x ULN with life-threatening consequences (e.g., signs and symptoms of liver failure).
≤ 28 days of age	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates	See Appendix A in Source DAIDS Table. Total Bilirubin for Term and Preterm Neonates
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65 to < 2.88*	11.5 to < 12.5 *2.88 to < 3.13*	12.5 to < 13.5 *3.13 to < 3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88 to < 3.10*	12.4 to < 12.9 *3.10 to < 3.23*	12.9 to < 13.5 *3.23 to < 3.38*	≥ 13.5 *≥ 3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95 to < 2.10*	7.0 to < 7.8 *1.75 to < 1.95*	6.1 to < 7.0 *1.53 to < 1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63 to < 1.88*	6.0 to < 6.5 *1.50 to < 1.63*	5.50 to < 6.0 *1.38 to < 1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10x ULN	10 to < 20 x ULN	≥ 20 x ULN

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Creatinine, High **Report only one*	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase to 1.3 to < 1.5 x participant's baseline	> 1.8 to < 3.5 x ULN OR Increase to 1.5 to < 2.0 x participant's baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x participant's baseline
Creatinine Clearance[14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life- threatening consequences	Increased lactate with pH < 7.3 with life-threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥ 190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*) *> 14 years of age*	2.0 to < LLN *0.65 to < LLN*	1.4 to < 2.0 *0.45 to < 0.65*	1.0 to < 1.4 *0.32 to < 0.45*	< 1.0 *< 0.32*
1 to 14 years of age	3.0 to < 3.5 *0.97 to < 1.13*	2.5 to < 3.0 *0.81 to < 0.97*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
< 1 year of age	3.5 to < 4.5 *1.13 to < 1.45*	2.5 to < 3.5 *0.81 to < 1.13*	1.5 to < 2.5 *0.48 to < 0.81*	< 1.5 *< 0.48*
Potassium, High (mEq/L; *mmol/L*)	5.6 to < 6.0 *5.6 to < 6.0*	6.0 to < 6.5 *6.0 to < 6.5*	6.5 to < 7.0 *6.5 to < 7.0*	≥ 7.0 *≥ 7.0*
Potassium, Low (mEq/L; *mmol/L*)	3.0 to < 3.4 *3.0 to < 3.4*	2.5 to < 3.0 *2.5 to < 3.0*	2.0 to < 2.5 *2.0 to < 2.5*	< 2.0 *< 2.0*
Sodium, High (mEq/L; *mmol/L*)	146 to < 150 *146 to < 150*	150 to < 154 *150 to < 154*	154 to < 160 *154 to < 160*	≥ 160 *≥ 160*
Sodium, Low (mEq/L; *mmol/L*)	130 to < 135 *130 to < 135*	125 to < 130 *125 to < 130*	121 to < 125 *121 to < 125*	≤ 120 *≤ 120*
Uric Acid, High (mg/dL; *mmol/L*)	7.5 to < 10.0 *0.45 to < 0.59*	10.0 to < 12.0 *0.59 to < 0.71*	12.0 to < 15.0 *0.71 to < 0.89*	≥ 15.0 *≥ 0.89*

*Reminder: An asymptomatic abnormal laboratory finding without an accompanying AE should not be reported to DAIDS in an expedited time frame unless it meets protocol-specific reporting requirements.

[13] Direct bilirubin > 1.5 mg/dL in a participant < 28 days of age should be graded as grade 2, if < 10% of the total bilirubin

[14] Use the applicable formula (i.e., Cockcroft-Gault in mL/min or Schwartz, MDRD, CKD-Epi in mL/min/1.73m2). Sites should choose the method defined in their study and when not specified, use the method most relevant to the study population.

*Reminder: Choose the method that selects for the higher grade

[15] To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114

Hematology

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Absolute CD4+ Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	300 to < 400 *300 to < 400*	200 to < 300 *200 to < 300*	100 to < 200 *100 to < 200*	< 100 *< 100*
Absolute Lymphocyte Count, Low (cell/mm^3; *cells/L*) *> 5 years of age (not HIV infected)*	600 to < 650 *< 0.600 x* 10^9 to < 0.650 x 10^9	500 to < 600 *0.500 x* 10^{9_9} *to* *< 0.600 x* 10^9	350 to < 500 *0350 x* 10^9 *to* *< 0.500 x* 10^9	< 350 *< 0.350 x* 10^9
Absolute Neutrophil Count (ANC), Low (cells/mm^3; *cells/L*) *> 7 days of age*	800 to 1,000 *0.800 x* 10^9 *to 1.000 x* 10^9	600 to 799 *0.600 x* 10^9 *to 0.799 x* 10^9	400 to 599 *0.400 x* 10^9 *to 0.599 x* 10^9	< 400 *< 0.400 x* 10^9
2 to 7 days of age	1,250 to 1,500 *1.250 x* 10^9 *to 1.500 x* 10^9	1,000 to 1,249 *1.000 x* 10^9 *to 1.249 x* 10^9	750 to 999 *0.750 x* 10^9 *to 0.999 x* 10^9	< 750 *< 0.750 x* 10^9
≤ 1 day of age	4,000 to 5,000 *4.000 x* 10^9 *to 5.000 x* 10^9	3,000 to 3,999 *3.000 x* 10^9 *to 3.999 x* 10^9	1,500 to 2,999 *1.500 x* 10^9 *to 2.999 x* 10^9	< 1,500 *< 1.500 x* 10^9
Fibrinogen, Decreased (mg/dL; *g/L*)	100 to < 200 *1.00 to < 2.00* OR 0.75 to < 1.00 x LLN	75 to < 100 *0.75 to < 1.00* OR ≥ 0.50 to < 0.75 x LLN	50 to < 75 *0.50 to < 0.75* OR 0.25 to < 0.50 x LLN	< 50 *< 0.50* OR < 0.25 x LLN OR Associated with gross bleeding
Hemoglobin[16], Low (g/dL; *mmol/L*)[17] *≥ 13 years of age (male only)*	10.0 to 10.9 *6.19 to 6.76*	9.0 to < 10.0 *5.57 to < 6.19*	7.0 to < 9.0 *4.34 to < 5.57*	< 7.0 *< 4.34*
≥ 13 years of age (female only)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
57 days of age to < 13 years of age (male and female)	9.5 to 10.4 *5.88 to 6.48*	8.5 to < 9.5 *5.25 to < 5.88*	6.5 to < 8.5 *4.03 to < 5.25*	< 6.5 *< 4.03*
36 to 56 days of age (male and female)	8.5 to 9.6 *5.26 to 5.99*	7.0 to < 8.5 *4.32 to < 5.26*	6.0 to < 7.0 *3.72 to < 4.32*	< 6.0 *< 3.72*
22 to 35 days of age (male and female)	9.5 to 11.0 *5.88 to 6.86*	8.0 to < 9.5 *4.94 to < 5.88*	6.7 to < 8.0 *4.15 to < 4.94*	< 6.7 *< 4.15*
8 to ≤ 21 days of age (male and female)	11.0 to 13.0 *6.81 to 8.10*	9.0 to < 11.0 *5.57 to < 6.81*	8.0 to < 9.0 *4.96 to < 5.57*	< 8.0 *< 4.96*
≤ 7 days of age (male and female)	13.0 to 14.0 *8.05 to 8.72*	10.0 to < 13.0 *6.19 to < 8.05*	9.0 to < 10.0 *5.59 to < 6.19*	< 9.0 *< 5.59*
INR, High (not on anticoagulation therapy)	1.1 to < 1.5 x ULN	1.5 to < 2.0 x ULN	2.0 to < 3.0 x ULN	≥ 3.0 x ULN
Methemoglobin (% hemoglobin)	5.0 to < 10.0%	10.0 to < 15.0%	15.0 to < 20.0%	≥ 20.0%
PTT, High (not on anticoagulation therapy)	1.1 to < 1.66 x ULN	1.66 to < 2.33 x ULN	2.33 to < 3.00 x ULN	≥ 3.00 x ULN
Platelets, Decreased (cells/mm^3; *cells/L*)	100,000 to < 125,000 *100.000 x 10^9 to < 125.000 x 10^9*	50,000 to < 100,000 *50.000 x 10^9 to < 100.000 x 10^9*	25,000 to < 50,000 *25.000 x 10^9 to < 50.000 x 10^9*	< 25,000 *< 25.000 x 10^9*
PT, High (not on anticoagulation therapy	1.1 to < 1.25 x ULN	1.25 to < 1.50 x ULN	1.50 to < 3.00 x ULN	≥ 3.00 x ULN
WBC, Decreased (cells/mm^3; *cells/L*) *> 7 days of age*	2,000 to 2,499 *2.000 x 10^9 to 2.499 x 10^9*	1,500 to 1,999 *1.500 x 10^9 to 1.999 x 10^9*	1,000 to 1,499 *1.000 x 10^9 to 1.499 x 10^9*	< 1,000 *< 1.000 x 10^9*
≤ 7 days of age	5,500 to 6,999 *5.500 x 10^9 to 6.999 x 10^9*	4,000 to 5,499 *4.000 x 10^9 to 5.499 x 10^9*	2,500 to 3,999 *2.500 x 10^9 to 3.999 x 10^9*	< 2,500 *< 2.500 x 10^9*

[16] Male and female sex are defined as sex at birth. For transgender participants ≥ 13 years of age who have been on hormone therapy for more than 6 consecutive months grade hemoglobin based on the gender with

which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

[17] The most commonly used conversion factor to convert g/dL to mmol/L is 0.6206. For grading hemoglobin results obtained by an analytic method with a conversion factor other than 0.6206, the result must be converted to g/dL using appropriate conversion factor for the particular laboratory

Urinalysis

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA
Hematuria (not to be reported based on dipstick findings or on blood believed to be of menstrual origin)	6 to < 10 RBCs per high power field	≥ 10 RBCs per high power field	Gross, with or without clots OR With RBC casts OR Intervention indicated	Life-threatening consequences
Proteinuria (random collection tested by dipstick)	1+	2+	3+ or higher	NA

Appendix A: Total Bilirubin Table for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Total Bilirubin[18], **High** (mg/dL; *µmol/L*)[19] ***Term Neonate***[20] *< 24 hours of age*	4 to < 7 *68.4 to < 119.7*	7 to < 10 *119.7 to < 171*	10 to < 17 *171 to < 290.7*	≥ 17 *≥ 290.7*
24 to < 48 hours of age	5 to < 8 *85.5 to < 136.8*	8 to < 12 *136.8 to < 205.2*	12 to < 19 *205.2 to < 324.9*	≥ 19 *≥ 324.9*
48 to < 72 hours of age	8.5 to < 13 *145.35 to < 222.3*	13 to < 15 *222.3 to < 256.5*	15 to < 22 *256.5 to < 376.2*	≥ 22 *≥ 376.2*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
72 hours to < 7 days of age	11 to < 16 *188.1 to < 273.6*	16 to < 18 *273.6 to < 307.8*	18 to < 24 *307.8 to < 410.4*	≥ 24 *≥ 410.4*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN
Preterm Neonate[20] *35 to < 37 weeks gestational age*	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).	Same as for ***Total Bilirubin, High, Term Neonate*** (based on days of age).
32 to < 35 weeks gestational age and < 7 days of age	NA	NA	10 to < 14 *171 to < 239.4*	≥ 14 *≥ 239.4*
28 to < 32 weeks gestational age and < 7 days of age	NA	NA	6 to < 10 *102.6 to < 171*	≥ 10 *≥ 171*
< 28 weeks gestational age and < 7 days of age	NA	NA	5 to < 8 *85.5 to < 136.8*	≥ 8 *≥ 136.8*
7 to 28 days of age (breast feeding)	5 to < 10 *85.5 to < 171*	10 to < 20 *171 to < 342*	20 to < 25 *342 to < 427.5*	≥ 25 *≥ 427.5*
7 to 28 days of age (not breast feeding)	1.1 to < 1.6 x ULN	1.6 to < 2.6 x ULN	2.6 to < 5.0 x ULN	≥ 5.0 x ULN

[18] Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

[19] A laboratory value of 1 mg/dL is equivalent to 17.1 µmol/L.

[20] Definitions: Term is defined as ≥ 37 weeks gestational age; near-term, as ≥ 35 weeks gestational age; preterm, as < 35 weeks gestational age; and neonate, as 0 to 28 days of age.

10.6. Appendix 6: CDC Classification for HIV infection (2014)

- Note that the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage in HIV infection stages 1, 2, and 3. The CD4+ T-lymphocyte percentage should only be considered if the count is missing.

- **HIV infection, stage 0**

- Indicates early HIV infection, inferred from a negative or indeterminate HIV test result within 180 days of a positive result. The criteria for stage 0 supersede and are independent of criteria used for other stages.

- **HIV infection, stage 1**

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of ≥500 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of ≥26%.

- **HIV infection, stage 2**

- Laboratory confirmation of HIV infection with no AIDS-defining condition, and
    - CD4+ T-lymphocyte count of 200 to 499 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of 14% to 25%.

- **HIV infection, stage 3 (AIDS)**

- Laboratory confirmation of HIV infection, and
    - CD4+ T-lymphocyte count of <200 cells/μL, or
    - CD4+ T-lymphocyte percentage of total lymphocytes of <14%, or
    - Documentation of an AIDS-defining condition (see below).

- Documentation of an AIDS-defining condition supersedes a CD4+ T-lymphocyte count of >200 cells/μL and a CD4+ T-lymphocyte percentage of total lymphocytes of >14%.

- **HIV infection, stage unknown**

- Laboratory confirmation of HIV infection, and
    - No information on CD4+ T-lymphocyte count or percentage, and
    - No information on presence of AIDS-defining conditions.

- **Stage-3-defining opportunistic illnesses in HIV infection**

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of oesophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary

- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 month's duration) or bronchitis, pneumonitis, or oesophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- Salmonella septicaemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV.

10.7. Appendix 7: Liver safety: actions, follow-up assessments, and study treatment guidelines

Table 11 Liver Chemistry Stopping Criteria: Required Actions and Follow up Assessments

Liver Chemistry Stopping Criteria	
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 total bilirubin ≥2xULN (>35% direct bilirubin)**
Cannot Monitor	**ALT ≥5xULN but <8xULN and cannot be monitored for 1 – 2 weeks**
Symptomatic[3]	**ALT ≥3xULN associated 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, Monitoring and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• Immediately discontinue study treatment • Report the event to the Medical Monitor **within 24 hours.** • Complete the liver event eCRF and complete an SAE data collection tool if	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;

Liver Chemistry Stopping Criteria	
the event also meets the criteria for an SAE[1]. • 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 treatment unless allowed per protocol and VSLC approval **is granted** (refer to Section 10.8.). • If restart is **not allowed or not granted**, permanently discontinue study treatment 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.	• 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 o 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). • Fractionate bilirubin, if total bilirubin ≥1.5xULN. • Obtain complete blood count with differential to assess eosinophilia. • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • International normalized ratio (INR)

Liver Chemistry Stopping Criteria	
	• Liver imaging (ultrasound, magnetic resonance, or computerized 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.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment 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. PK sample may not be required for participants known to be receiving placebo or non- ViiV/GSK standard-of-care treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. 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.

Table 12 Liver Chemistry Increased Monitoring Criteria With Continued Therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
• **Baseline ALT ≤1.5x ULN**: ALT ≥5x ULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity. • **Baseline ALT >1.5x ULN**: ALT ≥3x baseline and <5x baseline and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity	• Notify the Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return every 2 weeks for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolution or stabilization (ALT < 5xULN on 2 consecutive evaluations) • If at any time participant meets the liver chemistry stopping criteria, proceed as described above (Table 11)

10.8. Appendix 8: Liver Safety - Study Treatment Restart Guidelines

"Drug restart" can be approved by the VSLC for **defined non-drug-induced** liver injury if no evidence of:

- immunoallergic injury /HLA association with injury
- alcoholic hepatitis

Study treatment must be held while labs and evaluation are completed to assess diagnosis

10.8.1. Process to request VSLC approval for drug restart

- Principal Investigator (PI) requests consideration of study treatment restart for a participant stable or improving on study treatment , who has had liver chemistry elevation meeting participant stopping criteria, which is non-drug-related, and liver chemistries have improved.
- In setting of a definitive non-study-drug-related diagnosis (e.g., acute viral or syphilitic hepatitis), restart will be considered once ALT < 3x ULN (for participants with baseline ALT ≤1.5x ULN) or < 3x baseline ALT value (for participants with baseline ALT > 1.5x ULN).
- Medical Monitor to prepare slides presentation in power point including information as described in Table 14.
- Medical Monitor and Safety Physician to review the participant's diagnosis restart risk factors and complete checklist (Table 13).
- Relevant physicians (listed below) must review and agree on action to be taken regarding request for drug restart:
    - Safety Review Team Leader
    - Safety Development Leader or Senior Safety Physician
    - Clinical Development Lead
    - Global Medical Lead
- Request is taken to VSLC for final decision. The VSLC Chair may approve the restart Out of Committee or request that the team bring the case for discussion at the next VSLC meeting. VSLC may request additional information on the case to inform the decision on whether to restart and may request future updates on the case.

Table 13 Checklist for requesting VSLC approval for study treatment restart

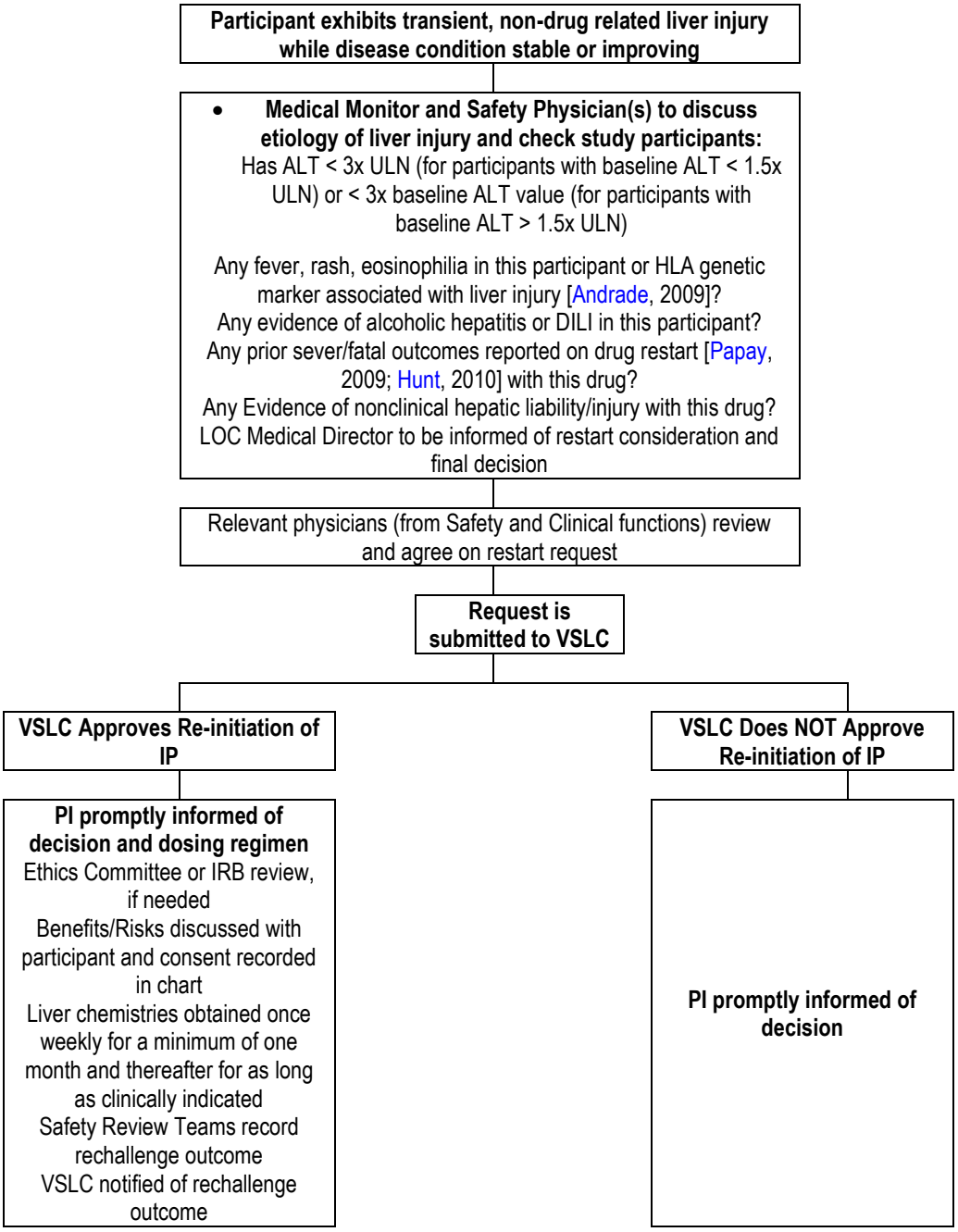
	Yes	No
Is there an alternative explanation for the liver event ?		
Do not restart if the following risk factors at initial liver injury:		
fever, rash, eosinophilia, or hypersensitivity		
drug-induced liver injury		
alcoholic hepatitis (AST>ALT, typically <10x ULN)		
IP has an HLA genetic marker associated with liver injury (e.g. lapatinib, abacavir, amoxicillin/clavulanate)		
Source data defining the participant's current resistance profile		
History of DILI with this IP		

Table 14 Minimum Information required from medical monitor and investigator to be included in presentation for VSLC to consider IP restart (any request type, i.e. out of committee or VSLC meeting)

CRF data or investigator's reports	Specifications	Date/duration
Study and participant numbers	NA	NA
Demographics	Age, gender, Country and ethnic group	NA
Participant's ARV	Description of current ARVs	Enrolment date
Concomitant medications	Relevant medications, including acetaminophen, vitamins and herbal supplements,	At time of liver event and ongoing
Participant's clinical conditions	Asymptomatic or describe symptoms	At liver event and current
Relevant medical history	CRF/investigator report	NA
Laboratory data *		
HIV RNA VL	Either table or text	At enrolment and at liver event
CD4 count	Either table or text	At enrolment and at liver event
Liver function tests (ALT, AST Alkaline phosphatase, Bilirubin total and fractionated)	In a separate table	Since Day 1 and all or most study visits including monitoring follow up
Liver panel specific tests (All)*	Either table or text	Available tests at enrolment and at LE
Question for VSLC	Formulate question in separate slide	NA

*Liver panel tests included in appendix

Figure 2 VSLC process for drug restart approval or disapproval



Medical Monitor and PI actions for restart following VSLC decision

- 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.
- The Safety Review Team must record restart outcomes and the Safety Physician must send these to the VSLC (see table template below).

- All severe reactions (associated with bilirubin >2x ULN or jaundice, or INR ≥ 1.5), SAEs or fatalities which occur following a drug restart must be immediately reported to sponsor line management, including: VSLC Chair (Chief Medical Officer), accountable Vice President from Research and Development (e.g., Head of Clinical Development or Global Research Strategy) and Head of Safety (who will inform European Union Qualified Person for Pharmacovigilance if relevant).

Table 15 Study treatment restart outcomes table template

Protocol	Participant ID	Restart? [Yes/No]	Safety outcome*	Drug benefit

*** 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

Actions to be taken by the Principal Investigator

- The PI must obtain Ethics Committee or Institutional Review Board approval of study treatment restart, as required.
- If VSLC approves restart, the participant must sign a new informed consent form containing a clear description of possible benefits and risks of study treatment administration including recurrent, more severe liver injury or possible death. An ICF specific to study treatment restart must be used.
- The participant's informed consent must be recorded in the study chart, and the study treatment administered at agreed dose, as communicated by Medical Monitor.
- Liver chemistries must be once weekly for 'restart' cases for a minimum of one month and thereafter for as long as clinically indicated following study treatment restart; laboratory monitoring may then resume as per protocol. Longer durations of close monitoring may be required for LA study treatment.
- If participant exhibits protocol-defined liver chemistry elevations, study treatment should be discontinued as per protocol specifications.

- Medical Monitor and the Ethics Committee or Institutional Review Board must be informed of the participant's outcome (0-4, as outlined above) following restart. Medical Monitor must then inform VSLC.

10.9. Appendix 9: Contraceptive and barrier guidance

10.9.1. Definitions

Women in the following categories are considered **WOCBP (fertile)** if they meet any of the below criteria:

- Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.
- From the time of menarche until becoming postmenopausal unless permanently sterile (see below).

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

Women in the following categories are considered **WONCBP (non-fertile)**:

1. Premenarchal: Tanner stage 1 (prepubertal)
2. Permanently sterile due to one of the following procedures:
    a. Documented hysterectomy
    b. Documented bilateral salpingectomy
    c. Documented bilateral oophorectomy

For permanently sterile individuals due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry. If reproductive status is questionable, additional evaluation should be considered.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is recommended.

- Females on HRT whose menopausal status is in doubt and who wish to continue their HRT during the study, should be recommended to use an appropriate form of contraception compatible with their HRT (see Section 5.3.2).

10.9.2. Contraception guidance

The following is an all-inclusive list of study-sanctioned methods of acceptable contraception, including:

- highly effective methods that meet the ICH, M3(R2) and Clinical Trial Facilitation Group (CTFG) definition of highly effective (i.e., have a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label).
- effective contraceptives, which are not necessarily highly effective, as outlined in the CTFG guidance.

The list would not apply to WOCBP with same-sex partners or for participants who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis during the entire period of risk with the study treatment, when this is their preferred and usual lifestyle.

Note: Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal, spermicides only, and lactational amenorrhea method (LAM) are **not** acceptable methods of contraception.

Table 16 List of study-sanctioned contraceptive methods

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• *Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]*
• *Intrauterine device (IUD)*
• *Intrauterine hormone-releasing system (IUS)[c]*
• *Bilateral tubal occlusion*
• *Azoospermic partner (vasectomized or due to a medical cause)* *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the individual 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.* *Note: documentation of azoospermia for a cis-male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*
Highly Effective Methods[b] That Are User Dependent
• *Combined (estrogen- and progestogen-containing) hormonal contraception associated with*

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
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 treatment. 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*
Effective Methodsc That Are Not Considered Highly Effective Failure rate of ≥ 1% per year when used consistently and correctly.
• *Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action* • *Male or female condom with or without spermicided* • *Cervical cap, diaphragm, or sponge with spermicide* • *A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)*
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.* *c. Considered effective, but not highly effective - failure rate of ≥1% per year.* *d. Male condom and female condom should not be used together (due to risk of failure from friction).* *Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction)*

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

10.10. Appendix 10: Pregnancy: information and guidance for managing pregnant participants

10.10.1. Introduction

- Pregnancy increases the risk of HIV progression, while HIV increases the risk for maternal complications from pregnancy and poses the risk of perinatal HIV transmission to the unborn fetus. Mother to child transmission (MTCT) of HIV can occur during pregnancy, labor, delivery or postpartum through breastfeeding. In the absence of any treatments, vertical HIV transmission rates approximate 35%, but fall below 5% with effective treatments [WHO, 2010]. In the United States and other developed countries, the risk of perinatal infection has decreased from 25% without treatment to less than 2% with treatment [WHO, 2012]. The HIV-positive mother who breastfeeds her infant while taking ARVs herself or giving ARVs to her infant reduces the risk of transmission to about 2% after 6 months of breastfeeding, or 4% over 12 months [UNAIDS, 2011].
- The WHO Guidelines thus recommend (strong recommendation, moderate-quality evidence) all pregnant and breastfeeding women with HIV should initiate triple ARVs (ART), which should be maintained at least for the duration of mother-to-child transmission risk. Women meeting treatment eligibility criteria should continue lifelong ART [WHO, 2021]. The global benefits anticipated from ART in pregnant women who are eligible for treatment include treatment of the mother's underlying HIV disease, eliminating pediatric transmission/infection and reducing sexual transmission of HIV.
- Recent recommendation updates to treatment guidelines have included objectives to increase HIV screening of patients, including pregnant women (noting the importance of adopting HIV screening to be a part of prenatal care).
- The ART recommendation for pregnant females prioritizes the health of women over potential risks and increased cost. For females who are on ARV therapy at the time that they become pregnant, the WHO recommends that they continue such therapy if they are responding to the ARV.
- In line with this recommendation, this study will allow participants that become pregnant on study to continue in the study, in order to maintain their effective regimen with minimal disruption. Pregnant participants can remain in the study and continue to receive study treatment, provided that the conditions and requirements outlined in Section 8.4.6 have been met (including the signing of a pregnancy-specific study ICF addendum).
- Safety and pregnancy outcomes (including maternal, birth and neonate outcomes) following treatment with the study treatments will be monitored.

10.10.1.1. Rationale for continued use in pregnancy

DTG/3TC

Although preliminary data (as of May 2018) from an ongoing birth surveillance study in Botswana suggested an association between NTDs and DTG exposure at the time of conception, updated results from this study, including over 9,000 pre-conception exposures to DTG at conception, show no statistically significant difference in the prevalence of these defects between regimens with and without DTG [Zash, 2022]. The APR assessing the effect of HIV drugs on pregnancy outcome has received reports of over 1200 exposures to dolutegravir during pregnancy resulting in live births, as of July 2022. Available data from the APR do not show an increased risk of major birth defects for DTG or 3TC compared to the background rate. In light of all the currently available data, participants who become pregnant whilst on study who are taking DTG/3TC will be offered the choice of whether to continue in the study on DTG/3TC in order to maintain their effective regimen with minimal disruption, or switch to an alternative antiretroviral regimen.

A consideration is that women who become pregnant while taking DTG/3TC will have already been exposed to DTG and 3TC during early pregnancy and switching to another regimen, which will likely comprise 3 or more different antiretrovirals, will potentially add to the risks.

10.10.1.2. Action to be taken if pregnancy occurs

- Any pregnancy that occurs during study participation must be reported using the Sponsor's (or CRO designee's) pregnancy reporting form. The Investigator should inform the Sponsor (or CRO designee) within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.3.7.7.
- Pregnant participants can remain in the study and continue to receive study treatment, provided that the conditions and requirements outlined in Section 8.4.6 have been met (including the signing of a pregnancy-specific study ICF addendum).
- Pregnant study participants who consent to remain in the study whilst pregnant will continue to have all clinical assessments (except for pregnancy tests) performed as per the SoA; see Section 10.10.5 further below for details. Additionally, as per treatment guidelines in the context of pregnancy [DHHS, 2023], pregnant participants continuing DTG/3TC post Week 12 study visit should be requested to return for additional unscheduled visits every 6 weeks (+/- 2 weeks) to perform plasma HIV-1 RNA and clinical chemistry assessments, to enable more frequent monitoring in between the study visits scheduled every 3 months or longer. AEs, SAEs, and concomitant medications should also be reported at these unscheduled visits.
- While pregnancy itself is not considered 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 will be reported as such; refer to Section 10.3.7.7.

- 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 treatment, must be promptly reported to the Sponsor (or CRO designee).

ViiV Healthcare/GSK will forward information about any on-study pregnancy and pregnancy outcomes to the Antiretroviral Pregnancy Registry (APR). This international registry is jointly sponsored by manufacturers or licensees of ARV products. Additional information and a list of participating manufacturers/licensees are available from: http://apregistry.com.

10.10.2. Benefit/risk assessment

The Investigator should discuss with the pregnant participant the benefit-risk of continuing in the study and continuing to receive DTG/3TC or being withdrawn from study, as a result of the pregnancy.

10.10.2.1. DTG/3TC

Refer to Section 10.10.1.1 and the DTG IB for additional information regarding the safety of DTG/3TC in pregnancy.

10.10.3. Clinical considerations

Use of supplements with study medications

During pregnancy, additional supplements including vitamins, minerals and other mediations including over the counter (OTC) medications may be prescribed to the pregnant participant. It is important for all pregnant participants who remain in the study to be aware of any potential DDIs that may occur with study medications and other agents used during pregnancy.

10.10.4. Overall benefit-risk conclusion

- All medications have AE profiles that must be assessed prior to use, allowing for an appropriate benefit-risk assessment. In the event of pregnancy, the benefit-risk of continuing the study treatment should be discussed with the participant.
- Updated results from an ongoing birth surveillance study in Botswana, including over 9,000 pre-conception exposures to DTG at conception, show no statistically significant difference in the prevalence of NTDs between regimens with and without DTG [Zash, 2022].
- Given the risk/benefit ratio for DTG/3TC dosing in WOCBP, coupled with concerns of increasing fetal exposure to several additional ARVs upon participant withdrawal, pregnant participants will be allowed to remain in the study and continue to receive study treatment, provided that the conditions and requirements outlined in Section

8.4.6 have been met (including the signing of a pregnancy-specific study ICF addendum).

- In summary, the potential risks identified in association with study treatments are justified by the anticipated benefits that may be afforded to pregnant participants living with HIV.

10.10.5. Study assessments and procedures specific to pregnant participants

- Participants who become pregnant while in the study, and who sign the pregnancy-specific ICF addendum may remain in the study and continue to receive DTG/3TC.
- **Note:** The HIV care provider is responsible for HIV care and will collaborate and share information with the participant's obstetric care provider, discuss the participant's participation in this study, the necessary procedures at delivery, to share HIV information, and to collect birth and infant outcomes from the participant's obstetric care provider and/or the pediatric health provider for the infant.
- Because obstetric and/or pediatric care will not be specifically provided via this study, the participant must also establish appropriate obstetric and pediatric care (including prenatal care) per local standard of care (SOC) in parallel. It may be necessary for the participant to provide a release of medical information to facilitate collection of pregnancy and pregnancy outcomes by the Investigator.
- All assessments will be conducted in accordance with the protocol, as described in the protocol in the SoA with additional unscheduled visits described in Section 10.10.1.2.
- When assessing routine laboratory results for potential drug toxicity, Investigators should take into consideration the effect pregnancy may have on laboratory values, in particular, liver enzymes and renal function. Considerations around liver stopping criteria should occur in conjunction with reference ranges for laboratory values in pregnancy and in consultation with an obstetrician. There are a number of pregnancy related conditions that can affect liver enzymes and the investigation and management of pregnant participants with abnormal liver enzymes requires a multi-disciplinary approach to optimize the safety of both the pregnant participant and the unborn child.

10.10.5.1. Plasma HIV-1 RNA

Women who become pregnant while on study and consent to stay on study will have plasma HIV-1 RNA testing obtained at every study visit during pregnancy, at every 6 weeks (+/-2 weeks) unscheduled visits post-Week 12 study visit and at the first post-partum visit.

10.10.5.2. Safety assessments

Pregnancy related complications and diagnoses, and outcomes will be captured as AEs and SAEs as outlined in the protocol in Section 10.3.7.7.

In the event of a pregnancy loss, after the loss is confirmed the participant may continue to receive study medications unless they meet criteria for discontinuation of study treatment. They may continue study treatment until these are locally approved and commercially available or until they no longer receive benefit.

10.11. Appendix 11: Child-Pugh Classification

A participant is classified with mild hepatic impairment (Class A) if their overall sum of scores is 5-6 points, moderate hepatic impairment (Class B) if their overall sum of scores is 7-9 points, and severe hepatic impairment (Class C) if their overall sum of scores is 10-15 based on the Child-Pugh system [Pugh, 1973] scoring described in the following table (Table 17). For participants requiring anticoagulation therapy, discussion with the study medical monitor will be required.

Table 17 Child-Pugh System

Finding	Points Scored for Each Observed Finding		
	1	2	3
Encephalopathy Grade[1]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin, SI units (µmol/L), Serum bilirubin, conventional units (mg/dL)	<34 <2	34 to 52 2 to 3	>52 >3
Serum albumin, SI units (g/L) Serum albumin, conventional units (mg/dL)	>35 >3.5	28 to 35 2.8 to 3.5	<28 <2.8
Prothrombin Time (seconds prolonged) or INR	<4 <1.7	4 to 6 1.7 to 2.3	>6 >2.3

1. Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity
[Pugh, 1973; Lucey, 1997]

10.12. Appendix 12: Protocol Recommendation for Assessment of Waist Circumference, Hip Circumference and Weight (Adapted from WHO STEPS Surveillance Manual, 2017) and for Resting Blood Pressure

[WHO, 2017]

10.12.1. Waist Circumference

Equipment

To take waist circumference measurements you will need a:

- Constant tension tape (for example, Figure Finder or Myo Tape Body Tape Measure);
    - Tape measures will be provided for the study
- Chair or coat stand for participants to place their clothes.

Privacy

A private area is necessary for this measurement. This could be a separate room, or an area that has been screened off from other people.

Preparing the participant

This measurement should be taken without clothing, meaning, directly over the skin.

If this is not possible, the measurement may be taken over light clothing (for example, a hospital gown, an undergarment or thin t-shirt). Thick or bulky clothing must be removed. Body shaping garments are not allowed to be worn during this measurement.

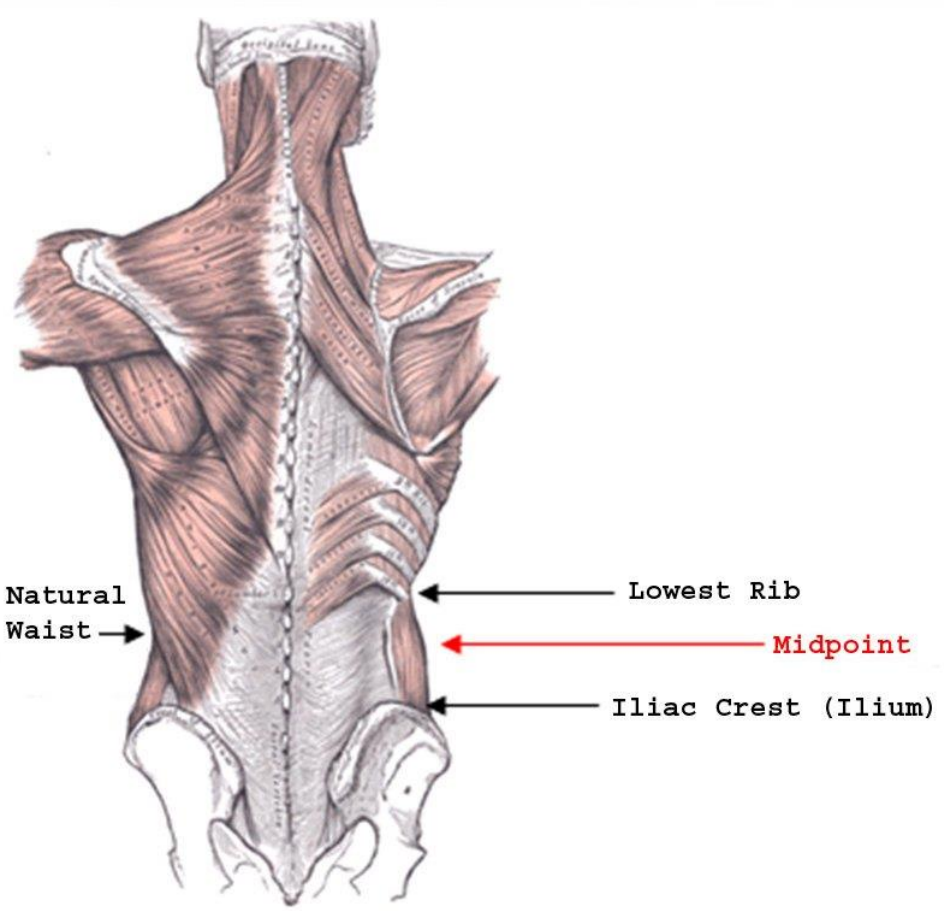
How to take the measurement

We recommend having the same study staff performing the measurement across visits for individual study participants.

This measurement should be taken:

- at the end of a normal expiration;
- with the arms relaxed at the sides;
- at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (hip bone).

Figure 3 Location of Midpoint for Waist Circumference Measurement



Procedure

Follow the steps below to measure the waist circumference of a participant:

1. Standing to the side of the participant, locate the last palpable rib and the top of the hip bone. You may ask the participant to assist you in locating these points on their body.
2. Wrap the tension tape around the participant and position the tape at the midpoint of the last palpable rib and the top of the hip bone, making sure to wrap the tape over the same spot on the opposite side.

   Note: Check that the tape is horizontal across the back and front of the participant and as parallel with the floor as possible.
3. Ask the participant to:
   - stand with their feet together with weight evenly distributed across both feet;
   - hold the arms in a relaxed position at the sides;
   - breathe normally for a few breaths, then make a normal expiration.

4. Measure waist circumference and read the measurement at the level of the tape to the nearest 0.1 cm, making sure to keep the measuring tape snug but not tight enough to cause compression of the skin.
5. Record the measurement, in **centimeters to one decimal place**, within the eCRF.

Note: Measure once and record.

10.12.2. Hip Circumference

Equipment

To take hip circumference measurements you will need a:

- Constant tension tape (for example, Figure Finder or Myo Tape Body Tape Measure);
    - Tape measures will be provided for the study
- Chair or coat stand for participants to place their clothes.

Privacy

A private area is necessary for this measurement. This could be a separate room, or an area that has been screened off from other people. Hip measurements are taken immediately after waist circumferences.

Preparing the participant

This measurement should be taken without clothing, that is, directly over the skin.

If this is not possible, the measurement may be taken over light clothing (for example, a hospital gown, an undergarment). Thick or bulky clothing must be removed. Body shaping garments are not allowed to be worn during this measurement.

How to take the measurement

We recommend having the same study staff performing the measurement across visits for individual study participants.

This measurement should be taken:

- with the arms relaxed at the sides
- at the maximum circumference over the buttocks.

Procedure

Follow the steps below to take hip circumference measurements.

1. Stand to the side of the participant and wrap the tension tape around them.
2. Position the measuring tape around the maximum circumference of the buttocks.
3. Ask the participant to:
    - Stand with their feet together with weight evenly distributed over both feet;
    - Hold their arms relaxed at the sides.
4. Check that the tape position is horizontal all around the body and snug without constricting.
5. Measure hip circumference and read the measurement at the level of the tape to the nearest 0.1 cm.
    - Record the measurement, in **centimeters to one decimal place**, within the eCRF.

Note: Measure once and record.

10.12.3. Weight

Equipment

To measure weight, you will need a weighing scale, (such as a SECA scale or the Tanita HS301 Solar Scale). Alternatively, a BMI scale measuring both height and weight (e. g. Growth Management Scale) can be used.

Ensure the scale has been regularly calibrated according to the manufacturer instructions and that calibration documentations are filed and available to the study CRA as required.

We recommend using the same scale across visits for individual study participants.

We recommend having the same study staff performing the measurement across visits for individual study participants.

We recommend that the time of day a participant's weight is measured is consistent for every participant at the site within the study. (ex. If measured at 10 a.m. at initial measurement, attempt to have the participant measured at 10 a.m. at subsequent visits).

Set up requirements

Make sure the scales are placed on a firm, flat surface. Do not place the scales on:

- carpet
- a sloping surface
- a rough, uneven surface.

Set up scales

Follow the steps below before measuring the weight of a participant:

1. Make sure the scale is on a firm, flat surface.
2. Turn on the scale and wait until the display shows 0.0.

Procedures

Follow the steps below to measure the weight of a participant:

1. Ask the participant to remove their footwear (shoes, slippers, sandals, etc.). They should also take off any heavy belts and remove all objects out of their pockets (example: mobile phones, wallets, coins).
2. Ask the participant to step onto scale with one foot on each side of the scale.
3. Ask the participant to:
    - stand still
    - face forward
    - place arms on the side and
    - wait until asked to step off.
4. Record the weight in **kilograms to one decimal place** in the eCRF.

10.12.4. Resting Blood Pressure

General instructions

- Ensure that healthcare professionals taking blood pressure measurements have adequate initial training and periodic review of their performance.
- Healthcare providers must ensure that devices for measuring blood pressure are properly validated, maintained and regularly recalibrated according to manufacturers' instructions.
- When measuring blood pressure in the clinic or in the study site, standardize the environment and provide a relaxed, temperate setting, with the person quiet and seated, and their arm outstretched and supported. Use an appropriate cuff size for the person's arm.
- Measure the blood pressure in one arm (after 5 minutes rest in semi-supine* position).

*Semi-supine position: Laying /sitting back (at 45° angle or variations) in a relaxed position with feet touching a flat surface.

10.13. Appendix 13: COVID-19 Pandemic and Clinical Trial Continuity

Background

The COVID-19 pandemic presented significant logistical challenges for many clinical sites around the world, with variable restrictions being placed on site resources and operations, and on individual participants' ability to attend clinic visits. In some places, medical visits were occurring, and in others, research clinics were operating with only emergency staff. With the advent of effective vaccinations and antivirals against SARS-CoV-2, the impact of the COVID-19 pandemic has lessened in many parts of the world. However, recognising the ongoing uncertainty of the pandemic, including the emergence of new viral variants and COVID-19 outbreaks occurring regionally, it is still necessary to maintain measures and procedures to protect participant safety, and to ensure that there are no gaps in HIV-1 treatment for study participants through continuous access to ART.

In order to maintain the scientific integrity of the study, and adhere to relevant guidance from regulators, procedures have also been put into place to ensure that the actions taken to mitigate against any impact of COVID-19 are well documented in the trial database.

This appendix outlines the measures which are approved for implementation within this clinical study, to protect participant safety and to ensure the integrity of the clinical trial, as a result of COVID-19 only. These measures may be implemented in accordance with any requirements and expectations set out by local Independent Review Boards/Independent Ethics Committees and National Competent Authorities, as necessary.

10.13.1. Changes to Study Visits and Study Procedures

- When site staff resources are limited due to COVID-19, abbreviated study visits may proceed without conducting all protocol-specified additional assessments (e.g. lab tests, questionnaires, etc.). If laboratory testing will be missed for more than one consecutive visit, medical monitor pre-notification is required, and all efforts should be made to find alternative approaches for lab testing.
- Consider alternative travel options for participants, if possible.
- 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 authorized/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 participant 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.
- 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 (CA)/IRB/IEC regulations.

10.13.2. 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 the participant sending a picture of his/her written consent to the investigator, or the investigator contacting the participant by telephone or video call and obtaining verbal consent, supplemented with email confirmation.

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.

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

10.13.3. Direct-to-patient (DTP) shipment of oral ART

If a participant is unable to travel to the clinic, to receive Study Treatment, sites are encouraged to consider DTP shipments of DTG/3TC study treatment, from the site, to the participant, to ensure access to medicines.

- If the study site is considering DTP shipment of DTG/3TC, the site must first verify if DTP 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. At no point will any member of the Sponsor/CRO study team have access to any personal identifiable information for any of the participants or have any direct involvement of DTP shipping, where DTP shipment of study treatment is being considered.
- DTG/3TC can be shipped at ambient temperatures via ground transport without a temperature monitoring device, with low risk of temperature excursions. Sites are encouraged to use discretion in determining the need for in-transit temperature monitoring based on the labelled storage requirements and the planned mode of transport and apply this as appropriate. Shipment of DTG/3TC via air courier continues to require appropriate temperature monitoring.
- In all cases, IP accountability must be maintained, and all DTP dispensing documentation should be reflected in source records and dispensing logs per GCP.
- Please refer to your CRA or local study manager for support with the DTP process, ensuring reference to current sponsor guidance and arrangement of a courier that can support shipment of IMP directly to participants.

10.13.4. COVID-19 therapeutic agents

If any treatments for COVID-19 are planned for a study participant, please consult with the study Medical Monitor to ensure that relevant drug interactions are considered and to ensure that continued study participation remains appropriate.

10.13.5. COVID-19-specific data capture

10.13.5.1. Capturing COVID-19-specific protocol deviations

In order to summarise the impact of COVID-19 in a systematic way and in line with regulatory authorities' recommendations, any participant-level deviation from normal study procedures related to COVID-19 will be documented as a protocol deviation. This will include the permissible actions summarized in this Appendix, which are taken to protect participant safety, including missed visits and assessments as a result of logistical challenges resulting from COVID-19.

Any protocol deviations resulting from COVID-19 will be clearly identified as such within the protocol deviation description and summarised separately.

10.14. Appendix 14: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC.

Amendment 01 (10 May 2023)

This amendment was considered substantial because it significantly impacted the conduct or management of the trial.

Overall rationale for the Amendment 01:

The primary reason for Protocol Amendment 1 was to introduce more regular follow-up of pregnant study participants who opt to remain on study to align with clinical management guidelines for pregnancy.

Further changes and clarifications were made as outlined below:

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
Appendix 10, Section 10.10.1.2. Action to be taken if pregnancy occurs	Addition of new unscheduled visits requested to be performed every 6 weeks (±2 weeks) post Week 12 for pregnant participants for plasma HIV-1 RNA and clinical chemistry assessments and collection of AEs, SAEs and concomitant medications.	Alignment to HIV treatment guidelines in the context of pregnancy.
Appendix 10, Section 10.10.5. Study assessments and procedures specific to pregnant participants	Addition of cross-reference to Section 10.10.1.2	Cross-reference to new unscheduled visits for pregnant participants.
Appendix 10, Section 10.10.5.1. Plasma HIV-1 RNA	Addition of the every 6 weeks (+/-2 weeks) unscheduled visits post-Week 12.	Alignment to HIV treatment guidelines in the context of pregnancy.
Appendix 10, Section 10.10.1.1: Rationale for	Additional sentence on the Antiretroviral Pregancy Registry (APR) available data on	Complement the information on available data on dolutegravir use

Section # and title	Description of change	Brief rationale
continued use in pregnancy	dolutegravir use during pregnancy.	in pregnancy and risk of birth defect.
Section 1.3: Schedule of activities	Removal of the requirement to perform Baseline ECG in triplicates.	Deemed not required.
Section 8.4.6.1: Collection of pregnancy information	Addition of new language encouraging Investigators to report pregnancies directly to the APR.	Alignment to current Sponsor operating procedures.
Section 3 Table 2: Objectives and Endpoints and Section 8.13: Implementation Science Interventions and assessments	Objective limited to participating countries. Edits to paragraph 1 of Strategy 2 in Section 8.13.	Restriction of the use of the Liverpool Combined Comorbidity Risk Calculator in countries where it is not considered a medical device (US, Canada, Mexico and the UK).
Appendix 4, Section 10.4: Toxicity Management	Deletion of 4th paragraph on Abacavir containing product	Correction as not applicable for this study
Appendix 13 Section 10.13.5.1. Capturing COVID-19-specific protocol deviations	Removal of reference to 'oral bridging'	Correction as not applicable for the study.
Appendix 13 Section 10.13.5.2. Capturing COVID-19-specific AEs and SAEs	Removal of this subsection.	Alignment to current Sponsor operating procedures.
Throughout the document	Typographical edits	Typographical edits

Amendment 02 (12 October 2023)

Overall rationale for Amendment 02: The primary reason for Protocol Amendment 02 was to address regulatory request to amend exclusion criterion 23.

This amendment was considered substantial based on the criteria defined in EU Clinical Trial Regulation No 536/2014 of the European Parliament and the Council of the European Union because it significantly impacts the safety of participants.

Section # and title	Description of change	Brief rationale
Section 1.3 Table 1	Addition of a footnote 'u' to highlight that qualitative interviews are restricted to the UK, Canada and US.	To address the request to remove qualitative interviews in European Countires.
Section 4.2: Scientific rationale for study design	Removal of reference to aquate power of the study.	This is not relevant in this section and statistical properties of the study are described in detail in Section 9.5.
Section 8.1.3	Removal of text "During the Screening period all participants will be offered to opt in to the use of a participant wearable (Actigraph) for a duration of 14 days to collect pre-switch information."'	This was removed as this is not relevant in this section, as it relates to an optional, non-clinical assessment, limited to certain countires. This is fully described elsewhere in the protocol (Section 8.12 and Section 8.13).
Section 8.12: Value evidence and outcomes	The text has been clarified to ensure (1) It is clear that the section relates to patient and provider data collection, and which instruments are used by whom. (2) That each survey provides unique insights not provided by other instruments (3) That qualitative interviews are only to be conducted in the US, Canada and UK. (4) That qualitative interviews provide a deeper understanding of the areas studies that quantitative data cannot provide.	This is a response to feedback provided that suggested (1) confusion between the surveys and interviews, and whom these related to. (2) a request to explain why all surveys are required (3) To address the request to remove qualitative interviews in European countries. (4) To justify the retention of qualitative interviews in some non-European countries.
8.13 Implementation Science Interventions and assessments	Addition of text and a footnote to highlight that qualitative interviews are restricted to the UK, Canada and US.	To address the request to remove qualitative interviews in European Countires.
Section 9.1.1: Multiplicty adjustment	Claification of subgroup analyses.	To claify that subgroup analyses are exploratory.
Section 9.2: Analysis sets	Updated wording for enrolled population	Using 'treated' for explanation of enrolled population more appropriate than 'needed'.
Section 9.3.4.1: Secondary Analyses	Additional information included about subgroup analyses	To state that due to the low number of expected VF events, subgroup

Section # and title	Description of change	Brief rationale
		analyses will be conducted on the seconday endpoint of VS.
Section 9.5: Sample size determination	Clarification of sample size determination	To add that the sample size allows for estimation of the effects of switching to DTG/3TC from BIC/F/TAF in important under-represented populations
Section 9.5.1: Sample size sensitivity	Removal of VF endpoint for the subgroups analysis and clarification on interpretation of subgroups results. And updated Section Title for clarification.	Expected to be very few VF events and thus a subgroup analysis of this small number of events may not be clinically meaningful..
Section 5.2; exclusion criterion #23 (Participants who are currently participating in or anticipate to be selected for any other interventional study after randomization unless previously approved by the study medical monitor (considerations include participant's ability to attend all visits on schedule, and possible drug and study procedure compatibility).	Removal of "after randomization unless previously approved by the study medical monitor (considerations include participant's ability to attend all visits on schedule, and possible drug and study procedure compatibility)." From criterion #23.	Request from the European Medical Agency to align with current directives.
Section 8.4.1 Time period and frequency for collecting AE, SAE, and other safety information	Timing of reporting of AEs was corrected to be from the start of study treatment and not from screening.	To clarify the correct timing of reporting of AEs (this was previously correct in the SOA).
Section 10.1.5 Data Protection	The following text was added to the Section: "GSK has a global, internal policy that requires all GSK staff and complementary	In response to Regulatory review requesting more details on measures taken in case of data breaches.

Section # and title	Description of change	Brief rationale
	workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws."	
New Section 10.14 Appendix 14	New appendix to describe the summary of historical changes of the prior protocol amendment.	This appendix was added to capture the previous protocol amendment 01 changes.
Throughout the document	Minor administrative Changes and typographical edits	Minor administrative Changes and typographical edits

Amendment 03 (30 September 2024)

Overall rationale for Amendment 03:

The 219516 (Eyewitness) study has observed a higher than expected rate of HIV-1 RNA Viral Load (VL) elevations (VL ≥50 c/mL), specifically in the low level range (VL 50-200 c/mL) as detected by the central lab, using the Roche Cobas® HIV-1 RNA quantitative assay on the Cobas® 6800 system. This has resulted in a higher than expected number of participants meeting protocol-defined virologic management and withdrawal criteria compared to previous pivotal DTG/3TC stable switch studies, 204862 (TANGO) and 208090 (SALSA), which utilized the Abbott RealTime HIV-1 assay. These observations prompted internal investigations to identify root causes and to ensure maintenance of study participant safety and data integrity. The most likely explanation appears to be increased variability, and increased sensitivity to proviral DNA coamplification, of the Roche Cobas® HIV-1 RNA quantitative assay on the Cobas® 6800 system relative to the Abbott RealTime HIV-1 assay.

As a result of this investigation, updated HIV-1 RNA sample handling and processing guidance (aimed to decrease proviral DNA introduction and coamplification) was instituted globally to study sites, and the global protocol amendment (PA) 03 is being implemented to ensure study data integrity. The PA 03 will include the following notable updates:

1. Remove the Precautionary Virologic Withdrawal (PVW) criteria, which requires participant withdrawal based on a maximum of 3 consecutive low-level viral loads between 50 and 200 c/mL (per Section 7.1.2 of PA 02). Historical inclusion of PVW criteria is based on more conservative virologic management criteria initially utilized for the pivotal 2 drug-regimen (2DR) stable switch studies (i.e., TANGO and SALSA) and are no longer necessary given the available efficacy data for DTG/3TC. Removing PVW criteria while also modifying the Confirmed Virologic Withdrawal (CVW) criteria, as described below, will reduce the risk of clinically unnecessary retesting burden and study withdrawal, as required under the current PA 02.
2. Modify the current CVW criteria, which requires participant withdrawal based on a viral load ≥200 c/mL preceded by a viral load ≥50 c/mL (per Section 7.1.2 of PA 02), to withdrawal after 2 consecutive viral loads ≥200 c/mL. This will better align participant virologic management in the study with current clinical practice and guideline recommendations, which define virologic failure as the inability to achieve or maintain suppression of viral replication to HIV-RNA level <200 c/mL (DHHS, 2024).
3. Implement an optional observational sub-study for participants who withdraw from the main study due to virologic concerns (e.g., baseline viral resistance, virologic withdrawal criteria, lack of efficacy). Participants withdrawn for any other reason, who have also been impacted by virologic-management related concerns during participation in the main study, may also be considered to participate in the sub-study. Participants who have already been withdrawn from the main study prior to the implementation of PA 03 may be eligible. This sub-study will permit additional efficacy and safety data collection, up to 6 months post-withdrawal from the main study, on post-study ART regimen(s). This will provide a more complete dataset to understand the study results and inform the scientific community.
4. Implement an internal safety review committee (iSRC) to further monitor participant safety and data integrity given the ongoing investigations and changes to virologic management and withdrawal criteria in PA 03.
5. Remove the Week 24 interim analysis, which was to be completed after the last participant evaluable completed the Week 24 visit or prematurely discontinued from the main study. The purpose of the Week 24 interim analysis was to allow early dissemination of study data prior to the Week 48 primary analysis. However, given the number of unexpected and unexplained reports of increased HIV-1 RNA viral load elevations, significant effort was made toward ensuring participant safety on study and preserving study integrity which required deferral of Week 24 interim analysis activities to permit conduct of a root cause investigation. The primary analysis is still planned to be completed after the last participant evaluable completes the Week 48 visit or prematurely discontinues from the study.

Further changes and clarifications were made as outlined below:

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
1.2. Schema	Updated safety follow-up visit indications.Reference to the Week 24 interim analysis was removed. Minor typographical updates.	To align with updates in Section 4.4.1. To align with updates in Section 9.4. Clarification.
1.3. Schedule of activities	Updated safety follow-up visit indications. Added a +6 week window around the baseline fibroscan.	To align with updates in Section 4.4.1. Clarification.
3. Objectives, Endpoints, and Estimands	Removed the definition for Confirmed Virologic Withdrawal (CVW).	To avoid discrepancy with the updated definition for CVW criteria defined in Section 7.1.2.
4.1: Overall Design. Table 3: Study Phases, duration, and treatment arms.	Added reference to iSRC. Added reference to the observational sub-study. Corrected the retrospective data collection time period. Updated safety follow-up visit indications.	To align with updates in Section 8.3.9. To align with updates in Section 10.15 Appendix 15. Error correction. To align with updates in Section 4.4.1.
4.4.1. Safety Follow-up visit.	Indications for the safety follow-up visit are expanded, further clarified, and aligned throughout the protocol.	To ensure inclusion of participants who could benefit from the safety follow-up visit and provide clarification in the protocol.
6.10. Prior and concomitant therapy.	Added details on the importance for the PI to confirm and document concomitant medications and supplements.	Administrative update; clarification.
7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal	Added reference to the observational sub-study.	To align with updates in Section 10.15 Appendix 15.

Section # and title	Description of change	Brief rationale
7.1.2. Virologic Criteria for Participant Management and Viral Resistance Testing. 7.1.2.1. Managing Participants Meeting SVW Criteria. 7.1.2.2. Managing Participants Meeting CVW Criteria. 7.1.2.3. HIV-1 RNA Blips.	Removed PVW critieria; updated CVW criteria; added Section 7.1.2.3 HIV-1 RNA Blips; clarified indication for PI collection and documentation of local HIV-1 RNA labs.	The virologic management and withdrawal criteria was amended to reduce risk of clinically unnecessary retesting burden and withdrawal required under the current PA 02, while better aligning study virologic management and withdrawal criteria with clinical practice and guidelines.
8. Study Assessments and Procedures	Clarified blood volume.	To align with ICF; clarification.
8.3.9. Safety Monitoring and iSRC.	Added an internal safety review committee (iSRC).	To further monitor participant safety and data integrity throughout the study.
8.8. Biomarkers	Clarified sample types for storage (added PBMCs) to perform further post-hoc assessments.	Clarification.
8.10. Viral Resistance	Clarified virology sample types indicated for genotype and phenotype testing.	Clarification.
9. Statistical Considerations	Removed the text “first interim” and replaced with “primary”.	To align with updates in Section 9.4.
9.2. Analysis sets	The definition for CVW was updated.	To align with updates in Section 7.1.2.
9.4: Interim analysis.	Removal of the week 24 interim analysis. Added reference to the iSRC.	To ensure continued participant safety and preserve study data integrity while prioritizing the week 48 primary analysis results. To align with updates in Section 8.3.9.

Section # and title	Description of change	Brief rationale
10.1.3. Informed consent process 10.1.7. Dissemination of Clinical Study Data 10.1.8. Data quality assurance 10.1.9 Source documents 10.1.11 Publication policy	Details added and minor updates made to listed sub-sections within Appendix 1.	Administrative updates.
10.1.6. Committee structure	Added an internal safety review committee (iSRC).	To further monitor participant safety and data integrity throughout the study.
10.2: Appendix 2: Clinical laboratory tests.	Corrected the Refitted, race-neutral CKD-EPIcr_R equation displayed. Added the Refitted, race-neutral CKD-EPI-cystatin C equation.	Error correction; clarification.
10.3.3. Solicited events	Removed text “events at the injection site”.	Not applicable to this study; simplification.
10.3.7.2 Assessment of intensity	Clarified DAIDS AE intensity grading for non-specified AEs.	Administrative update
10.4. Appendix 4: Toxicity Management	Added the text “approximately” prior to “2-4 weeks after the last dose of study treatment” in reference to the follow-up visit.	Clarification.
10.4.1.3. Decline in Renal Function	Removed reference to SRM for details on the collection and processing of urine samples. Removed text “CKD EPIcr_R”.	Error correction.
10.4.1.4. Proteinuria	Removed reference to SRM for details on the collection and processing of urine samples.	Error correction.

Section # and title	Description of change	Brief rationale
10.7. Appendix 7: Liver safety: actions, follow-up assessments, and study treatment guidelines.	Removed reference to SRM in footnote 4.	Error correction.
10.14. Appendix 14. Protocol amendment history	Moved summary of changes associated with the previous protocol amendment to the Appendix.	Administrative update
10.15. Appendix 15: A sub-study describing subsequent ART regimens after discontinuation from the main study	Added reference to and details of new observational sub-study.	A sub-study describing subsequent ART regimen(s) after discontinuation from the main study was added to permit additional efficacy and safety data collection, up to 6 months post-withdrawal, on subsequent ART regimen(s).
References	Removed unused and uncited references. Minor typographical corrections.	Error correction; clarification.
Header	Removed the TMF number. Updated document type and version.	To align with protocol template standard (note: a new TMF number has been assigned).
Throughout the document	Minor administrative changes and typographical edits.	Clarifications, typographical updates, adminsitrative edits. Alignment with updated protocol template version 3 and associated protocol library updates.

10.15. Appendix 15: A sub-study describing subsequent ART regimens after discontinuation from the main study

10.15.1. Sub-study rationale

This observational sub-study will describe virologic response to subsequent ART regimen(s) of participants who withdraw from the main study through 6 months post-withdrawal. The "main study" refers to the original interventional study as described throughout the 219516 study protocol, while the "sub-study" refers to a 6-month observational period after a participant withdraws from the main study, as further specified in this Appendix 15.

Eligible participants are those who withdraw from the main study due to virologic concerns (e.g., baseline viral resistance, virologic withdrawal criteria, lack of efficacy). Participants impacted by virologic-management related concerns (e.g., viral load elevations) prior to withdrawal from the main study for other reasons (e.g., AE/SAE, withdrawal by participant), may also be considered for participation in the sub-study. Refer to Section 10.15.3 for details on the sub-study design and eligibility.

The sub-study evaluation period will start from the time of participant withdrawal from the main study and will last for up to 6 months of follow-up post withdrawal to permit additional efficacy and safety data collection on subsequent ART regimen(s). This will provide a more complete dataset to further understand the study results from 219516 and inform the scientific community.

10.15.2. Sub-study objectives and endpoints

Table 18 Sub-study Objectives and Endpoints

Objective(s)	Endpoint(s)
Exploratory	
CCI [redacted]	

10.15.3. Sub-study design

This is an optional, observational, sub-study that will aim to include participants who withdraw from the main study, to permit collection of data generated in routine clinical care related to virologic response to subsequent ART regimens through 6 months of follow-up post withdrawal from the main study.

Participants are considered eligible for inclusion in the sub-study if they:

- Withdrawal from the main study due to virologic concerns (e.g., baseline viral resistance, virologic withdrawal criteria met as defined under any protocol amendment, lack of efficacy).
- Withdrawal from the main study due to non-virologic concerns (i.e., AE/SAE, withdrawal by participant) and have been impacted by virologic management related concerns (e.g., viral load elevations) at any point in study prior to withdrawal.
- Participants who have already been withdrawn from the main study due to virologic criteria prior to the implementation of Protocol Amendment 03 and this sub-study should also be considered for the sub-study.
- All participants must sign a separate sub-study ICF to be considered eligible.

The medical charts of participants who consent to the sub-study will be abstracted at baseline, approximately 3 and approximately 6 months after withdrawal from the main study, at a minimum. “Baseline” is considered the first available local visit with relevant assessment data (i.e., related to HIV care) after participant withdrawal from the main study. Of note, participants who withdraw from the main study are still expected to complete protocol-required visits and assessments upon discontinuation from study (i.e., early withdrawal visit, safety follow-up visit if indicated). Locally obtained data at these timepoints in scope of the sub-study, as described below, should be collected under the sub-study (in applicable eCRFs) for consenting participants.

For participants who attend a separate clinic for HIV care after withdrawal from the main study, the PI or designated site staff will be required to contact the clinic physician to collect the required information for the sub-study.

The following information will be obtained:

- ART regimen(s) that participants started after withdrawal from the main study (i.e., commercially accessible DTG/3TC, alternative suitable local standard-of-care ART regimen)
- Plasma HIV-1 RNA levels after withdrawal from the main study (upon initiation of subsequent/post-study ART regimens) and up to 6 months after. The type of local HIV-1 RNA assay/platform used will also be obtained.
- Reasons for virologic failure if/when the subsequent treatment regimen is changed during the sub-study (suboptimal adherence, tolerability, adverse event, etc.)
- Reasons for switching if/when the subsequent treatment regimen is changed during the sub-study (virologic failure, tolerability, safety, adherence, convenience, etc.)
- Adverse Events, SAEs or Death leading to ART discontinuation
- Adverse Drug Reactions, SAEs or Death related to ViiV Healthcare products
- Pregnancy while on ViiV Healthcare products

- Concomitant Medications (including prescription medications and over-the counter products, multivitamins and dietary supplements)
- Intercurrent illness

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.

Participants may withdraw consent for the sub-study at any time. Participants are considered to have completed the sub-study at the 6 month review or when there is no additional data expected for the participant.

Table 19 Sub-study Schedule of Activities (SoA)

Procedures	Baseline	3 months	6 months
Written informed consent[a]	X		
Current ART regimen	X	X	X
Local plasma HIV-1 RNA	X	X	X
Reasons for virologic failure		X	X
Reasons for switch (if subsequent regimen is changed)		X	X
HIV Genotypic Resistance	X	X	X
AEs, SAEs, or Death leading to ART discontinuation	X	X	X
Adverse drug reactions, SAEs, or Death related to ViiV Healthcare products	X	X	X
Pregnancy while on ViiV Healthcare products[b]	X	X	X
Concomitant medications	X	X	X
Intercurrent illness	X	X	X

Note: "Baseline" is considered the first available local visit with relevant assessment data (i.e., related to HIV care) after participant withdrawal from the main study. The subsequent timepoints for local data collection are approximate.

a. a. Written informed consent for the sub-study should ideally be obtained at the time of withdrawal from the main study, or at the next available opportunity. Participants who are eligible for the sub-study, who have already been withdrawn from the main study and transitioned to post-study/subsequent ART prior to implementation of this sub-study, should be given the opportunity to consent to the sub-study as soon as possible.

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

10.15.4. Sub-study data collection

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

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

AEs, 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/ViiV. 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/GSK according to ViiV Healthcare/GSK policy.

10.15.5. Sub-study statistical considerations and data analysis

This is a descriptive study only. No formal hypothesis will be tested. Further details will be provided in the SAP.

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