TITLE PAGE

Protocol Title: A Phase 3b multi-center, open label, single arm, 52-week pilot study, evaluating the feasibility, efficacy and safety of a rapid Test and Treat intervention in newly diagnosed HIV-1 infected adults using a fixed dose combination of dolutegravir plus lamivudine (DOVATO) as a first line regimen

Protocol Number: 212355/ 01

Compound Number: GSK1349572+GR109714 (GSK3515864)

Study Phase: PHASE IIIB

Short Title: Rapid Test and Treat dolutegravir plus lamivudine study in newly diagnosed HIV-1 infected adults

US IND Sponsor Name and Legal Registered Address:

ViiV Healthcare Company
Five Moore Drive
P.O. 13398
Research Triangle Park, NC 27709-3398, USA
Telephone: PPD

This study is sponsored by ViiV Healthcare. GlaxoSmithKline is supporting ViiV Healthcare in the conduct of this study.

PPD Inc is operationalizing this study with GlaxoSmithKline support.

Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): US IND: 127475/ EudraCT: 2018-000177-72

Approval Date: 06-JUN-2019

SPONSOR SIGNATORY:

PPD

June 6, 2019
Date

Kimberly Y. Smith, MD
Vice President and Head,
Global Research and Medical Strategy,
ViiV Healthcare

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY List dates of original protocol and all amendments in reverse chronological order.		
Document	**Date**	**DNG Number**
Amendment 1	06-Jun-2019	2019N398432_01
Original Protocol	25-MAR-2019	2019N398432_00

Amendment 01 06-June-2019

Overall Rationale for the Amendment:

A global protocol amendment was required to update the primary objective and endpoint based on FDA feedback. Additional changes were incorporated as a result of feedback and discussion from the Investigator Meeting held in May 2019. Administrative changes for clarity and corrections to minor errors in the previous version of the protocol were made. Changes were made in the Protocol Summary sections to reflect text changes in other sections of the protocol, as appropriate.

Section # and Name	Description of Change	Brief Rationale
Title Page 1.1 Synopsis 2.1 Study Rationale 4.2 Scientific Rationale for Study Design	Study Rationale was revised to more accurately state the goal for conducting this study	Modified study rationale to better reflect the primary goal of the study which is to provide pilot data regarding the feasibility, efficacy and safety of using DTG + 3TC FDC in a test and treat model of care setting
1.1 Synopsis 3 Objectives and Endpoints 4.1 Overall Design 8.1.1 Primary Efficacy Endpoint 8.1.2 Secondary Efficacy Endpoints 9.5.1 Efficacy Analysis 9.5.2 Secondary Analysis	Primary Objective modified to match the study rationale Primary Endpoint modified to reflect observed analysis at Week 24, per FDA feedback	Modified the primary objective to add to the evaluation of the "feasibility" of a Test and Treat Model of Care from evaluating the "efficacy and safety" of DTG + 3TC FDC in this setting Modified primary endpoint to remove the analysis using a modified FDA Snapshot Algorithm to an observed analysis based on FDA feedback
	Secondary endpoint modified to reflect an Observed analysis at Week 48, per FDA feedback	As in the primary endpoint the secondary endpoint was modified to remove the modified FDA Snapshot analysis
1.1 Synopsis 1.2 Schema 1.3 Schedule of Activities (SoA) 2.1 Study Rationale 2.3.1 Risk Assessment 3 Objectives and Endpoints 4.1 Overall Design 4.2 Scientific Rationale for the study 6.3 Measure to Minimize Bias 7.2.1 Screening/Day 1 Laboratory Safety Criteria 8 Study Assessments and Procedures 8.2.1 Physical Examinations 8.2.2 Vital Signs 9.3 First-line DTG + 3TC Regimen Modification 10.2 Clinical	Screening Visit and Day 1 Visit were merged into one visit and text changed to "...must be on the same day." Modifications were made for all activities and references to Screening and Day 1 as separate visits, to reflect merging them into one visit.	Screening and Day 1 were combined to better reflect the test and treat model of care setting where participants are diagnosed and initiate HIV-1 treatment on the same day

Section # and Name	Description of Change	Brief Rationale
Laboratory Tests 10.6.2 Study Intervention Restart after Stopping for Liver Criteria		
1.3 SoA 1.3.1 SoA for ART Regimen Modification 2.3.1 Risk Assessment 5.1 Inclusion Criteria 7.4 Other Additional Intervention Criteria 8.3.5 Pregnancy 10.2 Clinical Laboratory Tests 10.5 Contraceptive Guidance 10.10 Abbreviations	Gender neutral terms have replaced the use of females or women. The gender-neutral terms include: participants, females at birth, sex at birth, current gender, participants of childbearing potential (POCBP).	Text regarding females or women of childbearing potential or reproductive potential have been modified to gender neutral language to make the study protocol more Trans inclusive
2.3.1 Risk Assessment 5.1 Inclusion Criteria 5.2 Exclusion Criteria 7.4 Other Additional Intervention Criteria 8.3.5 Pregnancy 9.5.2 Secondary Analysis 10.2 Clinical Laboratory Tests 10.5.3 Collection of Pregnancy Information	Pregnancy status at the Screening/Day 1 visit has been modified to state that participants who are beyond the first trimester of a pregnancy are eligible to enrol in the study. Pregnancy during the study has been modified to state that participants who become pregnant during the study and are detected in the first trimester should immediately discontinue DTG + 3TC FDC and be started on an alternate regimen that does not contain DTG. If the pregnancy is after the first trimester, the participant can continue study treatment.	The allowance of pregnant participants to remain on study intervention if the pregnancy is detected after the first trimester as this is more consistent with the DOVATO label
1.1 Synopsis 4.1 Overall Design 9.6 Interim Analysis	The Week 12 interim analysis was been modified to state that this may be conducted.	Depending on the number of participants who require a change from first line regimen based on Screening/Day 1 labs, the Week 12 analysis may or may not be conducted.
1.3 Schedule of Activities (SoA)	Modified the text in the comment field for HIV Diagnostic Test by adding that the HIV-1 diagnosis is new “and confirmed”	Restating the need for the confirmation of the HIV-1 diagnosis by 2 tests
	Added collection of plasma samples at the Week 52 visit	Correction from original protocol

Section # and Name	Description of Change	Brief Rationale
	Added collection of HBV 3TC Resistance and HBV DNA samples for participants with confirmed HBV infection from Screening/Day 1 labs at Weeks 1 and Week 4	Added the check marks to match the comment associated with the collection of these samples for participants with HBV infection
1.3 Schedule of Activities (SoA) 10.2 Clinical Laboratory Assessments	HLA B5701 testing as needed was added	Testing for HLA B5701 was added if an Investigator is considering using abacavir when modifying ART
1.3.1 SoA for ART Regimen Modification 4.1 Overall Design 10.2 Clinical Laboratory Tests	Modified the comments to clarify when HBV 3TC Resistance and HBV DNA samples should be collected for ART modification visits are not at the Week 1 or at the Week 4 study visit, or if an HBV infection is acquired after Screening/Day 1"	Clarification of sample collection
	Modified the header note for clarification about what assessments need to be completed if either of the ART Modification Visits occurs at a scheduled study visit	Clarification of visit assessments
5.2 Exclusion Criteria	Exclusion Criteria 2: Created to capture changes in pregnancy status at Screening/Day 1	Created to exclude participants from the study who are in their first trimester of pregnancy
	Exclusion 3: Removed restrictions regarding known renal impairment and HBV infection status, and modified text for known HIV-1 resistance prior to Day 1	Removed restrictions as it is common for some sites to have this information as part of their usual clinical practice. Additionally, if the HepB serologies indicated the participant was HBV negative, the original exclusion criteria would have unnecessarily excluded that person
	Exclusion 4: Modified the study allowed CDC Class 3 stage diseases	Modified to include an exemption for cutaneous Kaposi's sarcoma not requiring systemic therapy as treatment of this condition does not pose an added safety risk for patients who are initiating ART, including DTG + 3TC in treatment of HIV-1
	Exclusion 5 was modified, and Exclusion 6 was added to create separate criteria for known or suspected hepatic impairment from known or suspected hepatitis B.	As hepatic impairment and hepatitis B are unique conditions, these were separated into 2 criteria
1.1 Synopsis 1.3 Schedule of Events 2.1 Study Rationale	Added text to clarify that Screening/Day 1 must be 14 days or less from the time of the "initial" HIV-1 infection diagnosis	Text added for clarification

Section # and Name	Description of Change	Brief Rationale
4.1 Overall Design 4.2 Scientific Rationale for Study Design		
Title Page 1.1 Synopsis 4.3 Justification of Dose	Use of DTG + 3TC FDC has been edited to DOVATO, where appropriate	Added to indicate that DOVATO is approved in the U.S.
2.3 Benefit/Risk Assessment 10.3.4 Recording and Follow-Up of AE and SAE 10.4.1.6 Rash 11 References	Addition of the Tivicay, Epivir and/or DOVATO Package inserts as references where appropriate.	Reference information
2.3.1 Risk Assessment 10.7 Prohibited Medications	Removed pilsicainide as a theoretical serious drug interaction	Pilsicainide was removed as this drug is not available in the U.S.
Throughout the Protocol	Revised all instances of DTG + 3TC to DTG + 3TC FDC when referring to study medication	Consistency and for clarity of when the FDC is applicable or the individual agents are applicable

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase IIIb multi-center, open label, single arm, 52-week pilot study, evaluating the feasibility, efficacy and safety of a rapid test and treat intervention in newly diagnosed HIV-1 infected adults using a fixed dose combination of dolutegravir plus lamivudine (DOVATO) as a first line regimen

Short Title: Rapid Test and Treat with dolutegravir plus lamivudine in newly diagnosed HIV-1 infected adults

Rationale:

Study 212355 is a pilot study being conducted to provide the first evaluation of the feasibility, effectiveness and safety of using a fixed dose combination (FDC) of Dolutegravir (DTG) plus Lamivudine (3TC) as a first line regimen of a rapid Test and Treat model of care over 48 weeks. Participants with a new and confirmed diagnosis of HIV-1 infection will initiate DTG + 3TC FDC immediately (or, for those participants referred from another site, within 14 days of initial diagnosis at the external clinic/testing center) at the Screening/Day 1 Visit, prior to safety laboratory tests and HIV-1 resistance mutation laboratory results being available for review. The Screening/Day 1 Visit is considered Baseline.

This study aims to evaluate the feasibility, efficacy and safety of using DTG + 3TC FDC as a first regimen in a rapid Test and Treat care setting in the U.S, where the prevalence of both transmitted M184V/I and co-infection with Hepatitis B virus is low.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To evaluate the feasibility and efficacy of a rapid Test and Treat model of care in participants with a new diagnosis of HIV-1 initiating treatment with DTG + 3TC FDC immediately (or, for those participants referred from another site, within 14 days of initial diagnosis at the external clinic/testing center).	• Percentage of all participants who have plasma HIV-1 RNA <50 c/mL at Week 24, regardless of ART regimen (observed analysis)
Secondary	
• To demonstrate the antiviral activity of DTG + 3TC FDC over 48 weeks	• Proportion of participants: • who have plasma HIV-1 RNA <50

Objective	Endpoint
	c/mL at Week 48, regardless of ART regimen (observed analysis) • with plasma HIV-1 RNA <50 c/mL at Week 24 and 48 using the FDA Snapshot algorithm • Time to suppression of HIV-1 RNA <50 c/mL
• To evaluate the barriers (e.g., HIV-1 resistance mutation results) to initiate and maintain DTG + 3TC FDC treatment in a Test and Treat Model of Care	• Proportion of participants who change first line regimen of DTG + 3TC FDC due to Baseline labs or HIV-1 resistance mutation results
• To assess viral HIV-1 resistance mutation in participants meeting confirmed virologic failure criteria	• Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and/or 3TC, or any other ART if treatment is modified, in participants meeting confirmed virologic failure criteria
• To evaluate the safety and tolerability of a rapid test and treat model of care using DTG + 3TC FDC as first line regimen	• Incidence and severity of adverse events and laboratory abnormalities • Proportion of participants who discontinue treatment due to AEs and drug-related AEs over 48 weeks of treatment
• To evaluate the immune effects of a rapid test and treat model of care using DTG + 3TC FDC as first line regimen	• Change from Baseline in CD4+ cell counts and CD4+/CD8+ ratio at Weeks 24 and 48 • Incidence of disease progression (stage 3 HIV-associated conditions, AIDS, and death) through Week 48
• To evaluate retention in care	• Proportion of participants o who completed their Week 24 and Week 48 Visit; o who complete their Week 24 and Week 48 Visit and have a HIV-1 RNA <200 c/mL
Exploratory	
• To evaluate the effect of participant demographics and Baseline	• Proportion of participants with plasma HIV-1 RNA <50 c/mL at

Objective	Endpoint
characteristics on the feasibility and efficacy of a test and treat model of care using DTG + 3TC FDC as first line regimen	Weeks 24 and 48 by participant subgroup(s) by Observed Analysis
• To asses change in treatment symptom index for participants under a rapid test and treat model of care using DTG + 3TC FDC as a first line regimen	• Change from Baseline in overall symptom bother score from the HIV Symptom Distress Module at Weeks 4, 8, 12, 24, 36, and 48
• To assess change in specific symptoms for participants treated with DTG + 3TC FDC	• Change from Baseline in 20 item-specific symptoms from the HIV Symptom Distress Module at Weeks 4, 8, 12, 24, 36, and 48
• To assess adherence to study treatment	• Adherence will be assessed by participant recall on number of doses missed over the 7 days prior to the Visit

Overall Design:

This is a Phase IIIb multi-center, open label, single arm, 52-week pilot study, evaluating the feasibility, efficacy and safety of once daily dolutegravir plus lamivudine fixed dose combination (FDC) regimen in a rapid test and treat intervention in newly diagnosed HIV-1 infected adults.

The study will enrol participants in the U.S. with a new and confirmed diagnosis of HIV1 infection and are willing to initiate anti-retroviral therapy (ART) immediately (or, for those participants referred from another site, within 14 days of initial diagnosis at the external clinic/testing center).

Study 212355 will include a Screening/Day 1 Visit, and visits at Weeks 1, 4, 8, 12, 24, 36, 48, 52 and a potential Follow-up Visit.

The Screening/Day 1 Visit must be the same day. Labs will be drawn prior to initiating study treatment on Day 1. The Screening/Day 1 Visit is considered Baseline. Investigators will review safety labs as they become available and schedule a visit with the participant to review (Week 1 Visit). HIV-1 resistance mutation results will be reviewed as they are made available (Week 4 Visit).

When all participants complete their Week 12 Visit, an Interim Analysis may be conducted to review the proportion of participants requiring a modification in treatment.

The primary endpoint is the proportion of all participants with plasma HIV-1 RNA <50 c/mL at Week 24, regardless of ART regimen, using an observed analysis).

The Week 48 analysis will take place after the last participant has completed the Week 52 Visit. Participants who require a virologic retest at Week 48, must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later, which will be captured under the Week 52 Visit. All participants who remain in the study at Week 48 will complete the Week 52 Visit where study intervention stop date will be captured and collect and follow-up on AEs and SAEs.

An in-clinic Follow-Up Visit will be conducted 4 weeks after the last dose of study medication for participants with ongoing SAEs and non-serious AEs of special interest, regardless of attributability. The investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Disclosure Statement: This is a single group, open-label, treatment study with 1 arm.

Number of Participants:

The study will recruit approximately 120 individuals. It is expected around 150 individuals to be screened to meet this number of enrolled individuals. If less than 120 individuals have been enrolled after 150 individuals have been screened, screening will continue until enrolment of approximately 120 individuals is met.

Intervention Groups and Duration:

A participant's total time in the study will be approximately 13 months and includes a maximum of 14 days from the time of the initial HIV-1 diagnosis to the Screening/Day 1 Visit and initiation of study drug, a 52-week treatment period and a 4-week follow-up phase.

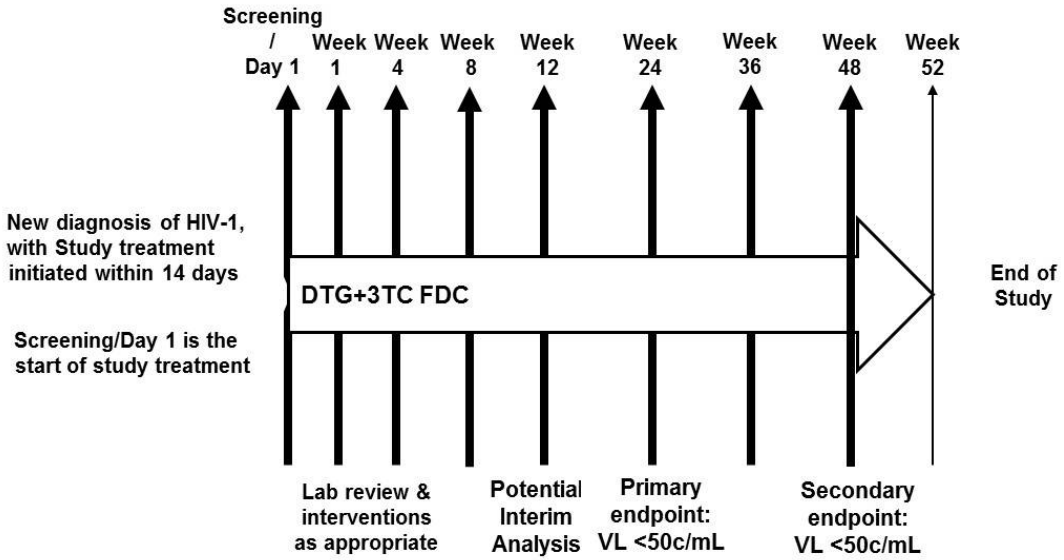
Study intervention, 50 mg DTG + 300 mg 3TC will be provided to all participants as a fixed dose combination (FDC) as first line therapy. DTG + 3TC FDC will be taken orally, once daily, with or without food.

Participants meeting safety criteria and HIV-1 resistance mutation criteria (e.g., M184I, M184V, K65R) based on the Screening/Day 1 laboratory data will modify their current DTG + 3TC FDC treatment and will remain in the study. Criterion for the management of virologic non-response criteria are prespecified for study visits at and after Week 8.

Data Monitoring Committee: No

1.2. Schema

Figure 1 Study Schematic



The study will enrol participants with a new and confirmed diagnosis of HIV-1 infection and are willing to initiate anti-retroviral therapy (ART) immediately (or, for those participants referred from another site, within 14 days of initial diagnosis at the external clinic/testing center). If participants HIV-1 resistance mutation results are known prior to Day 1, they will be excluded.

The Screening Visit and Day 1 Visit must be the same day. Labs will be drawn prior to study treatment on Day 1. Investigators will review safety labs as they become available and schedule a visit with the participant to review (Week 1 Visit). HIV-1 resistance mutation results will be reviewed as they are made available (Week 4 Visit).

When all participants complete their Week 12 Visit, an Interim Analysis may be conducted to review the proportion of participants requiring a modification in treatment for any reason (e.g., Screening/Day 1 HIV-1 resistance mutation, Screening/Day 1 abnormal laboratory results, etc).

The primary endpoint is the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24, regardless of ART Regimen (Observed Analysis).

Additional visits will be at Weeks 8, 36, 48, 52 and a potential Follow-up Visit.

1.3. Schedule of Activities (SoA)

Procedures	Screening / Day 1 (Baseline) [a, b]	Intervention Period Weeks								Withdrawal	Follow-up [i]	Comments
		1 [c]	4 [d]	8 [e]	12 [f]	24 [g]	36	48 [g, h]	52 [h]			

a. The Screening/Day 1 Visit is to assess the participant's appropriateness for the study, confirm the participant has a new diagnosis of HIV-1 infection and is willing to initiate ART on the same day. For those participants referred from another site, Screening/Day 1 must be 14 days or less from the initial diagnosis at the external clinic/testing center.

b. If the participant meets all study inclusion and exclusion criteria, participant will start study treatment (DTG + 3TC FDC) at the end of Screening/Day 1 Visit after all other assessments have been completed.

c. Participants will attend a Week 1 Visit after notification from the sites once the Screening/Day 1 laboratory results become available. Investigators should review the safety labs and assess whether any additional interventions are required (see Section 7.2 Discontinuation and Additional Intervention Criteria).

d. Participants will attend a Week 4 Visit after notification from the sites once the HIV-1 Resistance mutation results become available. Investigators should review the resistance data and assess whether additional interventions are required (see Section 7.2 Discontinuation and Additional Intervention Criteria).

e. At Week 8, if the decrease HIV-1 RNA is less than 2.0 log10 c/mL, a retest should be scheduled 2-4 weeks later, unless plasma HIV-1 RNA is <200 c/mL.

f. At Week 12, participants will require a virologic retest if HIV-1 RNA ≥1000 c/mL.

g. At Week 24 and Week 48 participants will require a virologic retest if HIV-1 RNA ≥50 c/mL. At Week 36, participants will require a virologic retest if HIV-1 RNA ≥200 c/mL.

h. Participants who require a virologic retest at Week 48, must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later, which will be captured under the Week 52 Visit.

i. An in-clinic Follow-up Visit will be conducted 4 weeks after the last dose of study medication only for participants with the following conditions at the last on-study visit: All ongoing SAEs and non-serious AEs of special interest (as defined in Section 2.3.1), regardless of attributability. However, the investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Procedures	**Screening / Day 1 (Baseline)** [a, b]	**Intervention Period Weeks**								**Withdrawal**	**Follow-up** [i]	**Comments**
		1 [c]	**4** [d]	**8** [e]	**12** [f]	**24** [g]	**36**	**48**[g, h]	**52** [h]			
Clinical and Other Assessments												
Informed consent	X											
Inclusion and exclusion criteria	X											Inclusion/exclusion criteria will be fully assessed at the Screening/Day 1 Visit.
Demography	X											Sex at birth and current gender by subject will be collected.
Medical history (includes active substance usage)	X											Full medical history will be conducted prior to initiating study intervention and include assessments of cardiovascular, metabolic (e.g., Type I or II diabetes mellitus), psychiatric (e.g., depression), renal (e.g., nephrolithiasis, nephropathy, renal failure), hepatobiliary disorders (e.g., history of jaundice, icterus, ascites) and bone disorders.
Current Medical Conditions	X											
Symptom Directed Physical Exam	X											Limited physical examination to include blood pressure (recorded in eCRF) for Framingham score assessment. Physical exams should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Abnormalities noted during any exam must be recorded in the eCRF (e.g. in the current medical conditions or AE logs).

Procedures	Screening / Day 1 (Baseline) [a, b]	Intervention Period Weeks								Withdrawal	Follow-up [i]	Comments
		1 [c]	4 [d]	8 [e]	12 [f]	24 [g]	36	48 [g, h]	52 [h]			
Cardiovascular risk assessment	X											At Diagnosis Visit, assessment for cardiovascular risk will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. Body mass index (BMI) will be calculated within the eCRF.
Vital signs	X	X	X	X	X	X	X	X		X	X	Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
Body Weight	X	X	X	X	X	X	X	X		X	X	BMI will be calculated within the eCRF. The same scale should be used at each study visit.
Prior PEP/PREP Therapy	X											Participants who received HIV post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) in the past are allowed as long as the last PEP/PrEP dose was >6 months from HIV diagnosis or there is documented HIV sero-negativity at least 2 months after the last prophylactic dose and before the date of HIV diagnosis.
HIV risk factors and mode of transmission	X											
CDC Classification for HIV-1 Infection	X											Review the Baseline laboratory results as they become available and record in the eCRF (see Section 10.9).
HIV associated conditions	X	X	X	X	X	X	X	X		X		

Procedures	Screening / Day 1 (Baseline) [a, b]	Intervention Period Weeks								Withdrawal	Follow-up [i]	Comments
		1 [c]	4 [d]	8 [e]	12 [f]	24 [g]	36	48 [g, h]	52 [h]			
Suicidality Assessment	X	X	X	X	X	X	X	X	X	X	X	Investigator must assess participant suicidality using their usual clinical practice.
HIV Symptom Distress Module	X		X	X	X	X	X	X		X		Questionnaire/Surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. See Section 8.9 for additional information on how this questionnaire should be completed.
Laboratory assessments												
HIV Diagnostic Test	X*											*Participants must have a new and confirmed diagnosis of HIV-1 infection based on the criterion outlined in Section 5.1 (Inclusion Criteria). HIV Diagnostic test results should be stored in the participant source documents.
Quantitative plasma HIV-1 RNA	X	X	X	X	X	X	X	X	X	X		See Section 7.3 Virologic Failure Criteria for more information on how to manage suspected and confirmed viral failures. If a subject requires a regimen modification (e.g., based on Baseline labs, a Confirmed Virologic Failure, or an AE), see SoA ART Regimen Modification Section 1.3.1.
Whole Blood	X					X		X		X*		*Collect sample only if Withdrawal Visit is replacing the Week 24 or Week 48 Visit.
Lymphocyte subset	X		X		X	X	X	X		X		

Procedures	**Screening / Day 1 (Baseline)** [a, b]	**Intervention Period Weeks**								**Withdrawal**	**Follow-up** [i]	**Comments**
		1 [c]	**4** [d]	**8** [e]	**12** [f]	**24** [g]	**36**	**48**[g, h]	**52** [h]			
Plasma for HIV genotyping	X											An additional plasma for HIV genotyping will be included at the time of regimen change in case of Baseline HIV-1 resistance mutations (see Section 1.3.1).
Plasma for storage	X	X	X	X	X	X	X	X	X	X		Plasma samples for storage will be collected at each visit, including unscheduled visits (e.g. for HIV-1 RNA levels and immunological parameters). Additionally, these samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable or as a priority need for genotypic and/or phenotypic analyses when participants meet Confirmed Virologic Failure criteria.
Clinical Chemistry	X		X	X	X	X	X	X		X	X	
Hematology	X		X	X	X	X	X	X		X	X	
Lipid Panel	X					X		X				
HBsAg, anti-HBc, anti-HBs, and HBV DNA	X											HBV DNA testing will be performed for participants with positive anti-HBc and negative HBsAg and negative anti-HBs.

Procedures	**Screening / Day 1 (Baseline)** [a, b]	**Intervention Period Weeks**								**Withdrawal**	**Follow-up** [i]	**Comments**
		1 [c]	**4** [d]	**8** [e]	**12** [f]	**24** [g]	**36**	**48**[g, h]	**52** [h]			
HBV 3TC Resistance and HBV DNA (only for participants with chronic HBV infection)	X	X*	X*									*Testing for HBV 3TC resistance will be performed using samples from Week 1 or Week 4 (depending on when ART modification occurs) as well as Baseline samples. For these participants, HBV DNA will also be obtained at the Week 1 and/or Week 4 visit.
HCV antibody	X											
Rapid plasma reagin (RPR)	X											
Urinalysis	X		X		X	X	X	X		X		A morning specimen is preferred. Reflex microscopic.
Pregnancy test (POCBP only)	S/U	S	S	S	S	S	S	S	S	S		Pregnancy testing will be conducted (participants of childbearing potential only) on serum (S) samples. At Screening/Day 1 Visit (before start of study treatment), a urine (U) test must be used to confirm pregnancy status prior to administration of study treatment. Remind participants of childbearing potential at each study visit of the need to avoid pregnancy and to adhere to the study's contraception requirements.

Procedures	Screening / Day 1 (Baseline) [a, b]	Intervention Period Weeks								Withdrawal	Follow-up [i]	Comments
		1 [c]	4 [d]	8 [e]	12 [f]	24 [g]	36	48 [g, h]	52 [h]			
FSH	X											A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in females at birth not using hormonal contraception or hormonal replacement therapy (HRT).
HLA B5701*												*Testing for HLA B5701 may be required before adding or modifying ART therapy and should be discussed with the Medical Monitor. Please schedule this test using the Unscheduled Q2 requisition.
Study treatment												
IWRS	X				X	X	X					Screening/Day 1 is the day the participant initiates study treatment. At Week 36, an extra bottle of study intervention should be provided so that all participants will have treatment until Week 52 in case a virologic retest is required.
Dispense DTG + 3TC FDC study treatment	X				X	X	X					Participants must return their pill container. Site should remind participants of the importance of adherence. ART may be modified as described in Section 7. Required ART modification assessments are outlined in Section 1.3.1.
Treatment Adherence		X	X	X	X	X	X	X	X	X		7-day participant recall. All study treatment stop and start dates must be recorded.

Procedures	Screening / Day 1 (Baseline) [a, b]	Intervention Period Weeks								Withdrawal	Follow-up [i]	Comments
		1 [c]	4 [d]	8 [e]	12 [f]	24 [g]	36	48 [g, h]	52 [h]			
Adverse Event (AE) review	X	←==========X==========→							X	X	X	Only AEs related to study related events will be collected between obtaining informed consent and initiation of study treatment on Screening/Day 1. After Day 1, all AEs and SAEs will be collected through the Follow-up Visit. See additional information in the SAE Review on Follow-up assessments.
Serious Adverse Event (SAE) review	X	←==========X==========→							X	X	X	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 drug at the Screening/Day 1 Visit. Only Participants with ongoing SAEs and non-serious AEs of special interest (as defined in Section 2.3.1), regardless of attributability, will attend a Follow-up Visit approximately four weeks after their last dose of study treatment. Assessments at the Follow-up Visit should reflect any ongoing complaints (e.g. blood draws to follow a laboratory abnormality). The investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up
Prior and Concomitant medication review	X	←==========X==========→							X	X	X	Prior medications over the last 4 weeks will be collected at the Screening/Day 1 Visit.

1.3.1. SoA for ART Regimen Modifications

Procedures	ART Regimen Modification [a]	Post-ART Regimen Modification [b]	**Note:** If the ART Regimen Modification Visit or the Post-ART Regimen Modification Visit occurs at a scheduled visit (Section 1.3), assessments should be completed at the scheduled visit and only the additional assessments in this table should be completed.
a. The ART Regimen Modification visit is used when modifying a participants ART regimen (e.g., based on Baseline labs, a Confirmed Virologic Failure, or an AE) between scheduled visits. b. Four weeks after the ART modification, the participant must return for the Post ART regimen Modification Visit; participants will resume the regular study visit schedule after this visit.			
Clinical and Other Assessments			
Vital signs	X	X	Blood pressure to be measured after resting in a semi-supine position for at least 5 minutes.
Body Weight	X	X	BMI will be calculated within the eCRF. The same scale should be used at each study visit.
Suicidality Assessment	X	X	Investigator must assess participant suicidality using their usual clinical standards.
HIV associated conditions	X	X	
HIV Symptom Distress Module	X	X	Questionnaire/Surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. See Section 8.9 for additional information on how this questionnaire should be completed.
Laboratory assessments			
Quantitative plasma HIV-1 RNA	X*	X	*If the ART modification is based on Baseline laboratory results, a HIV-1 RNA sample is not required at the ART Regimen Modification Visit. If the ART Modification Visit is not aligned with a regular study visit and an HIV-1 RNA assessment in the last 4 weeks is not available, a HIV-1 RNA sample should be collected at this visit.
Whole Blood		X	
Lymphocyte subset		X	

Procedures	**ART Regimen Modification** [a]	**Post-ART Regimen Modification** [b]	**Note:** If the ART Regimen Modification Visit or the Post-ART Regimen Modification Visit occurs at a scheduled visit (Section 1.3), assessments should be completed at the scheduled visit and only the additional assessments in this table should be completed.
Plasma for storage	X	X	Plasma samples for storage will be collected (e.g. for HIV-1 RNA levels and immunological parameters). These samples will be used when needed such as when samples are lost or arrive at the laboratory unevaluable or as a priority need for genotypic and/or phenotypic analyses when participants meet Confirmed Virologic Failure criteria.
Clinical Chemistry		X	
Hematology		X	
HBV 3TC Resistance and HBV DNA (only for participants with chronic HBV infection)	X*		* A sample should be taken for HBV 3TC resistance and HBV DNA if the ART modification visit is not at the Week 1 or at the Week 4 study visit, or if a chronic HBV infection is acquired during the study after Baseline.
Urinalysis		X	A morning specimen is preferred. Reflex microscopic.
Pregnancy test (POCBP only)	S	S	Pregnancy testing will be conducted (participants of childbearing potential only) on serum (S) samples. Remind participants of childbearing potential at each study visit of the need to avoid pregnancy and to adhere to the study's contraception requirements.
Study treatment			
Treatment Adherence	X	X	7-day participant recall. All study treatment stop and start dates must be recorded.
Adverse Event (AE) review	X	X	
Serious Adverse Event (SAE) review	X	X	
Concomitant medication review	X	X	

2. INTRODUCTION

Early initiation of antiretroviral therapy (ART) reduces morbidity and mortality for individuals infected with HIV. Supressing viral replication with ART also reduces the potential for transmission of HIV. Because of this, ART is recommended for all persons with HIV viremia regardless of CD4 count. Delays between diagnosis and treatment results in many individuals not engaging in their care. Thus, rapid ART initiation (Test and Treat) at the time of HIV-1 diagnosis is imperative for increasing the proportion of individuals starting ART earlier and achieving and maintaining viral suppression DHHS, 2018].

The goal of rapid Test and Treat is for adults with newly diagnosed HIV-1 infection to be offered and start ART, as well as counselling as soon as possible [Saag, 2018; WHO, 2017]. The International AIDS Society (IAS) Guideline [Saag, 2018] and the World Health Organization (WHO) [WHO, 2017] recommend a rapid start of ART. The rapid start strategy has been tested in multiple randomized controlled, pilot clinical studies [Bacon, 2018; Rosen, 2016; Koenig, 2017]. Recent studies have demonstrated the efficacy of immediate ART at entry into care. Same day ART improves the rate of viral suppression, reduces the time to viral suppression, improves retention in care, and reduce the risk of transmission. The percentage of naïve patients initiating therapy the same day as diagnosis has increased almost 50% since 2015 to 19% in 2017. However, for a variety of reasons, not all ART regimens are suitable for use in a rapid test& treat setting.

2.1. Study Rationale

Study 212355 is a 52-week pilot study that will evaluate the feasibility, efficacy and safety of using a fixed dose combination (FDC) of Dolutegravir (DTG) plus Lamivudine (3TC) as a first line regimen in a Test and Treat model of care. Participants with a new diagnosis of HIV-1 infection will initiate DTG + 3TC FDC within 14 days of the initial diagnosis at the Screening/Day 1 Visit, prior to safety laboratory results, Hepatitis B serologies, and HIV-1 drug resistance genotype results being available for review.

There are possible barriers to DTG + 3TC FDC use in a rapid Test and Treat model of care due to concerns over the potential initiation of therapy in participants with transmitted M184V, M184I or K65R mutation or HBV-HIV co infection. This study aims to evaluate the feasibility, efficacy and safety of using DTG + 3TC FDC as a first regimen in a rapid Test and Treat care setting in the U.S, where the prevalence of both transmitted M184V/I and co-infection with HBV is low.

2.2. Background

FDCs and once-daily single tablet regimen have greatly simplified the treatment of people living with HIV and may be of greater importance in people with lifestyles or care commitments that may impair adherence to dosing schedules, including some women and those in underserved populations. In a study by Paterson et. al. [Paterson, 2000], a linear relationship between levels of adherence and viral load suppression was observed. Adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Among regimens of comparable efficacy, physicians and people

living with HIV-1 who receive ART rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving adherence. Drug resistant virus eventually emerges in most people who struggle with consistent adherence. To achieve successful long-term treatment, the prevention of drug resistance has become the most significant challenge.

DTG is a potent dual cation binding INSTI, exhibiting rapid reduction in viral load, best in class efficacy, and a high barrier to resistance. These properties and its safety profile make it an optimal core agent for 2-drug regimens. In addition, due to its mechanism of metabolism, DTG lacks many of the frequent DDIs associated with other medications commonly taken by people living with HIV. To date, the efficacy, pharmacokinetics (PK), safety and drug interaction potential of DTG has been evaluated in an extensive program of Phase I to IIIB clinical trials [TIVICAY Package Insert, 2018; DTG IB, 2018].

3TC is a potent cytidine nucleoside analogue without major side effects and has a well proven safety profile. Available since 1995 as a single agent (EPIVIR) [EPIVIR Package Insert, 2018], it is also available as part of three FDC products (zidovudine (ZDV)/3TC, COMBIVIR, abacavir (ABC)/3TC, EPZICOM/KIVEXA, ABC/3TC/DTG, TRIUMEQ). 3TC monotherapy is known to select for resistance due to a single point mutation that reduces antiviral activity. However, it is predicted that 3TC, when combined with DTG with its high barrier to resistance and ability to confer a very rapid decline in HIV-1 RNA, may be less likely to select for resistance consistent with clinical studies combining DTG, 3TC and ABC [Walmsley, 2013; Walmsley, 2015; Cahn, 2018].

A pilot study (PADDLE) evaluated the anti-viral efficacy, safety and tolerability of a 2-drug regimen with DTG 50 mg and 3TC 300 mg, both dosed once daily [Cahn, 2017]. Twenty treatment naïve participants were enrolled, with a median baseline viral load of 24,128 c/mL. A rapid decline in viral load was observed, with a median viral load decay from baseline to Week 12 of 2.74 logs. At Week 48, 90% (18 of 20) reached a viral load of <50 c/mL. Four subjects were enrolled with baseline HIV-RNA ≥100,000 c/mL; all achieved HIV-RNA <400 c/mL at Week 3, and <50 c/mL at Week 8. No major tolerability issues were observed.

The AIDS Clinical Trial Group (ACTG) Study A5353 evaluated DTG + 3TC in 120 treatment-naïve HIV-1 infected participants, including with HIV-1 RNA ≥1000 c/mL and <500,000 c/mL [Taiwo, 2018]. The median viral load was 4.61 log10 at baseline; 37 of the 120 participants had viral load ≥100,000 c/mL. Virologic efficacy (<50 c/mL) at Week 24 was 108/120 (90%), with comparable results in the >100,000 c/mL (89%) and the ≤100,000 (90%) strata's. One participant discontinued the study at Week 18 due to non-compliance with study treatment and met confirmed virologic failure criteria at Week 24 (off ART) with the M184V plus the mixture R263R/K mutations detected (no mutation seen at baseline). Two participants experienced Grade 3 possible/probable treatment-related AEs; no participants discontinued study treatment due to AEs.

DTG + 3TC FDC provides a novel, well-tolerated two-drug first-line regimen for HIV infected treatment- naïve patients that, by having one less anti-retroviral (ARV) in the regimen may potentially limit the cumulative risk of drug-related toxicities. GEMINI 1

and GEMINI 2 showed that in adult HIV 1 infected ART-naïve participants with a Screening HIV-1 RNA of ≤500,000 copies/mL (c/mL) and with no drug-resistance mutations, DTG + 3TC was non-inferior to DTG + TDF/FTC at Week 48 [Cahn, 2019]. The proportion of participants with plasma HIV-1 RNA <50 c/mL was similar in each treatment group. At least 90% of participants in each treatment group had plasma HIV-1 RNA <50 c/mL using the Snapshot algorithm. DTG + 3TC was effective across a diverse spectrum of ART-naïve participants, including those with high Baseline HIV-1 RNA (>100,000 c/mL). Over 48 weeks, the pooled safety data was consistent with the known safety profile for the individual products. There was a small number of AEs leading to withdrawal of study drug; few were considered drug-related. Clinical laboratory assessments demonstrated there were no newly identified laboratory signals of concern. DTG + 3TC was associated with lower impact on renal and bone biomarkers compared with DTG + TDF/FTC FDC.

One of the potential risks of a two-drug regimen, such as DTG + 3TC FDC, is the increase in virologic failure associated with the emergence of HIV-1 resistance mutations. DTG, with its higher barrier to resistance, may reduce treatment-emergent resistance in participants taking a two-drug regimen. The overall efficacy data from the pivotal Phase III studies of DTG in ART-naïve participants are extensive, with no resistance mutations being identified through 144 weeks of treatment (SINGLE, ING114467) [Walmsley, 2015]. The absence of treatment-emergent mutations to DTG or background agents in ART-naïve individuals, rapid virologic response demonstrated for DTG-based regimens, and the *in vitro* potency and well-tolerated safety profile of both DTG and 3TC all provide a strong rationale for the development of a DTG + 3TC single tablet regimen as a treatment option for people living with HIV. In the Gemini studies, there was no emergent INSTI or NRTI resistance observed for participants meeting confirmed virologic withdrawal criterion in either the DTG + 3TC or DTG + TDF/FTC treatment arms [Cahn, 2019].

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of DTG, 3TC or DTG + 3TC FDC may be found in the most recent version of the Investigator's Brochure (IB) and any IB supplements and the product labels [TIVICAY Package Insert, 2018; EPIVIR Package Insert, 2018; DOVATO Package Insert, 2019].

The following section outlines the risk assessment and mitigation strategy for DTG and 3TC in this protocol.

2.3.1. Risk Assessment

The following table outlines the risk assessment and mitigation strategy for this protocol. Additionally, all participants will be closely monitored over the first 12 weeks of study intervention (Weeks 1, 4, 8 and 12 Visits), with visits every 12 weeks thereafter.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Study Intervention [DTG, 3TC] **Refer to DTG IBs and *country product* labels for additional information**		
DTG: Hypersensitivity reaction (HSR) and rash	**DTG:** HSR has been observed uncommonly with DTG. Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and erythema multiforme were reported.	Specific/detailed toxicity management guidance is provided for HSR and rash (Section 10.4.1.6). The participant informed consent form (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	**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 hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG- containing ART, along with inadequate therapy for HBV co-infected participants, likely contributed to significant elevations in liver chemistries. A review of post-marketing data found that the number of cases reporting particularly severe liver dysfunction was found to be very low in the context of exposure to DTG and DTG/ABC/3TC. The reported cases of severe liver dysfunction (including acute hepatic failure) are complex with potential confounding factors but in a very small number of cases, drug-induced liver injury is likely and the role of DTG containing regimens cannot be ruled out particularly in those involving DTG with ABC/3TC or DTG/ABC/3TC. **3TC:** Current treatment guidelines [DHHS, 2018; EACS, 2017] do not recommend monotherapy with 3TC for participants with HBV infection, which is what participants randomised to DTG + 3TC FDC, 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	Participants will be tested for chronic hepatitis B at Baseline (Screening/Day 1). Participants with chronic hepatitis B infection as shown by either of the following should either have Tenofovir added to their regimen or switch to a Tenofovir containing regimen. • Positive for HBsAg; • Negative for HBsAg and HBsAb, and positive for HBcAb and HBV DNA. For participants with chronic HBV infection, testing for HBV 3TC resistance will be performed using samples from Week 1 and Week 4 (depending on when ART modification occurs) as well as Baseline samples. HBV DNA will also be obtained at the Week 1 or Week 4 visit. Liver chemistries will be monitored. Specific/detailed liver stopping criteria and toxicity management guidance is provided for suspected DILI or other clinically significant liver chemistry elevations (Section 10.6).

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Study Intervention [DTG, 3TC] Refer to DTG IBs and *country product* labels for additional information		
	HBV. Additionally, discontinuation of 3TC in HBV co-infected participants can result in severe exacerbations of hepatitis B.	
DTG: Psychiatric disorders	DTG: Psychiatric disorders including suicidal ideation and behaviours are common in people living with HIV. Events of suicidal ideation, attempt, behaviour and completion were observed in clinical studies of DTG, primarily in participants with a pre-existing history of depression or other psychiatric illness. The psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety and abnormal dreams) was similar to RAL- or favourable compared with EFV- based regimens.	Participants who in the investigator's judgment, pose a significant suicidality risk, are excluded from participating. Because of the elevated risk in the HIV- infected population, treatment emergent assessment of suicidality will be monitored during this study. See Section 8.2.4 for additional information. Investigators must assess participant suicidality using their usual clinical practice at every study visit. Investigators are advised to consider mental health consultation or referral for participants who experience signs of suicidal ideation or behaviour. The participant informed consent form includes information on this risk of depression and suicidal ideation and behaviours.
DTG and 3TC: Increased rates of virologic failure/ Observed Resistance	**DTG:** Week 96 and Week 144 analyses for the Phase III/IIIb clinical studies supported the efficacy findings from earlier analyses and demonstrated robust maintenance of viral suppression with no finding of HIV-1 resistance in treatment-naïve participants. **3TC**: M184V, M184I and K65R (associated with resistance on TDF treatment failure) single mutations that confer resistance to 3TC.	Subjects with evidence of primary viral resistance based on the presence of M184I, M184V or K65R or any DTG primary resistance associated mutation will have their antiretroviral regimen modified based on the results of Baseline resistance genotype as they become available (Week 4 Visit) (see Section 7.2.2). Subjects will have HIV-1 RNA measured at each study visit. Subjects who meet the Confirmed Virologic Failure criteria will have a resistance genotype/phenotype performed, and their regimens may be modified based on the results of the resistance test.
DTG: Theoretical serious drug interaction with dofetilide	Co-administration of DTG may increase dofetilide plasma concentration via inhibition of organic cation transporter (OCT-2), resulting in potentially life-threatening toxicity.	The co-administration of DTG with dofetilide is prohibited in the study (Section 10.7).
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 inhibition of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate	Due to requirements for dose reduction of 3TC in participants with renal dysfunction, participants with a creatinine clearance (CrCL) <30 mL/min/1.73 m2 will have DTG + 3TC FDC discontinued and

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Study Intervention [DTG, 3TC] Refer to DTG IBs and *country product* labels for additional information		
	(GFR) or effective renal plasma flow. **3TC**: 3TC is eliminated by renal excretion and exposures increase in participants with renal dysfunction. 3TC is not recommended to treat participants with a creatinine clearance <50 mL/min.	modify to a new ART regimen. Creatinine Clearance (CrCl) will be calculated in all participants and renal function (creatinine clearance and serum phosphate) will be monitored at all study visits.
DTG: Neural tube defects	In one ongoing birth outcome surveillance study in Botswana, early results from an unplanned interim analysis show that 4/426 (0.9%) of cis women who were taking DTG when they became pregnant had babies with neural tube defects compared to a background rate of 0.1%.	1. A participant who is female at birth is eligible to participate if not pregnant, if pregnant and past the first trimester , or of childbearing potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Participants of Childbearing Potential (Section 10.5.2) for at least 2 weeks after the last dose of study medication. 2. Participants of childbearing potential who plan to become pregnant during the study are excluded; 3. Participants who become pregnant and are in the first trimester should immediately discontinue DTG + 3TC FDC and an alternate ART regimen that does not contain DTG should be started, unless no suitable alternative is available, in consultation with the Medical Monitor. If the pregnancy is post first trimester, the participant can continue study treatment. Any participant who becomes pregnant during the study can remain in the study, including those who needed to modify the ART Regimen. 4. Participants who desire to be pregnant while in the study, or who state they no longer are willing to comply with the approved pregnancy avoidance methods, will have DTG + 3TC FDC discontinued and switched to a new ART regimen. 5. Participants of childbearing potential are reminded re: pregnancy avoidance and adherence to contraception requirements at every study visit.

Potential Risk of Clinical Significance	Data/Rationale for Risk	Mitigation Strategy[a]
Study Intervention [DTG, 3TC] Refer to DTG IBs and *country product* labels for additional information		
		6. Pregnancy status is monitored at every study visit.

a. Careful monitoring of events will be conducted using serious adverse event (SAE) reports and alerts for Grade 3 or 4 laboratory toxicities (per Division of Acquired Immune Deficiency Syndrome [DAIDS] toxicity gradings for HIV-infected participants). Serious/severe events will be managed appropriately including, but not limited to, withdrawal of study drug, and will be followed to resolution as per Sponsor's standard medical monitoring practices.

b. Clinical Safety Data will be routinely reviewed in GlaxoSmithKline (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.

2.3.2. Benefit Assessment

Individually, DTG and 3TC are conveniently dosed once daily without regard to meals, without need for a PK booster, and with limited safety implications resulting from theoretical or actual DDIs compared to other ART agents (including EFV and those requiring a PK booster). In addition, the high barrier to HIV-1 resistance mutation observed with DTG should help protect against the development of resistance to both components of the DTG + 3TC FDC regimen. Individually, DTG and 3TC in combination with other ARVs have demonstrated durable virologic and immunologic response.

In general, ART immediately after diagnosis may increase participants' engagement to care and increase adherence to ART. Study participants also may benefit from the medical tests and 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 participating in this study, the potential risks identified in association with DTG + 3TC FDC are justified by the anticipated benefits that may be afforded to study participants who rapidly initiate this 2-drug regimen.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the feasibility and efficacy of a rapid Test and Treat model of care in participants with a new diagnosis of HIV-1 initiating treatment with DTG + 3TC FDC immediately (or, for those participants referred from another site, within 14 days of initial diagnosis at the external clinic/testing center)	• Percentage of all participants who have plasma HIV-1 RNA <50 c/mL at Week 24, regardless of ART regimen (observed analysis)
Secondary	

• To demonstrate the antiviral activity of DTG + 3TC FDC over 48 weeks	• Proportion of all participants:
	  • who have plasma HIV-1 RNA <50 c/mL at Week 48, regardless of ART regimen (observed analysis)
	  • with plasma HIV-1 RNA <50 c/mL at Week 24 and 48 using the FDA Snapshot algorithm
	• Time to suppression of HIV-1 RNA

Objectives	**Endpoints**
	<50 c/mL
• To evaluate the barriers (e.g., HIV-1 resistance mutation results) to initiate and maintain DTG + 3TC FDC treatment in a Test and Treat Model of Care	• Proportion of participants who change first line regimen of DTG + 3TC FDC due to Baseline laboratory results or HIV-1 resistance mutation results.
• To assess viral resistance in participants meeting confirmed virologic failure criteria	• Incidence of treatment-emergent genotypic and phenotypic resistance to DTG and/or 3TC, or any other ART if treatment is modified, in participants meeting confirmed virologic failure criteria
• To evaluate the safety and tolerability of a rapid test and treat model of care using DTG + 3TC FDC as first line regimen	• Incidence and severity of adverse events (AEs) and laboratory abnormalities • Proportion of participants who discontinue treatment due to AEs and drug-related AEs over 48 weeks of treatment
• To evaluate the immune effects of a rapid test and treat model of care using DTG + 3TC FDC as first line regimen	• Change from Baseline in CD4+ cell counts and CD4+/CD8+ ratio at Weeks 24 and 48 • Incidence of disease progression (stage 3 HIV-associated conditions, AIDS, and death) through Week 48
• To evaluate retention in care	• Proportion of participants o who completed their Week 24 and Week 48 Visit; o who complete their Week 24 and Week 48 Visit and have a HIV-1 RNA <200 c/mL
Exploratory	
• To evaluate the effect of participant demographics and Screening/Day 1 characteristics on the feasibility and efficacy of a test and treat model of care using DTG + 3TC FDC as first line regimen	• Proportion of participants with plasma HIV-1 RNA <50 c/mL by at Weeks 24 and 48 by participant subgroup(s) by Observed Analysis
• To asses change in treatment symptom	• Change from Baseline in overall

Objectives	Endpoints
index for participants under a rapid test and treat model of care using DTG + 3TC FDC as a first line regimen	symptom bother score from the HIV Symptom Distress Module at Weeks 4, 8, 12, 24, 36, and 48
• To assess change in specific symptoms for participants treated with DTG + 3TC FDC	• Change from Baseline in 20 item-specific symptoms from the HIV Symptom Distress Module at Weeks 4, 8, 12, 24, 36, and 48
• To assess adherence to study treatment	• Adherence will be assessed by participant recall on number of doses missed over the 7 days prior to the visit

4. STUDY DESIGN

4.1. Overall Design

Study 212355 is a Phase IIIb, multicentre, 52-week, open label, single arm, pilot study in adults with a new diagnosis of HIV-1, who are willing to start study treatment (DTG + 3TC FDC) immediately. Eligible participants will be enrolled and started on DTG + 3TC FDC, without waiting for Screening/Day 1 laboratory results. The Screening/Day 1 Visit is considered Baseline.

The study will be conducted in the U.S., with approximately 120 participants with a new HIV-1 diagnosis who are willing to start DTG + 3TC FDC within 14 days of diagnosis.

A participant's total time in the study will be approximately 13 months and includes a maximum of 14 days between the initial diagnosis of HIV-1 infection and initiation of study drug at the Screening/Day 1 Visit, a 52-week treatment period and a 4-week follow-up phase if required.

This study will comprise:

- The Screening/Day 1 Visit is the date the site assesses the participant's appropriateness for the study and consents for and initiates study treatment. Diagnosis may have occurred at an external clinic/testing center prior to participant visiting the site.
    - Participants are considered HIV-1 infected when they have positive results from 2 different HIV Rapid tests (different assay or manufacturer), or they are positive with an FDA-approved antigen/antibody combination immunoassay (4^{th} generation assay) or an FDA approved HIV antibody immunoassay that detects HIV-1 and HIV-2 antibodies (3^{rd} generation assay) confirmed by an FDA-approved antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies or an HIV western blot or an HIV-1 RNA.

  - For participants who are referred to the study site with a single positive Rapid HIV test, a second and different Rapid HIV test (different assay or manufacturer) should be conducted. If the second Rapid HIV test is nonreactive, the participant is presumed to be HIV-negative. If both tests are reactive, the participant is confirmed HIV-infected.

  - Screening/Day 1 labs should be taken prior to the administration of study treatment.

- Investigator should review the Baseline laboratory findings as they become available and schedule a study visit (Week 1), see Section 7.2 for additional information. If results for HBV surface antigen (HBsAg) or HBV core antibody (anti-HBc) and HBV DNA are not available, this review should be completed at the Week 4 Visit when the HIV-1 resistance mutation results are available.

  Note: For participants with chronic HBV infection, testing for HBV 3TC resistance will be performed using samples from Week 1 or Week 4 (depending on when ART modification occurs) as well as Baseline samples. In these participants, HBV DNA will also be obtained at the Week 1 or Week 4 visit.

- A visit should be scheduled when the central laboratory data from Baseline genotype for HIV-1 drug resistance mutations are available (Week 4 Visit) and additional intervention should be performed if required (see Section 7.2.2 for more details). If the HBV surface antigen (HBsAg) or HBV core antibody (anti-HBc) and HBV DNA data were not available at the time of the Week 1 Visit, these results should be reviewed at Week 4. The investigator should also review the tolerance to DTG + 3TC FDC, AEs, assess adherence to study treatment and enforce the importance of adherence.

- Virologic non-response criteria for Week 8, Week 12, and on or after Week 24 are defined in Section 7.3.

- Additional study visits are scheduled at Weeks 12, 24, 36, 48, 52, and a potential Follow-up Visit. At Week 36, study participants will be provided DTG + 3TC FDC to ensure that they have enough study intervention until Week 52.

When the Investigator is modifying a participants ART regimen between scheduled visits, the study assessments shown in the SoA in Section 1.3.1 should be followed. During the ART Regimen Modification Visit, the date of the modification and the new ART regimen will be captured. Four weeks after the ART modification (Post ART Regimen Modification Visit), the participant must return for another visit to determine adherence, safety of and virologic response to the new regimen. The participants will resume regular study visit schedule after this visit. If the ART Regimen Modification Visit or the Post-ART Regimen Modification Visit occurs at a scheduled visit (Section 1.3), assessments should be completed at the scheduled visit and only the additional assessments at the ART Modification visit should be completed.

When all participants complete the Week 12 Visit, an interim analysis may be conducted to review the proportion of participants that required a modification in ART regimen.

Additional details of the potential Interim Analysis at Week 12 can be found in Statistical Considerations Section 9.6.

The primary analysis at Week 24 will take place after the last participant has had their Week 24 viral load assessed, including any retests.

All participants who remain in the study will complete the Week 52 Visit (which can occur anytime within 2-4 week of the Week 48 Visit), where study intervention stop date will be captured, and collect and follow-up on AEs and SAEs. Participants who require a virologic retest must have HIV-1 RNA level re-assessed by a second measurement performed 2-4 weeks later, which will be captured under the Week 52 Visit.

4.2. Scientific Rationale for Study Design

Individuals who receive a diagnosis of HIV-1 infection should be started on ART as soon as possible after diagnosis. Recently diagnosed individuals are often referred to HIV care providers for evaluation, follow-up and management, resulting in a delay between initiation and time ART is prescribed. This delay between diagnosis and treatment results in many individuals not engaging in their care. Thus, rapid ART initiation (Test and Treat), ideally on the same day of HIV-1 diagnosis may increase the proportion of individuals who start ART earlier and achieve and maintain viral suppression [DHHS, 2018; Saag, 2018].

When ARTs are started before HIV-1 resistance mutation results are available, the DHHS Guidelines recommend either DRV/r or DRV/c plus Tenofovir/FTC or DTG plus Tenofovir/FTC DHHS, 2018]. No specific type of tenofovir is favoured. They do not recommend NNRTIs or the use of ABC. Transmitted mutations conferring NNRTI resistance are more likely than mutations associated with PI or INSTI resistance. HLA-B*5701 results may not be available rapidly. Transmitted resistance to DRV and DTG is rare, and these drugs have high barriers to resistance. First generation INSTIs are not recommended because of lower barriers to resistance. BIC/TAF/FTC is not recommended because of lack of data.

The IAS Guidelines also recommend a rapid ART initiation for all HIV infected individuals willing to start ART [Saag, 2018]. Current IAS guidelines recommend DTG plus TAF (or tenofovir disoproxil fumarate [TDF]), emtricitabine (or lamivudine)) or bictegravir/TAF/emtricitabine or boosted darunavir TAF (or TDF), emtricitabine (or lamivudine) as initial rapid therapy. Because of concerns about transmitted drug resistance (e.g., K103N mutation), immediate ART should not be nonnucleoside reverse transcriptase inhibitor (NNRTI)–based. Participants requiring abacavir should not begin until the result of testing for the HLAB* 5701 allele is available [Saag, 2018].

Phase 3 Studies GEMINI 1 and GEMINI 2 demonstrated that a 2-drug regimen of DTG + 3TC was non-inferior to DTG + TDF/FTC in HIV-1 infected ART naïve participants, with comparable safety results observed between the 2 treatment groups [Cahn, 2019]. In both studies, Kaplan-Meier estimates of the time to viral suppression (<50 c/mL) through Week 48 indicated that participants reached viral suppression at a similar time point, irrespective of whether they received DTG + 3TC or a standard of care triple drug regimen in both treatment groups, with a median time to viral suppression of

29.0 days. The proportion of participants with HIV-1 RNA <50 c/mL by visit in the DTG + 3TC group in GEMINI 1/GEMINI 2 was 73%/71% at Week 4, 85%/ 89% at Week 8, 87%/90% at Week 12 and 92%/94% at Week 24. No statistically significant evidence of heterogeneity between the Baseline HIV-1 RNA subgroups (≤ or >100,000 c/mL) was observed for the difference in the proportion of participants with HIV-1 RNA <50 c/mL at Week 48 between arms. 2% of participants in both groups had baseline viral loads of 500,000 c/mL or more, Week 48 efficacy outcomes in these participants were similar in the two-drug regimen group (11 [85%] of 13) and three-drug regimen group (12 [80%] of 15). At Week 12, the median (IQR) log 10 c/mL change from baseline was -2.840 (-3.290, -2.450) in GEMINI 1 and -2.800 (-3.250, -2.360) in GEMINI 2.

However, there are possible barriers to DTG + 3TC use in a rapid Test and Treat model of care due to concerns over transmitted M184V, M184I and K65R resistance mutations and/or HBV-HIV co infection. Study 212355 is a pilot study being conducted to assess the feasibility, effectiveness, safety and ease of use of DTG + 3TC FDC as a first line therapy in a rapid Test and Treat model of care.

Study 212355 is a multi-center, open-label, one arm pilot study in newly diagnosed adult HIV-1 participants. Participants will start study treatment at the time of or within 14 days of the initial diagnosis and prior to the availability of Screening/Day 1 labs. The Screening/Day 1 Visit is to review participant inclusion/exclusion criteria and initiate study intervention. The Screening/Day 1 Visit will be no more than 14 days since the initial day of diagnosis. Study visits at Week 1 and Week 4 are included so that all participants will have a review of central labs and resistance genotypic data as they become available from Baseline Visit labs to confirm that DTG + 3TC FDC is an appropriate therapy (see also Section 7.2.1 and Section 7.2.2). Study visits will also occur at Week 8, Week 12 and then every 12-weeks through Week 48 to ensure compliance with study treatment, and to assess the efficacy and safety and tolerability of DTG + 3TC FDC.

4.3. Justification for Dose

The efficacy, PK, safety, and drug interaction potential of DTG and 3TC as individual agents and in combination (DTG + 3TC) have been evaluated in extensive clinical development programmes. DTG + 3TC FDC is approved in the US and marketed as DOVATO. In addition, DTG and 3TC are approved and marketed as TIVICAY 50 mg once daily and EPIVIR 300 mg once daily, respectively.

4.4. End of Study Definition

A participant is considered to have completed the study if they have completed all study visits to Week 52, which includes the Week 48 HIV-1 RNA retest if needed.

The end of the study is defined as the date of the last visit of the last participant in the study.

A Week 52 Visit is included to allow for the collection of any viral load re-test from the Week 48 Visit and to collect the end date of study intervention.

An in-clinic Follow-Up Visit will be conducted approximately 4 weeks after the last dose of study medication only for participants with ongoing AEs of interest or SAEs regardless of attributability (as defined in Section 2.3.1) at the last on-study visit. Assessments at the Follow-up Visit should reflect any ongoing complaints (e.g., blood draws to follow a laboratory abnormality). The investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

5. STUDY POPULATION

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the investigational product or other study interventions that may impact participant eligibility is provided in the Product Insert(s) for DTG and 3TC.

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or participant safety. Therefore, adherence to the criteria as specified in the protocol is essential. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

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 good clinical practice (GCP).

5.1. Inclusion Criteria

Eligible participants must:

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

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

Age

1. Participant must be ≥18 at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants must have a new confirmed diagnosis of HIV-1 infection based on the criterion below, and are willing to initiate ART immediately (or, for those

participants referred from another site, within 14 days of initial diagnosis at the external clinic/testing center); as documented in source documents.

- Participant must have an initial positive rapid HIV test

  NOTE: This includes participants whose first rapid test was positive either at the study site or those who are referred to the study site with a single positive rapid HIV test. The study site must have viewable documentation of the positive rapid test available and placed into the study source documents.

  AND

- Participant has a second positive confirmatory rapid HIV test, using a test kit from a different manufacturer than the first test

  NOTE: If the second Rapid HIV test is nonreactive, the participant is presumed to be HIV-negative. If both tests are reactive, the participant is confirmed HIV-infected.

OR

- Participant has been identified as HIV-1 infected using an FDA-approved 4th generation assay antigen/antibody combination immunoassay or 3rd generation immunoassay that detects and differentiates HIV-1 and HIV-2 antibodies

  AND

- has a confirmatory HIV western blot OR an HIV-1 RNA

OR

- Participant has a positive FDA-approved 4th generation assay and a positive 3rd generation immunoassay that detects and differentiates HIV-1 and HIV-2 antibodies.

3. Antiretroviral-naïve. Participants who received HIV post-exposure prophylaxis (PEP) or pre-exposure prophylaxis (PrEP) in the past are allowed as long as the last PEP/PrEP dose was >6 months from HIV diagnosis or there is documented HIV seronegativity at least 2 months after the last prophylactic dose and prior to the date of HIV diagnosis. The study site must have viewable documentation of the seronegative test available and placed into the study source documents.

Sex

4. Male and/or female

Participants who are female at birth:

Participants who are female at birth are eligible to participate if at least one of the following conditions applies:

- Not pregnant, as confirmed by a negative urine human chorionic gonadotropin (hCG) test at Screening/Day 1

- Pregnant and post the first trimester (the physician and patient should decide whether enrolling in this study is in the participants best interest during the consent process)
- Not a participant of childbearing potential (POCBP) (see Section 10.5.1).

OR

- A POCBP who agrees to follow the contraceptive guidance as defined in Section 10.5.2, is currently taking hormonal contraceptives and continues for at least 2 weeks after the last dose of study medication.

Participants who are female at birth and who are in the following categories are not considered POCBP

a) Premenarchal

b) Premenopausal with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

c) Postmenopausal:

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in participants who are female at birth and not using hormonal contraception or hormonal replacement therapy (HRT).
- Participants who are female at birth on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study.

The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

All participants in the study should be counselled on safer sexual practices including the use and benefit/risk of effective barrier methods (e.g., male condom) and on the risk of HIV transmission to an uninfected partner.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a participants who are female at birth with an early undetected pregnancy.

Informed Consent

5. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Participants who are breastfeeding, plan to become pregnant or breastfeed during the study

2. Participants who are in their first trimester of pregnancy;

3. HIV-1 drug resistance genotype test results are known prior to Screening/Day 1;

4. Any evidence of an active Centers for Disease Control and Prevention (CDC) Stage 3 disease [CDC, 2014], except for esophageal candidiasis and cutaneous Kaposi's sarcoma not requiring systemic therapy;

5. Participants with known or suspected Hepatitis B infection;

6. Known or suspected severe hepatic impairment or unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones);

7. Known moderate to severe renal impairment (creatinine clearance $<30ml/min/1.73m^2$);

8. Ongoing malignancy other than basal cell carcinoma, or resected, non-invasive cutaneous squamous cell carcinoma, or cervical, anal or penile intraepithelial neoplasia; other localised malignancies require agreement between the investigator and the Study Medical Monitor for inclusion of the participant;

9. Participants who in the investigator's judgment, poses a significant suicidality risk.

10. Any pre-existing physical or mental condition which, in the opinion of the Investigator, may interfere with the participant's ability to comply with the dosing schedule and/or protocol evaluations or which may compromise the safety of the participant.

11. Participants with substance abuse disorders or social restraints that the Investigator considers to be possible deterrents to successful initiation of ART.

12. History or presence of allergy or intolerance to the study drugs or their components

Exclusionary Treatments Prior to Initiation of DTG + 3TC FDC

13. Treatment with any of the following agents within 28 days of the first dose of study treatment

    - radiation therapy,
    - cytotoxic chemotherapeutic agents,
    - any systemic immune suppressant.

14. Participants receiving any prohibited medication (see Section 10.7) and who are unwilling or unable to switch to an alternate medication.

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 study treatment.

5.3. Lifestyle Considerations

This section is not applicable to this study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but do not meet all inclusion criteria or meet at least one of the exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Participants are not allowed to re-screen for this study.

Source documentation to verify entry criteria must be reviewed by the Principal Investigator or designee prior to first study treatment dose. If a participant is referred to the site for treatment, evidence of HIV-1 infection must be confirmed and documented in source documents prior to starting study treatment.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

In this study, study intervention refers to DTG + 3TC FDC. All study interventions will be administered at the approved dosages. The study intervention DTG + 3TC FDC will be supplied by ViiV Healthcare/GSK as the fixed dose combination tablet. For subjects requiring ART modification as part of this trial, provisions will be in place, as needed and

after discussion with the study team, to provide financial assistance for patients in obtaining their additional ART during the study.

DTG + 3TC FDC must be stored in a secure area under the appropriate physical conditions for the product. Access to and dispensing of the DTG+ 3TC FDC will be limited to the investigator and authorized site staff. Study intervention must be dispensed or administered only to participants enrolled in the study and in accordance with the protocol. For further details on storage, access and administration of study interventions, refer to the SRM.

Study intervention, 50 mg DTG + 300 mg 3TC FDC will be provided to all participants as first line therapy. DTG + 3TC FDC will be taken orally, once daily, with or without food.

6.1. Study Intervention Administered

Table 1 Study Intervention

ARM Name	DTG + 3TC FDC
Intervention Name	Dolutegravir + Lamivudine = GSK3515864
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	50mg DTG, 300mg 3TC
Dosage Level(s)	Take one tablet daily
Route of Administration	oral
IMP	Yes
Sourcing	Provided centrally by the Sponsor.
Packaging and Labeling	White oval film-coated tablets, debossed with 'SV 137' on one side and plain on the other, are packed in high density polyethylene (HDPE) bottles with induction seals and child-resistant closures. Each 60mL bottle contains 30 tablets and a 2-gram silica gel desiccant. Each bottle will be labelled as required per country requirement.

6.2. Preparation/Handling/Storage/Accountability

No special preparation of study intervention is required.

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability and record maintenance (i.e., receipt and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual (SRM).

- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from ViiV/GSK.
- DTG + 3TC FDC accountability will not be evaluated using pill counts. Adherence will be assessed by participant recall on number of doses missed over the 7 days prior to the visit.

6.3. Measures to Minimize Bias: Study Intervention and Blinding

This is an open-label, single arm study. The site will contact the IWRS prior to the initiation of DTG + 3TC FDC at the Screening/Day 1 Visit and record the intervention assignment on the applicable CRF.

6.4. Study Intervention Compliance

Compliance with DTG + 3TC FDC will be assessed through querying the participant during the site visits and documented in the source documents and CRF. Participants will be asked about any missed doses in the previous 7 days. A record of the number of DTG + 3TC FDC tablets dispensed to each participant must be maintained with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Dose Modification

No dose modifications are allowed for DTG + 3TC FDC. Section 7 details discontinuation and additional ART interventions allowed in this study.

6.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

Refer to Section 10.7 for a full list of prohibited medications. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants should be advised to notify their investigator of any current or proposed concomitant medication, whether prescribed or over-the-counter, because of the potential DDIs between such treatments and the study interventions. The investigator should evaluate any potential DDIs at every visit, including reviewing the most current version of the U.S. or local prescribing information for DTG and 3TC, especially if any new concomitant medications are reported by participants. All concomitant medications (including oral contraception, implants or oral or topical hormone replacement therapy) taken during the study will be recorded in the eCRF.

Concomitant medications (prescription and non-prescription) should be prescribed by the relevant health care provider/investigator and administered only as medically necessary during the Randomized and Continuation phases of the study (except prohibited medications described in Section 10.7). Chemoprophylaxis for HIV-associated conditions is encouraged, if appropriate, at the discretion of the participant and their physician. All concomitant medications, blood products, and vaccines taken during the study will be recorded in the eCRF with dates of administration.

6.6.1. Permitted Medications and Non-Drug Therapies

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 HIV-1 plasma RNA at the next scheduled assessment.

DTG + 3TC FDC should be administered 2 hours before or 6 hours after taking antacid or laxative products containing polyvalent cations (e.g. aluminium and magnesium), sucralfate, or calcium supplements. Proton pump inhibitors and H2-antagonists may be used in place of antacids with no scheduling restrictions. Concurrent administration with multivitamins is acceptable. Iron supplements can be taken with study treatment

provided that all are taken together with a meal. Under fasted conditions, DTG +3TC FDC 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 glycaemic control.

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

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.

6.7. Treatment after the End of the Study

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

7. STUDY INTERVENTION DISCONTINUATION CRITERIA

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study.

7.2. Additional Intervention Criteria

7.2.1. Baseline Laboratory Safety Criteria:

Participants meeting any of the below safety criteria based on the Baseline (Screening/Day 1) laboratory results as they become available (Week 1 Visit) will be evaluated for potential modification in their current DTG + 3TC FDC treatment and will remain in the study. See Section 1.3.1 for the assessments required when ART is modified.

- Creatinine clearance of <30 mL/min/1.73 m2 via the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method.
- Evidence of active chronic HBV infection (Investigator should consider either adding tenofovir or modifying to a tenofovir-based regimen):
    - Participants positive for HBsAg.
    - Participants negative for HBsAg and anti-HBs, positive for anti-HBc and positive for HBV DNA.

NOTE: If these results are not available for the Week 1 Visit, they should be reviewed at Week 4. Participants who are diagnosed with active chronic hepatitis B infection will have samples from the ART Modification Visit and Baseline Visit sent for HBV 3TC-resistance testing.

- Any Grade 3 or Grade 4 laboratory abnormality from the Baseline Visit, which, in the opinion of the Investigator, would end the participant's participation in this study.

7.2.2. Baseline Resistance Mutation Criteria:

Participants meeting any of the HIV-1 resistance mutation criteria based on Baseline laboratory assessments will be evaluated for additional ART interventions as the data are made available (Week 4). See Section 1.3.1 for the assessments required when ART is modified.

Participants with Baseline mutations that confer resistance to 3TC (e.g. M184V/I, K65R, etc.) or with DTG primary resistance associated mutation will discontinue study treatment but remain in the study. Investigators should modify the participants regimen based on the Baseline genotype results, in consultation with the medical monitor. A plasma sample will be obtained at Week 4 and will be sent for genotypic and phenotypic resistance testing and the result made known to the study investigator when available.

7.3. Virologic Failure Criteria

For the purposes of clinical management in this study, the criteria detailed below will apply:

Suspected Virologic Failure: A single HIV-1 RNA value as defined by Virologic Non-response or Virologic Rebound

Confirmed Virologic Failure: Any of the below conditions are met once the Investigator has confirmed participant compliance:

- **Virologic Non-Response Criteria**:
  - A decrease in Baseline plasma HIV-1 RNA of less than 2.0 log10 c/mL at Week 8, with subsequent confirmation, unless plasma HIV-1 RNA is <200 c/mL.
  - Confirmed plasma HIV-1 RNA ≥1000 c/mL at Week 12.
  - Confirmed plasma HIV-1 RNA ≥200 c/mL on or after Week 24.
- **Virologic Rebound Criteria**:
  - Confirmed rebound in plasma HIV-1 RNA to ≥200 c/mL after prior suppression to <200 c/mL.

7.3.1. Confirmatory testing of virologic non-response:

The participant must have received full doses of study treatment for at least two weeks at the time confirmatory plasma HIV-1 RNA is conducted, if at all possible. DTG + 3TC FDC (or current ART regimen) should continue to be administered and no additional ART should be added during re-testing.

Upon notification that a participant's HIV-1 RNA plasma level initially meets one of the above criteria, the investigator should query the participant regarding intercurrent illness, recent immunization, interruption of therapy or inadequate adherence.

All cases meeting "virologic management" criterion must be confirmed by a second measurement performed at least two weeks but not more than 4 weeks apart from 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 2-4 weeks following resolution of any intercurrent illness, during which time the participant should receive full dose of all antiretrovirals in the regimen.

- Confirmatory testing should be scheduled at least 4 weeks following any immunization, during which time the participant should receive full dose of all antiretrovirals in the regimen.

- If therapy is interrupted due to toxicity management, non-compliance, or other reasons, confirmatory testing should be scheduled 2-4 weeks following resumption of full dose of all antiretrovirals in the regimen.

- The participant should have received full doses of study interventions 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.

7.3.2. Management of Virologic Non-Response

Once a participant has been determined as meeting a protocol defined virologic failure criterion, a plasma sample from the Suspected Virologic Failure time point, will be sent for genotypic and phenotypic HIV-1 resistance testing and the result made known to the study investigator when available to advise on a new ARV-regimen. Plasma samples from storage will also be obtained at unscheduled visits including the time of Confirmed Virologic Failure criteria.

Plasma HIV-1 RNA values determined by the central laboratory only will be used to assess virologic management criteria. Upon notification that a participant's HIV-1 RNA plasma level qualifies him/her as meeting a virologic failure criterion, the Investigator

should query the participant regarding intercurrent illness, recent immunisation, adherence, or interruption of therapy.

Participants may continue to receive study intervention at the discretion of the investigator until results of HIV-1 resistance testing are available. Based on the results of the resistance testing, the ART regimen may be modified (see Section 7.2.2).

When the Investigator is modifying a participants ART regimen between scheduled visits, the study assessments shown in the SoA in Section 1.3.1 should be followed.

A participant who meets virologic failure criterion (Section 7.3) can remain in the study. Selection of ART regimen for participants meeting confirmed virologic failure criteria will be recorded in the eCRF.

The protease (PRO)/reverse transcriptase (RT)/integrase assays used in this study are not validated for plasma HIV-1 RNA levels <500 c/mL. Nevertheless, for all participants who meet confirmed virologic failure criteria, plasma samples will be analysed in an attempt to obtain genotype/phenotype data on samples with HIV-1 RNA ≥200 c/mL, as possible. Participants with confirmed HIV-1 RNA levels between 200 c/mL and <500 c/mL should be transitioned off study intervention within 30 days even if no HIV-1 resistance mutation results become available, as genotype/phenotype data may not be reliably generated from plasma samples collected from these participants.

Participants who meet a suspected or confirmed virologic failure can remain in the study. For participants meeting confirmed virologic failure, "Meeting Confirmed Virologic Failure" will be recorded in the eCRF as reason for the modification to a new ARV-regimen.

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

7.4. Other Additional Intervention Criteria:

Participants that meet any of the following criteria should discontinue DTG + 3TC FDC and will remain in the study. The Investigator and Medical Monitor should consult on how to medically manage these participants.

- A pregnancy (intrauterine) detected in the first trimester, should have DTG + 3TC FDC immediately discontinued and an alternative regimen that does not contain DTG should be started unless no suitable alternative is available [DHHS, 2018]. Pregnancies detected after the first trimester may continue DTG + 3TC FDC. All participants will remain in the study and will be followed until completion of pregnancy. As a reminder, participants of childbearing potential (POCBP) who change their minds and desire to be pregnant, or who state they are no longer willing to comply with the approved pregnancy avoidance methods, should have DTG + 3TC FDC discontinued and start an alternate ART regimen.

- Liver toxicity where stopping criteria are met and no compelling alternate cause is identified, these participants will discontinue study treatment and will continue in the study (see Section 10.6).

- Renal toxicity criteria are met, and no compelling alternate cause is identified (see Section 10.4.1.3);

- Grade 4 clinical AE considered causally related to study drug;

- Allergic reaction or rash criteria are met, and no compelling alternate cause is identified.

- The participant requires concurrent prohibited medications during the course of the study. The participant will discontinue study treatment and may remain in the study.

7.5. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets conditions outlined in Section 10.6.

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study intervention discontinuation is in the best interest of the participant.

Liver Safety Required Actions and Follow up Assessments can be found in Section 10.6.

7.5.1. Temporary Discontinuation

Participants may have a temporary interruption to their study intervention for management of toxicities. Such interruption of study intervention does not require withdrawal from the study. However, consultation with the Medical Monitor is required. Start and stop dates of study treatment and reason for temporary interruption will be recorded in the eCRF.

7.5.2. Study Intervention Restart

If participant meets liver chemistry stopping criteria do not restart the participant with study intervention unless:

- ViiV Healthcare Safety and Labelling Committee (VSLC) approval **is granted**,

- Ethics and/or IRB approval is obtained, if required, and
- Separate consent for treatment restart is signed by the participant.
- Refer to Section 10.6.2 for full guidance.

If GSK/ViiV Medical Governance approval to restart/re-challenge participant with study intervention **is not granted**, then participant must discontinue study intervention and may continue in the study with alternate ART interventions.

7.6. Participant Discontinuation/Withdrawal from the Study

Participants may be discontinued from the study for any of the following reasons:

- Participant or Investigator non-compliance;
- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early Withdrawal Visit should be conducted, as shown in the SoA (Section 1.3). The SoA has the 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 may be permanently discontinued both from the study intervention and from the study at that time.

- 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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

- At the request of, GSK or ViiV Healthcare;
- The participant requires concurrent prohibited medications during the course of the study (Section 10.7). 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. Alternatively, the participant can have study intervention discontinued and remain in the study with additional ART interventions.

Refer to the SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

All data from the Withdrawal Visit will be recorded, as they comprise an essential evaluation that should be done prior to discharging any participant from the study. An in-clinic Follow-Up Visit will be conducted 4 weeks after the last dose of study medication for participants with ongoing SAEs regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant (as defined in Section 2.3.1), at the last on-study visit. The investigator, in consultation with

the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

Participants are not obligated to state the reason for withdrawal. However, a reason for withdrawal must be documented by the Investigator on the Completion/Withdrawal section of the electronic case report form (eCRF). Every effort should be made by the Investigator to follow-up participants who withdraw from the study.

7.7. Lost to Follow Up

A participant will be considered lost to follow-up if he or she 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 and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not 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, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA in Section 1.3.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- 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. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for Screening/Day 1 purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.

Screening/Day 1 Assessments

Written informed consent must be obtained from each potentially eligible participant by study site personnel prior to the initiation of any Screening procedures as outlined in this protocol. The consent form must have been approved by the IRB. After signing an informed consent, participants will complete Screening assessments to determine participant eligibility. Each participant being screened for enrolment evaluation will be assigned a participant number at this Visit. This number will be given sequentially in chronological order of participant presentation according to a numeric roster provided by PPD.

Eligibility criteria must be assessed carefully at the Screening/Day 1 Visit (Section 5.1 and Section 5.2). Physical examinations should be conducted as part of normal routine clinical care but will not be collected systematically in the eCRF. Cardiovascular medical history/risk factors, including vital signs (as detailed in the eCRF) will be assessed and assessments will include height, weight, blood pressure, smoking status and history, pertinent medical conditions (e.g., hypertension, diabetes mellitus), and family history of premature cardiovascular disease. Background information to be collected includes demography (year of birth, sex at birth and current reported gender, race and ethnicity), prior PEP/PrEP history, medical history and current medical conditions, menopause history, concomitant medications, and an assessment of CDC HIV-1 classification, as detailed in Section 1.3.

Participants are considered HIV-1 infected when they have positive results from 2 different HIV Rapid tests (different assay or manufacturer), or they are positive with an FDA-approved antigen/antibody combination immunoassay (4th generation assay) or an FDA approved HIV antibody immunoassay that detects HIV-1 and HIV-2 antibodies (3rd generation assay) confirmed by an FDA-approved antibody immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies or an HIV western blot or an HIV-1 RNA. See Inclusion Criteria for additional information (Section 5.1).

- For participants who are referred to the study site with a single positive Rapid HIV test, a second and different Rapid HIV test should be conducted. If the second Rapid HIV test is nonreactive, the participant is presumed to be HIV-negative. If both tests are reactive, the participant is confirmed HIV-infected.

Medical records/Source documents from external testing centers or medical facilities must be received, reviewed and included in the site source documentation to confirm participant has a new diagnosis of HIV-1 infection.

Other Screening/Day 1 information to be collected prior to the first dose of study intervention includes assessment of HIV risk factors and mode of transmission, general medical history and current medical conditions. Laboratory and health outcomes assessments will also be collected. Questionnaire/surveys are recommended to be administered at the beginning of the visit before any other assessments are conducted. Refer to the SoA Section 1.3 for a summary of all procedures at the Screening/Day 1 Visit.

Week 1 Review of Baseline laboratory results

The Investigator should review the Screening/Day 1 laboratory findings as they become available and schedule a study visit (Week 1 Visit).

A review of creatinine clearance and HBV surface antigen (HBsAg) or HBV core antibody (anti-HBc), and HBV DNA if available, (if not available at Week 1, review at Week 4) and grade 3 or 4 laboratory abnormalities should be completed to determine if the participant should stop study intervention and initiate an alternate ART regimen (see Section 7.2.1).

Subjects Co-infected with Hepatitis B Virus (HBV)

- Investigators should consult current treatment guidelines [Saag, 2018]) and Section 7.2.1 when considering choice of ART regimen for subjects with chronic HBV infection (HBsAg positive OR anti-HBc positive with HBV DNA present).

- In addition, clinical trial and marketed use of 3TC, FTC and TDF have shown that some subjects with chronic HBV disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of 3TC, FTC or TDF, which may have more severe consequences in subjects with decompensated liver disease. Subjects with HBV co-infection should be advised against self-discontinuation of any medications with anti-HBV activity. If 3TC, FTC, TDF or TAF is discontinued in subjects co-infected with HBV, periodic monitoring of both liver chemistry tests and markers of HBV replication should be performed.

- Entecavir and telbivudine are permitted, in appropriate clinical situations, for treatment of hepatitis B (e.g. prior intolerance or viral resistance to TDF or TAF, viral resistance to 3TC/FTC) after discussion and agreement between the investigator and the medical monitor.

Subjects Co-infected with Hepatitis C Virus (HCV)

- Investigators should consult current treatment guidelines when considering choice of therapy for subjects with chronic HCV infection.

- For participants with a requirement for HCV therapy during the conduct of the study, the Investigator must consult with the medical monitor. HCV treatment based on interferon or any other medications that have a potential for adverse drug-drug interactions with study treatment, is prohibited during the conduct of the study.

Review of Resistance Mutation Data when available (Week 4)

A visit should be scheduled when the central laboratory data from Screening/Day 1 genotypic HIV-1 drug resistance mutation data are available (Week 4) and additional intervention should be performed if required (see Section 7.2.2). The investigator should also review the tolerance to DTG + 3TC FDC, AEs, assess adherence to study treatment and enforce the importance of adherence.

At Week 8, if the decrease HIV-1 RNA is less than 2.0 log10 c/mL, a plasma HIV-1 RNA retest should be scheduled 2-4 weeks later, unless plasma HIV-1 RNA is <200 c/mL; after the retest the Investigator in consultation with the Medical Monitor should determine if a modification in ART intervention is warranted.

If a subject requires a regimen modification (e.g., based on Baseline labs or a Confirmed Virologic Failure), a plasma HIV-1 RNA retest should be scheduled 4 weeks after the regimen modification (Section 1.3.1). Post the retest, the participant should continue the regular study visit schedule.

Participants who have an ART modification due to Baseline laboratory or HIV-1 resistance data as described in Section 7.2.1 and Section 7.2.2, respectively, and require subsequent modification(s) will remain in the study.

8.1. Efficacy Assessments

Plasma HIV-1 RNA

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

See Section 7.3 (Virologic Failure Criteria) for HIV-1 RNA re-test criterion.

Lymphocyte Subsets

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

CDC HIV-1 Classification and HIV Associated Conditions

HIV-associated conditions will be recorded as per the Schedule of Activities (Section 1.3). HIV associated conditions will be assessed according to the 2014 CDC Revised Classification System for HIV Infection in Adults (see Section 10.9). When assessing CDC stage at Screening/Day 1, consider only the latest available CD4+ T-cell count, except when the participant had an active Stage 3 event. Indicators of clinical disease progression are defined as:

CDC Stage 1 at enrolment → Stage 3 event;

CDC Stage 2 at enrolment → Stage 3 event;

CDC Stage 3 at enrolment → New Stage 3 Event;

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

8.1.1. Primary Efficacy Endpoint

The primary endpoint will be the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24, regardless of ART Regimen (Observed Analysis) (see Section 9.5).

8.1.2. Secondary Efficacy Endpoints

- Proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 48, regardless of ART Regimen (Observed Analysis).
- Proportion of participants with plasma HIV-1 RNA <50 c/mL at Weeks 24 and 48 using the FDA Snapshot algorithm.
- Time to suppression of HIV-1 RNA <50 c/mL.
- Proportion of participants who modify first line regimen of DTG + 3TC FDC due to Baseline lab or HIV-1 resistance mutation data (see Section 7.2).
- Change from Baseline in CD4+ cell counts and CD4+/CD8+ ratio at Week 24 and Week 48.
- Incidence of disease progression (HIV-associated conditions, AIDS and death).

8.2. Safety Assessments

- Incidence and severity of AEs and laboratory abnormalities.
- Proportion of participants who discontinue treatment due to AEs and drug-related AEs over 48 weeks of treatment

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

8.2.1. Physical Examinations

A brief physical examination at the Screening/Day 1 Visit will include, at a minimum, assessments of the [e.g., skin, lungs, cardiovascular system]. Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

8.2.2. Vital Signs

- At the Screening/Day 1 Visit, vital signs will be measured in semi-supine position after 5 minutes rest and will include height, weight, systolic and diastolic blood pressure and Body Mass Index (BMI). Vital signs and body weight will also be assessed at each visit according to the Schedule of Activities (SoA) (Section 1.3).

8.2.3. Clinical Safety Laboratory Assessments

Refer to Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.

- All protocol required laboratory assessments must be performed by central laboratory services. Laboratory assessments must be conducted in accordance with the Laboratory Manual, and SoA (Section 1.3). Laboratory requisition forms must be completed, and samples must be clearly labelled with the participant number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by Q^2 Solutions and are detailed in the laboratory manual. Reference ranges for all safety parameters will be provided to the site by Q^2 Solutions.
- If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification) the results must be recorded in the eCRF.
- Labs will be graded automatically by the central laboratory according to the DAIDS toxicity scales (See Section 10.8 "Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events").
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study intervention should be repeated until the values return to normal or Baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If such values do not return to normal/Baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.
- Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Section 10.2.

8.2.4. Suicidal Ideation and Behaviour Risk Monitoring

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, there have been some reports of depression, suicidal ideation and behaviour (particularly in people with a pre-existing history of depression or psychiatric illness) in some people being treated with INIs, including DTG. Therefore, it is appropriate to monitor and closely observe

participants prospectively before and during treatment for suicidal ideation and/or behaviour, or any other unusual changes in behaviour.

Participants should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. Investigator must assess participant suicidality using their usual clinical practice. It is recommended that the investigator consider mental health consultation or referral for participants who experience signs of suicidal ideation or behaviour. Participants presenting with new onset/treatment emergent depression should be advised to contact the investigator immediately if symptoms of severe acute depression (including suicidal ideation/attempts) develop, because medical intervention and discontinuation of the study medication may be required.

The investigator will collect information using the Possible Suicidality-Related AE (PSRAE) eCRF form in addition to the AE (non-serious or SAE) eCRF form on any participant that experiences a possible suicidality-related AE while participating in this study. This may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. PSRAE forms should be completed and reported to ViiV/GSK within 1 week of the investigator diagnosing a possible suicidality-related AE. All sites should have a plan in place for managing possible risks for suicide related events.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3.1 and Section 10.3.2, respectively.

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue the study intervention (see Section 7.2 and Section 7.4).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period and frequency for collecting AE and SAE information is as follows:

- All SAEs will be collected from the start of intervention until the Follow-up Visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a ViiV/GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of study intervention until the Follow-up Visit, at the time points specified in the SoA (Section 1.3).

- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee 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.
- Investigators are not obligated to actively seek AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

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.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 2.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.7). Further information on follow-up procedures is given in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

Details of all pregnancies in participants will be collected after the start of study intervention and ending at the final Follow-up Visit. If a pregnancy is reported, the investigator should inform ViiV/GSK/PPD within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.5.3. Participants who become pregnant and are in the first trimester should immediately discontinue DTG + 3TC FDC and an alternate ART regimen that does not contain DTG should be started, unless no suitable alternative is available, in consultation with the Medical Monitor. If the pregnancy is after the first trimester, the participant can continue study treatment. Any participant who becomes pregnant during the study can remain in the study, including those who needed to modify the ART Regimen.

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

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

- GSK's central safety department will forward this information to the ART Pregnancy Registry. The international registry is jointly sponsored by manufacturers or licensees of ARV products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.

8.3.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

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

The events or outcomes listed in the CDC Classification System for HIV-1 Infections (Section 10.9) 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), or
- The event or outcome is in the investigator's opinion of greater intensity, frequency or duration than expected for the individual participant, or
- Death occurring for any reason during a study, including death due to a disease-related event, will always be reported promptly.
- Lymphomas and invasive cervical carcinomas are excluded from this exemption; they must be reported as SAEs even if they are considered to be HIV-related.

8.4. Treatment of Overdose

For this open-label study, any tablet intake exceeding the daily tablet of DTG + 3TC FDC will be considered an overdose [TIVICAY Product Insert, 2018; EPIVIR Product Information, 2018]. ViiV Healthcare does not recommend specific treatment for an overdose of DTG + 3TC FDC. As appropriate, the Investigator should use clinical judgment in the treatment of an overdose.

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 10.3). 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 AE/SAE and laboratory abnormalities until DTG + 3TC FDC can no longer be detected systemically (at least 2 days).
3. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

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

8.5. Pharmacokinetics

PK parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not being evaluated in this study.

8.9. Health Economics and Outcome Research

Health outcomes assessments will be conducted according to the SoA (Section 1.3). In the event of translations being unavailable, no such assessments will be conducted, and the responses will be considered as missing in the final analyses. Assessments are recommended to be administered at the beginning of the visit prior to collection of blood for analysis and other scheduled assessments.

Questionnaires will be administered on paper and should be completed by participant without the assistance of others where possible. If a subject is unable to read, it is acceptable for site personnel to read the questions and response options directly as written with no further interpretation or assistance. In these situations, subject must clearly indicate their responses which may be recorded on paper form by site personnel. Sites should enter participant responses into eCRF and retain the paper forms in the participants chart.

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

The Symptom Distress Module (also called the HIV Symptom Index or Symptoms Impact Questionnaire) is a 20-item self-reported measure that addresses the presence and perceived distress linked to symptoms commonly associated with HIV or its treatment [Justice, 2001].

8.10. HIV-1 Polymerase Viral Genotyping and Phenotyping

Whole venous blood samples will be obtained from each participant to provide plasma for storage samples according to the Schedule of Activities in Section 1.3 (for potential viral genotypic and phenotypic analyses). Participants meeting Confirmed Virologic Failure criteria or having HIV-1 resistance mutations to study drugs detected at Baseline will have plasma samples tested for HIV-1 PRO and RT genotype and phenotype and HIV-1 integrase genotype and phenotype from samples collected at the time of meeting Suspected Virologic Failure criteria; these results will be reported to the investigator as

soon as available to provide guidance for selection of an alternative regimen (see Section 7.3)

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

A secondary endpoint of the study will be the incidence of observed genotypic and phenotypic resistance to DTG or 3TC in participants meeting Confirmed Virologic Failure criteria. If participants meet a second Confirmed Virologic Failure after initiating a new ART regimen during the study, susceptibility to any ART therapy received will also be assessed.

8.10.1. HIV-1 Exploratory Analysis

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is a single arm study; no formal statistical hypothesis will be tested.

9.2. Sample Size

The study will recruit approximately 120 individuals. It is expected around 150 individuals to be screened to meet this number of enrolled individuals. If less than 120 individuals have been enrolled after 150 individuals have been screened, screening will continue until enrolment of approximately 120 individuals is met.

9.2.1. Sample Size Considerations

This is a single-arm study with no statistical testing being performed therefore the sample size is not statistically powered. The study will enrol approximately (±5%) 120 HIV-1 treatment naïve individuals. The sample size of 120 participants allows estimation of the response rate at Weeks 24 and 48 (i.e. HIV-1 RNA <50 c/ml), with precision shown in Table 2, assuming a high number of participants (i.e. ≥80% of participants) will be responders. Table 2 shows the estimated response rate, 95% Confidence Interval (CI) based on the Clopper-Pearson method and precision measured by 95% CI width, assuming various numbers of responders for the given sample size of 120 participants.

Table 2 Estimated Response Rate, 95% Confidence Interval and precision assuming various number of responders

Sample Size	Number of Responders	Response Rate	95% Confidence Interval	Precision (95% CI Width)
120	96	80%	71.7% - 86.7%	15.0%
120	102	85%	77.3% - 90.9%	13.5%
120	108	90%	83.2% - 94.7%	11.5%
120	114	95%	89.4% - 98.1%	8.7%

9.2.2. Sample Size Sensitivity

Figure 2 shows sensitivity of expected response rate precision (measured by the width of the 95% CI) versus sample size, assuming four population response rates (i.e. 80%, 85%, 90% and 95%). Note that a much larger sample size than 120 participants is required to achieve higher precision in the estimated response rate for all four assumed observed rates. For example, to get a ~40% more precise response rate estimate (for any of the four assumed response rates) a sample size of ~300 participants is needed.

Figure 2 Sample Size Sensitivity

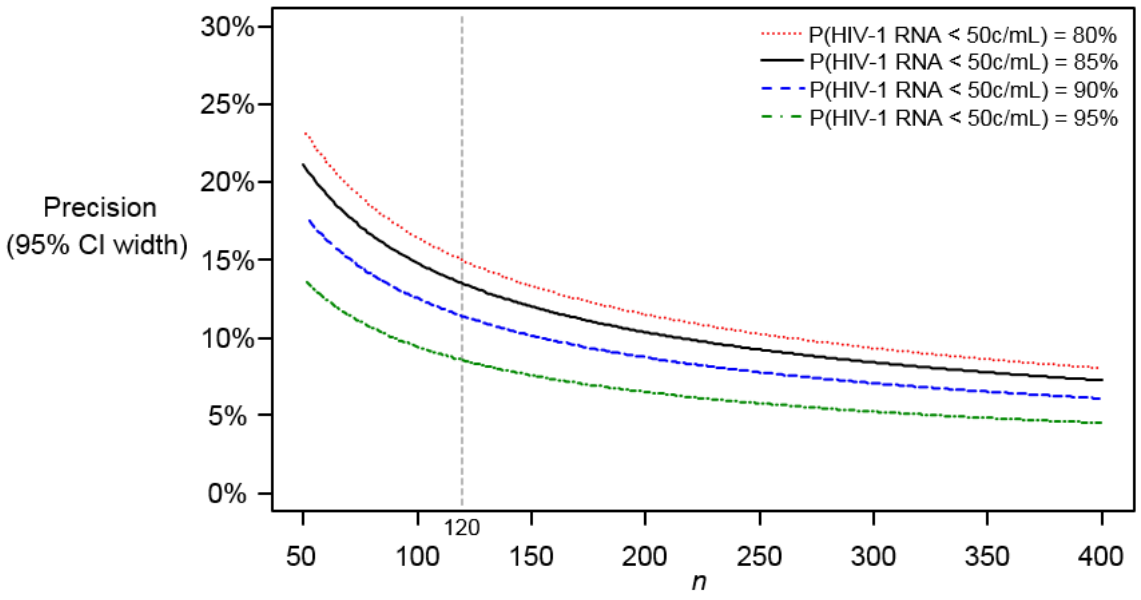


Figure 2: Expected precision (measured by 95% CI width) of estimated proportion of participants with HIV-1 RNA < 50 c/mL assuming four population response rates (i.e. 80%, 85%, 90%, 95%) versus sample size. Clopper-Pearson 95% CI widths have been calculated. The vertical grey dash line corresponds to a sample size of 120 participants which is the sample size used in the current study.

9.3. First-line DTG + 3TC FDC Regimen Modification

Participants meeting any of the safety criteria described in Section 7.2.1 (i.e. Creatinine clearance of <30 mL/min/1.73m2, evidence of active HBV infection, Grade 3 or 4 laboratory abnormality) will be evaluated for potential modification in their current first line DTG + 3TC FDC treatment and participants with Screening/Day 1 genotypic data that confer resistance to 3TC (e.g. M184V/I, K65R etc.) or with DTG primary resistance associated mutation will discontinue study treatment. Assuming that the probability a participant to have a modification from first line DTG + 3TC FDC regimen because of any of the above reasons ranges from 1% to 5%, the probability at least one participant to modifying ART because of the above reasons ranges from 70% to 100%, assuming a sample size of 120 participants.

9.4. Data Analysis Considerations

9.4.1. Analysis Populations

For purposes of analysis, the following populations are defined:

Table 3 Analysis Populations

Population	Description
Enrolled	All participants who sign the ICF
Intent to Treat Exposed (ITT-E)	All participants who receive at least one dose of study drug. This population will be used in all efficacy analyses.
Safety	This population will be the same as the ITT-E population and will be used in all Safety analyses

The analysis populations for genotypic and phenotypic analyses and other populations potentially needed for other analyses will be fully described in the reporting and analysis plan (RAP).

9.5. Key Elements of the Analysis Plan

9.5.1. Efficacy Analysis

Primary analysis will be conducted when all Week 24 assessments have been performed at the Week 24 Visit, including any viral load re-test, if needed.

The primary analysis will be the proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24 Visit, regardless of the ART regimen (Observed Analysis).

The primary Week 24 Observed Analysis will classify participants into Virologic Success or Virologic Failure categories as follows:

Virologic Success

Participants with HIV-1 RNA < 50 c/mL at Week 24 will be classified as Virologic Successes irrespective of the ART regimen they take at Week 24 (switch from DTG + 3TC FDC to another ART is not penalised); re-test at Week 24 will be considered.

Virologic Failure

The following cases will be classified as Virologic Failure:

- Participants with plasma HIV-1 RNA ≥ 50 c/mL at Week 24 (re-test considered)
- Participants with missing plasma HIV-1 RNA assessment at Week 24, but still on study
- Participants who withdrew from study for any reason before Week 24 visit

Further details of the primary analysis will be provided in the RAP.

9.5.2. Secondary Analyses

Analysis of proportion of participants with HIV-1 RNA <50 c/mL at Week 48 Visit, regardless of the ART Regimen (Observed Analysis, similar to the primary analysis at Week 24).

Analysis of proportion of participants with plasma HIV-1 RNA <50 c/mL at Week 24 and Week 48, using the FDA's Snapshot algorithm.

FDA's Snapshot algorithm will classify all participants without plasma HIV-1 RNA data at the visit of interest, i.e. Week 24/48, either due to missing plasma HIV-1 RNA assessment but on study, or due to permanent discontinuation of study treatment prior to visit window as Virologic non-Success. Participants who will switch from first line regimen of DTG + 3TC FDC for any reason prior to the visit of interest will also be classified as Virologic non-Successes. Participants still on DTG + 3TC FDC at the time of last HIV-1 RNA assessment at the visit interest will be classified as Virologic Successes if plasma HIV-1 RNA < 50 c/mL, or as Virologic Failures if plasma HIV-1 RNA ≥50 c/mL.

Full details of the FDA's Snapshot algorithm will be provided in the RAP.

Other key efficacy secondary analyses:

- Proportion of participants with ART modifications from the first line regimen due to abnormal Baseline laboratory or Baseline genotypic resistance data. Proportion of participants with a modification from the first line regimen due to any reason.

- The incidence of HIV-1 disease progression (AIDS and death).

- Subgroup analyses of proportion of participants with plasma HIV-1 RNA <50 c/mL using the Observed Analysis and changes from Baseline in CD4+ cell count will be summarised by age, gender, race, Baseline CD4 counts and Baseline HIV-1 RNA levels.

- A time to event analysis for the time to first HIV-1 RNA < 50 c/ml.

Full details of all secondary efficacy endpoints will be provided in the RAP.

Given that participants are allowed to remain in the study after ART modification (e.g. due to Baseline laboratory or HIV-1 resistance mutation results, meet Suspected or Confirmed Virologic Failure criteria, toxicity etc.) or protocol deviations (e.g. administration of prohibited medication, first trimester pregnancy etc.) a very small number of early study withdrawals is expected (mainly due to lost to follow-up or withdraw consent). Data will be allocated to visit windows using actual visit dates rather than nominal visit dates. Data collected from extra visits within a visit window will be listed and will be included in the derivation of the Observed and Snapshot response at analysis visits of interest, but summary tables (e.g. change in CD4+) using observed case datasets will only use the data captured closest to the target visit date. Detailed explanations of the definition of visit windows will be included in the RAP. Any deviations from planned analyses will be detailed in the clinical study report (CSR).

9.5.3. Safety Analyses

The observed case dataset will be the primary dataset used for analysis of safety endpoints. All safety analyses will be based on the Safety analysis population.

All Safety analyses will be based on period under treatment with DTG + 3TC FDC. In addition, selected safety endpoints will also be analysed including data after participants have ART modifications from DTG + 3TC FDC.

Exposure to first line regimen of DTG + 3TC FDC, measured by the number of weeks on study drug, will be summarized.

The proportion of participants reporting AEs will be tabulated. The following summaries of AEs will be provided for AEs with onset under treatment with DTG + 3TC FDC (i.e. AEs occurred after DTG + 3TC FDC modification will be excluded) at the analysis time period:

- Incidence and severity of all AEs;

- Incidence and severity of treatment related AEs;

- Incidence and severity of AEs leading to withdrawal; and

- Incidence of SAEs.

In addition, the following summaries of AEs will be provided including those occurring after treatment modification from DTG + 3TC FDC:

- Incidence and severity of all AES;
- Incidence and severity of treatment related AEs;
- Incidence and severity of AEs leading to withdrawal; and
- Incidence of SAEs

Laboratory and vital signs data will be summarised by visit including data under treatment with DTG + 3TC FDC (i.e. data after ART modification to be excluded) only. In addition, the number and percentage of participants with graded laboratory toxicities (based on DAIDS categories; Section 10.8) will be summarised for those occurring when under treatment with DTG + 3TC FDC and for the overall period under study treatment (i.e. data after DTG + 3TC FDC modification to be considered). Further details of safety analyses will be included in the RAP.

9.5.3.1. Viral Genotyping/Phenotyping Analyses

The incidence of treatment-emergent genotypic and phenotypic resistance to DTG and 3TC will be summarised for participants meeting Confirmed Virologic Failure criteria (Section 7.3). Details of genotypic/phenotypic analyses to be performed will be specified in the RAP.

9.5.4. Other Analyses

The Symptom Bother analysis will be described in the reporting and analysis plan.

9.6. Interim Analyses

One analysis will be conducted to evaluate the primary objective of the protocol when all subjects have completed their Week 24 Visit.

A Week 12 interim analysis may be conducted after the last participant completes the Week 12 Visit. It is not required for participants to have completed a Week 12 viral load re-tested, if needed, for this analysis. The main purpose of the analysis, if conducted, will be to assess the proportion of participants that required a modification in the first line ART regimen, following the evaluation of Baseline laboratory and Baseline genotypic resistance mutation results. Results of the potential Week 12 analysis may be publicly presented before the publication of primary Week 24 results. There are no planned modifications to the study based on the interim analysis results.

A Week 48 analysis will be conducted when all participants have had their Week 52 Visit and follow-up visit (if required). This includes any visits for viral load re-test following the Week 48 Visit. The Week 48 analysis will be the last (End of Study) analysis and the only planned analysis after the primary Week 24 analysis. Results from Week 24 and 48 analyses will be publicly presented.

As the potential Week 12 analysis and the Week 48 analysis are secondary and the study is single arm with no statistical hypothesis testing performed, no adjustment for multiplicity is needed.

The Reporting and Analysis Plan will describe the planned analyses in greater detail.

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:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
    - Notifying the IRB of SAE or other significant safety findings as required by IRB procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, 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 his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB or study center.
- 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 re-consented 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 or the participant's legally authorized representative.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. 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.
- The participant must be informed that his/her personal 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.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ViiV/GSK site or other mutually-agreeable location.
- ViiV/GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with ViiV/GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical

Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

10.1.8. 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 CRF 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 can be found in the SRM.

10.1.9. Study and Site Closure

ViiV/GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of ViiV/GSK. 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:

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing
  - Refer to Section 5.1 Inclusion Criteria for Screening/Day 1 pregnancy criteria.
  - Pregnancy testing (urine and/or serum) should be conducted at all study visits.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, to establish the absence of pregnancy at any time during the participant's participation in the study.
  - Study intervention should be discontinued if a pregnancy is detected in the first trimester, and the participant can remain in the study on a modified (new, non-DTG based) ART regimen. Pregnancies detected after the first trimester can continue DTG + 3TC FDC.

Table 4 Protocol-Required Safety Laboratory Assessments

Hematology:			
Platelet count		Automated WBC differential:	
RBC count		Neutrophils	
WBC count (absolute)		Lymphocytes	
Hemoglobin		Monocytes	
Hematocrit		Eosinophils	
MCV		Basophils	
MCH			
Clinical Chemistry:			
BUN	Potassium	AST	Total bilirubin Direct bilirubin[a]
Creatinine	Chloride	ALT[a]	Albumin
Glucose	Total CO2	Alkaline phosphatase	GFR/Creatinine clearance[b]
Sodium		Phosphate	Cystatin-C (Day 1 only)
Calcium		Protein	
Lipid Panel			
Total cholesterol			
HDL cholesterol			
LDL cholesterol			
Triglycerides			
Urinalysis			
specific gravity, pH, glucose, protein, blood and ketones by dipstick (with microscopic examination if blood or protein is abnormal), urine albumin/creatinine ratio, urine protein/creatinine ratio			
Other Tests			
Plasma HIV-1 RNA[c]			
CD4+ and CD8+ lymphocyte counts, CD4+/CD8+ cell count ratio			
Hepatitis B (HBsAg, anti-HBc, anti-HBs, HBV DNA); HBV 3TC Resistance[e], HBV DNA[e]			
Hepatitis C (anti-HCV)			
Pregnancy test for participants of childbearing potential[d]			
HLA B5701 test[f]			

1. MCV = mean corpuscular volume, MCH = mean corpuscular haemoglobin, RBC = red blood cells, WBC = white blood cells, BUN = Blood urea nitrogen, AST=aspartate aminotransferase, ALT = alanine aminotransferase, CO_2 = carbon dioxide, HDL = high density lipoprotein, LDL = low density lipoprotein, HbsAg= hepatitis B virus surface antigen, anti-HBc = Hepatitis B Core Antibody, HBV = Hepatitis B virus.

a) Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.5 and Section 10.6. 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 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI-creatinine) [Levey, 2009]. In addition, GFR will be estimated by the central laboratory using the CKD-EPI-cystatin C [Inker, 2012] at Screening/Day 1 and when indicated by renal toxicity criteria.

c) For participants meeting virologic failure criteria, plasma samples and whole blood may be analyzed in attempt to obtain genotype/phenotype data.

d) Urine pregnancy test/ serum pregnancy test will be performed according to the Schedule of Activities.

e) For participants with chronic HBV infection, testing for HBV 3TC resistance will be performed using samples from Week 1 and Week 4 (depending on when ART modification occurs) as well as Screening/Day 1 samples. HBV DNA will also be obtained at the Week 1 or Week 4 visit.

f) Please consult with the Medical Monitor.

10.3. Appendix 3: Adverse Events: 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 intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the

investigator to be more severe than expected for the participant's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**

- **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.

Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or 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.

Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical

significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect
Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF 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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports)

related to the event.

- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. 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 GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the categories in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events ("DAIDS AE Grading Table") in Section 10.8:

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

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment [TIVICAY Package Insert,

2018; EPIVIR Package Insert, 2018; DOVATO Package Insert, 2019].

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to ViiV/GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to ViiV/GSK/PPD.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by ViiV/GSK/PPD to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide ViiV/GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE and other events to ViiV/GSK/PPD

Reporting of SAEs and other events to ViiV/GSK/PPD

- The primary mechanism for reporting SAE to ViiV/GSK/PPD 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) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to study intervention/study participation (causality) within

72 hours of SAE entry into the eCRF.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line 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 off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to ViiV/GSK/PPD via Paper CRF

- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and scan and email it to the Medical Monitor
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

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 Section 10.8). Additional information regarding detecting, documenting and reporting AEs and SAEs are available in Section 10.3.

Study intervention may be interrupted at the discretion of the investigator and according to the severity of the AE. If DTG + 3TC FDC is held due to toxicity or AEs, all additional ART medications that were added per protocol, should be held to reduce the risk of development of HIV-1 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 interventions will be allowed. Study intervention 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 intervention or temporary interruption of one but not all drugs within the ART regimen must be discussed with the Medical Monitor and 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 intervention interruptions based on the severity of the AE for specific toxicities. All modifications in study intervention 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 intervention at the discretion of the investigator. The investigator may also choose to discontinue DTG + 3TC FDC and change to an alternate ART and participant can remain in the study. Participants who choose to withdraw from the study due to a Grade 1 or 2 AE should have the 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 intervention, 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 interventions should have study intervention withheld and be rechecked each week until the AE returns to Grade 2. Once the AE is Grade ≤2, study intervention may be restarted.

Should the same Grade 3 AE recur within 28 days in the same participant, study intervention should be permanently discontinued, evaluated to have a new ART treatment initiated, and can remain in the study. Participants experiencing Grade 3 AEs requiring

permanent discontinuation of study intervention should be followed weekly until resolution of the AE. Participants who choose to withdraw from the study should have the Follow-up Visit performed 4 weeks after the last dose of study interventions.

Participants with 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 intervention if the investigator has compelling evidence that the toxicity is not related to study intervention.

Exceptions are noted for rash in Section 10.4.1.6 and lipid abnormalities in Section 10.4.1.7.

Grade 4 Toxicity/Adverse Event

Participants who develop a Grade 4 AE or toxicity should have study intervention discontinued. However, if the investigator has compelling evidence that the AE is not causally related to the study interventions, 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 intervention should have a new ART regimen initiated and can remain in the study. These participants should be followed weekly until resolution of the AE. Participants who choose to withdraw from the study are encouraged to complete the Withdrawal and Follow-up evaluations.

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 intervention. Exceptions are noted for lipid abnormalities in Section 10.4.1.7.

An in-clinic Follow-Up Visit will be conducted approximately 4 weeks after the last dose of study medication for participants with ongoing AEs, serious adverse events (SAEs) regardless of attributability, and any laboratory abnormalities that are considered to be AEs or potentially harmful to the participant (as defined in Section 2.3.1), at the last on-study visit. The investigator, in consultation with the medical monitor, should follow-up with the participant until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up.

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 intervention are provided below.

Participants who permanently discontinue study intervention for reasons of toxicity may remain in the study and have a new ART regimen initiated. The participant should be followed weekly until resolution of the AE. Participants who choose to withdraw from the study are encouraged to complete the Withdrawal and Follow-up evaluations.

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 aetiology during administration of study intervention and the follow-up period. For a complete listing of stopping and follow-up criteria refer to Section 10.6.1.

10.4.1.2. Restarting Study Intervention

Refer to Section 10.6.2 for details on drug restart following transient resolving liver events not related to study intervention.

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, urine albumin/creatinine and urine total protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker , 2012] should also be done at this confirmatory visit. If the creatinine increase is confirmed, the investigator should contact the study medical monitor to discuss additional follow-up and medical management.

Participants who experience progression to an estimated GFR (using the CKD-EPI-creatinine) of <30 mL/min/1.73m^2 must return for a confirmatory assessment within 2 weeks [Levey, 2009]. A urinalysis, urine albumin/creatinine and urine protein/creatinine ratios, serum cystatin C and an estimated GFR using the CKD-EPI (cystatin C) [Inker , 2012] should be done at this confirmatory visit. If an estimated GFR of <30 mL/min/1.73m^2 is confirmed using the CKD-EPI (cystatin C), then study intervention should be discontinued, and new ART initiated.

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.

Refer to the SPM for details on the collection and processing of these urine samples.

10.4.1.5. Allergic reaction

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

Participants with Grade ≥3 allergic reactions that are considered to be possibly or probably related to the study intervention should permanently discontinue study intervention, and a new ART regimen initiated. Participants should be treated as clinically appropriate and followed until resolution of the AE. Participants who choose to withdraw from the study are encouraged to complete the Withdrawal and Follow-up evaluations.

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 characterisation of HSR and rash observed with DTG-containing ART, please see the current version of the IB and any IB supplements [DTG IB, 2018; TIVICAY Product Insert, 2018].

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

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

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

The rash and any associated symptoms should be reported as adverse events and appropriate toxicity ratings should be used to grade the events (based on DAIDS toxicity gradings, Section 10.8.

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

REFERENCE:

Inker LA, Schmid CH, Tighiouart H, Eckfeldt J.H, Feldman H.I, Greene T, et al; Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *N Engl J Med*. 2012;367:20-9.

Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III A.F, Feldman H.I, et.al. A new equation to estimate glomerular filtration rate. *Ann Int Med*. 2009;150:604-12.

10.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

10.5.1. Definitions:

Participants of Childbearing Potential (POCBP)

A female at birth is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Participants who are female at birth in the following categories are not considered POCBP

1. Premenarchal
2. Premenopausal with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in participants who were females at birth and not using hormonal contraception or hormonal replacement therapy (HRT).
   - Females at birth on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study.

10.5.2. Contraception Guidance:

Participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 5.

The list does not apply to participants of child bearing potential who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar,

ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Table 5 List of Highly Effective Contraceptive Methods

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

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

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

• Sexual abstinence   • *Note: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant*
a. Contraceptive use by participants 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. 1. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure with friction)

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

10.5.3. Collection of Pregnancy Information:

Participants who become pregnant and are in the first trimester should immediately discontinue DTG + 3TC FDC and an alternate ART regimen that does not contain DTG should be started, unless no suitable alternative is available, in consultation with the Medical Monitor. If the pregnancy is after the first trimester, the participant can continue study treatment. Any participant who becomes pregnant during the study can remain in the study, including those who needed to modify the ART Regimen.

- Investigator will collect pregnancy information on any female participant at birth, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to ViiV/GSK/PPD within 24 hours of learning of a participant's pregnancy.
- Participants will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to ViiV/GSK/PPD. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. GSK's central safety department will forward this information to the Antiretroviral Pregnancy Registry. The international registry is jointly sponsored by manufacturers and licensees of antiretroviral products. Additional information and a list of participating manufacturers/licensees are available from http://www.apregistry.com/.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age), congenital anomalies, or ectopic pregnancy are considered SAEs and must be reported.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study intervention by the investigator, will be reported to GSK as described in Section 10.3. 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.

10.6. Appendix 6: Liver Safety Required Actions and Follow-up Assessments and Study Intervention Rechallenge Guidelines

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

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

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

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

Liver Chemistry Stopping Criteria - Liver Stopping Event	
If baseline ALT ≤1.5x ULN	
ALT-absolute	ALT ≥8xULN
ALT Increase	ALT ≥5xULN but <8xULN persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥3xULN **and** bilirubin ≥2xULN (>35% direct bilirubin)
Cannot Monitor	ALT ≥5xULN but <8xULN and cannot be monitored every 1 - 2 weeks
Symptomatic[3]	ALT ≥3xULN with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
If baseline ALT >1.5x ULN	
ALT-absolute	ALT ≥5x baseline OR >500 U/L (whichever occurs first)
ALT Increase	ALT ≥3x baseline but <5x baseline persists for ≥2 weeks (with bilirubin <2xULN and no signs or symptoms of acute hepatitis or hypersensitivity)
Bilirubin[1, 2]	ALT ≥3x baseline OR >300 U/L (whichever occurs first) **and** bilirubin ≥2xULN
Cannot Monitor	ALT ≥3x baseline but <5x baseline and cannot be monitored every 1 - 2 weeks

Symptomatic[3]	ALT ≥3x baseline and symptoms (new or worsening) believed to be related to liver injury or hypersensitivity.

Required Actions and Follow up Assessments following ANY Liver Stopping Event

Actions	Follow Up Assessments

• Immediately discontinue study intervention.
• Report the event to the Medical Monitor **within 24 hours**.
• Complete the liver event eCRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2].
• Complete the liver imaging and/or liver biopsy eCRFs if these tests are performed.
• Perform liver event follow up assessments.
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below).
• **Do not restart** participant with study intervention unless allowed per protocol and VSLC approval **is granted** (refer to Section 10.6.2).
• If restart is **not allowed or not granted**, permanently discontinue study intervention and may continue participant in the study for any protocol specified follow up assessments.
 	
MONITORING:
• Make every reasonable attempt to have participants return to clinic within **24 hours** for repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments.
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline.
• A specialist or hepatology consultation is recommended.
	Make every attempt to carry out liver event follow-up assessments at the central laboratory as described below:
	• Viral hepatitis serology, including:
	  • Hepatitis A immunoglobulin M (IgM) antibody;
	  • HBsAg and hepatitis B core antibody;
	  • Hepatitis C RNA;
	  • Hepatitis E IgM antibody.
	• Cytomegalovirus IgM antibody.
	• Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing).
	• Syphilis screening.
	• Drugs of abuse screen, including alcohol.
	• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). The site must contact the Medical Monitor when this test is required.
	• 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). • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form. • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake eCRF.

1. CPK - creatine phosphokinase

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention for that participant if ALT ≥3xULN **and** bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥3xULN **and** bilirubin ≥2xULN (**>**35% direct bilirubin) **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required, and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)

Liver Chemistry Increased Monitoring Criteria with Continued Therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
If baseline ALT ≤1.5x ULN, ALT ≥5x ULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, monitor participant every 2 weeks until resolution to ALT <5x ULN.	• Notify the Medical Monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study intervention • Participant must return every 1 – 2 weeks for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until resolution or stabilisation (ALT <5×ULN on 2 consecutive evaluations) • If at any time participant meets the liver chemistry stopping criteria, proceed as described above
If 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, monitor participant every 2 weeks until resolution to ALT <3x baseline	

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et.al... Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

10.6.2. Study Intervention Restart after Stopping for Liver Criteria

If a participant meets liver chemistry stopping criteria do not restart/rechallenge participant with study treatment unless:

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

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

Drug restart may be considered for liver events with a clear underlying cause (e.g., biliary, pancreatic events, hypotension, acute viral hepatitis), if not associated with drug-

induced liver injury, alcoholic hepatitis or hypersensitivity, and drug not associated with human leukocyte antigen (HLA) marker of liver injury, when liver chemistries improve to within 1.5x Screening/Day 1 and ALT<3xULN) (Table 6, Figure 3).

Drug Restart

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

- immunoallergic injury /HLA association with injury
- drug-induced liver injury (DILI)
- alcoholic hepatitis

Study intervention is held while labs and evaluation are completed to assess diagnosis.

VSLC Decision Process for Drug Restart Approval or Disapproval (Figure 3):

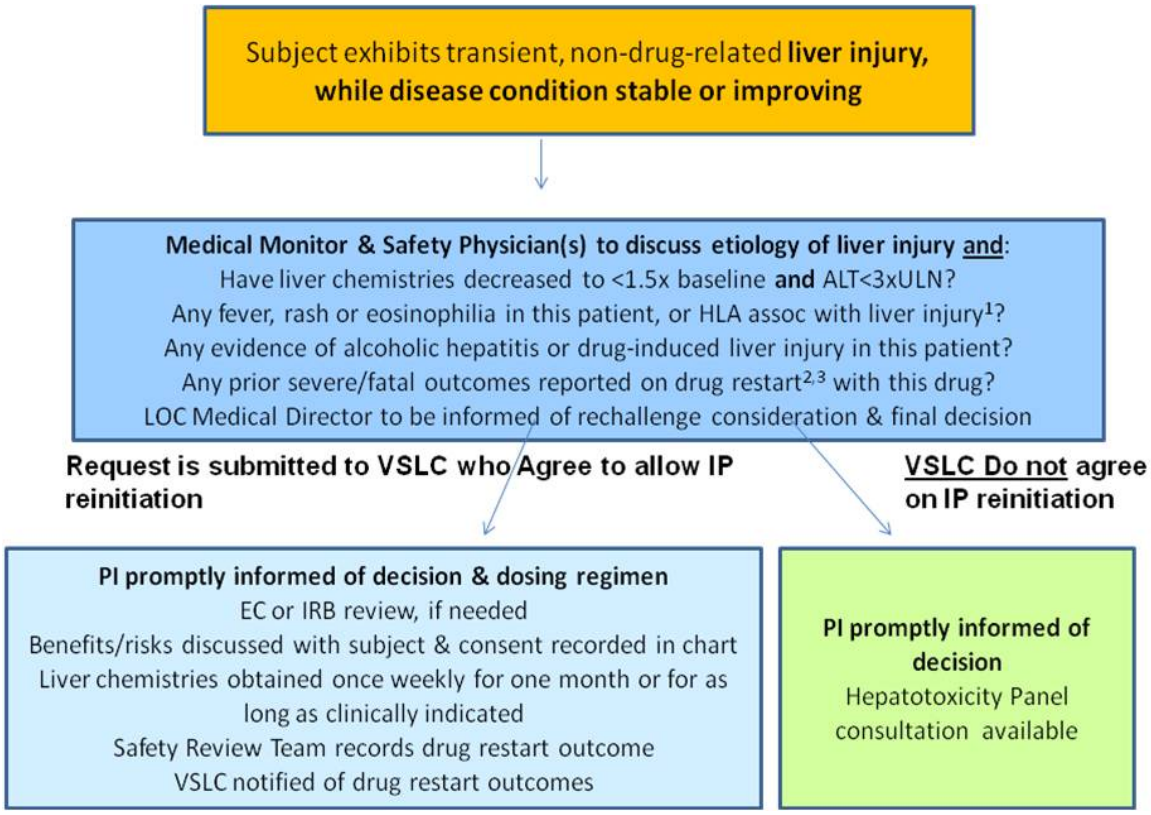
- Investigator requests consideration of drug re-initiation for a participant stable or improving on study intervention, who exhibits liver chemistry elevation meeting participant stopping criteria, which is transient, non-drug-related, and liver chemistries improve to within 1.5x baseline and ALT< 3xULN.
  - 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 and Clinical Safety Physician to review the participant's diagnosis, restart risk factors and complete checklist (Table 6).
  - The LOC medical director (ViiV Healthcare and GSK where applicable) should be informed that study intervention restart is under consideration and of the final decision, whether or not to proceed.

Table 6 Checklist for Phase III drug restart after well-explained liver injury (e.g., biliary, pancreatic, hypotensive events, congestive heart failure, acute viral hepatitis), improving to liver chem.≤1.5x baseline & ALT<3xULN

	Yes	No
Was participant stable or improving on study intervention?		
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 <10xULN)		
• study intervention has an HLA genetic marker associated with liver injury (e.g., lapatinib, abacavir, amoxicillin/clavulanate)		
Previous drug history		

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

Figure 3 VSLC process for drug restart approval or disapproval



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

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

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

- Medical Monitor must notify PI of VSLC's restart decision and recommended dosing regimen in writing and Medical Monitor must record note in study files.
- The Safety Review Team must record restart outcomes and the GCSP Physician must send these to the VSLC
  - All severe reactions (restart associated with bilirubin>2xULN or jaundice, or INR≥1.5), SAEs or fatalities with drug restart must be immediately reported to Line Management, VSLC Chair, VP Global Medical Strategy and EU Qualified Person for Pharmacovigilance.

Principal Investigator Actions:

- The PI must obtain Ethics Committee or Institutional Review Board approval of drug restart, as required.

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

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

Restart safety outcomes:

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

References

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

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

Papay JI, Clines D, Rafi R, Yuen N., Britt S.D., Walsh J.S., Hunt C.M. Drug-induced liver injury following positive drug rechallenge. Regul Tox Pharm. 2009; 54:84-90.

10.7. Appendix 7: Prohibited Medications

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, cytotoxic chemotherapy, or radiation therapy may not be administered.
- Systemically administered immunomodulators (such as interleukin and interferon agents) are prohibited (a list of examples is provided in the SRM). This includes topical agents with substantial systemic exposure and systemic effects. Use of topical imiquimod is permitted.
- For participants with an **unanticipated** requirement for HCV therapy during study, interferon or any other medications that have a potential for adverse drug-drug interactions with study intervention are prohibited during the conduct of the study.
- Acetaminophen (paracetamol) cannot be used in participants with acute viral hepatitis [James, 2009].

The following medications or their equivalents may cause decreased concentrations of DTG. Therefore, the following medications must not be administered concurrently with DTG.

- Carbamazepine
- Oxcarbamazepine
- Phenobarbital
- Phenytoin
- Rifampin
- St. John's wort (*Hypericum perforatum*)

Dofetilide is prohibited as DTG may inhibit their renal tubular secretion resulting in increased dofetilide concentrations and potential for toxicity.

Note: Any 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 added during the study, please consult the local prescribing information.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et.al.. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

10.8. Appendix 8: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.1, March 2017

VERSION 2.1, March 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 utilised for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term [DAIDS, 2017].

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-THREATENING
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 parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	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 indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
< 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, hypotensive shock)
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 mucosal bleeding
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Proctitis	Rectal discomfort with no intervention indicated	Symptoms causing greater than minimal interference with usual social & functional activities OR Medical intervention indicated	Symptoms causing inability to perform usual social & functional activities OR Operative intervention indicated	Life-threatening consequences (e.g., perforation)
Rectal Discharge	Visible discharge	Discharge requiring the use of pads	NA	NA
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., IV fluids)	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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 the setting	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
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 examination	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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
< 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)
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	RADE 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)
< 12 years of age *(based on a 1, 2, 3, 4, 6 and 8 kHz*	> 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	Audiologic indication for cochlear implant and additional speech-language related services indicated (where available)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
audiogram)			(where available) OR Hearing loss sufficient to indicate therapeutic intervention, including hearing aids	
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	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 ***Direct 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
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).

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 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. < *1.53*
< 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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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 < 2.0x 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
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*

eGFR - estimated glomerular filtration rate

*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 *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 femaile 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*
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*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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.

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10.9. Appendix 9: CDC Classification for HIV-1 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.

10.10. Appendix 10: Abbreviations and Trademarks

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
ABC/3TC	Abacavir/lamivudine, EPZICOM, KIVEXA
ACTG	International AIDS Society
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
Anti-HBc	Hepatitis B Core Antibody
ARV	Antiretroviral
ART	Antiretroviral therapy
AST	Aspartate aminotransferase
BIC	Bictegravir
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
c/mL	Copies/milliliter
CDC	Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRF	Case Report Form
COMBIVIR	Lamivudine and zidovudine
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CrCl	Creatinine Clearance
CSR	Clinical Study Report
CV	Cardiovascular
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug-Drug Interaction
dL	Deciliter
DHHS	Department of Health and Human Services
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
DTG	Dolutegravir, TIVICAY
EACS	European AIDS Clinical Society
ECG	Electrocardiogram
eCRF	Electronic case report form
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSH	Follicle stimulating hormone
FTC	Emtricitabine
GCP	Good Clinical Practice
GCSP	GSK's Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline

GFR	Glomerular Filtration rate
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	High density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HRT	Hormonal replacement therapy
HSR	Hypersensitivity reaction
IAS	International AIDS Society
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	Informed Consent Form
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational medicinal product
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
INR	International normalized ratio
IQR	Interquartile range
IRB	Institutional Review Board
ITT-E	Intent-to-treat exposed
IUD	Intrauterine device
IUS	Intrauterine hormone-replacing system
IWRS/IWRS	Interactive Voice/Web Recognition System
LDL	Low density lipoprotein
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical dictionary for regulatory activities
µMol/L	Micromole/Liter
Mg	Milligram
Mg/dL	Milligram per deciliter
Mg/min	Milligram per minute
MSDS	Material Safety Data Sheet
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OC	Observed Case
OCT-2	Organic cation transporter
PEP	Post-exposure prophylaxis
PI	Protease inhibitor
PK	Pharmacokinetic
POCBP	Participants of childbearing potential
PPD	Pharmaceutical Product Development

PrEP	Pre-exposure prophylaxis
PRO	Protease
PSRAE	Possible suicidality-related adverse event
QTc	Corrected QT interval
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBC	Red blood cell
RNA	Ribonucleic acid
RPR	Rapid plasma reagin
RT	Reverse transcriptase
SAE	Serious adverse event
SDM	Symptom Distress Module
SoA	Schedule of Activites
SJS	Stevens-Johnson syndrome
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
TAF	Tenofovir alafenamide
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine, Truvada
TEN	Toxic epidermal necrolysis
TRIUMEQ	Abacavir, dolutegravir, and lamivudine
ULN	Upper limit of normal
VSLC	ViiV Safety and Labelling Committee
WBC	White blood cell
WHO	World Health Organization
ZDV/3TC	Zidovudine/lamivudine, COMBIVIR

Trademark Information

Trademarks of ViiV Healthcare	Trademarks not owned by the ViiV Healthcare
COMBIVIR	Abbot Realtime HIV-1
DOVATO	GenoSure
EPIVIR	Monogram Biosciences
EPZICOM/ KIVEXA	PhenoSense
TIVICAY	Symptom Distress Module
TRIUMEQ	Truvada
ZIAGEN	

10.11. Appendix 11: Protocol Amendment History

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

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