Sponsor:

D3 (Penta 21)

A randomised non-inferiority trial with nested PK to assess DTG/3TC fixed dose formulations for the maintenance of virological suppression in children with HIV infection aged 2 to <15 years old

Version: **2.0**
Date: **04-October-2021**

Collaborating academic groups:

MRC CTU at UCL ID: **D3**
ISRCTN #: **ISRCTN17157458**
EudraCT #: **2020-001426-57**
NCT #: **NCT04337450**

Authorised by:
Name: **Dr Anna Turkova**
Role: **Trial Chief Investigator**
Signature:

DocuSigned by:
Anna Turkova
87F3D3BCFF1C4AF...

Date: **07-October-2021**

Funder:

Name: **Professor Carlo Giaquinto**
Role: **Chair of Fondazione Penta Onlus**
Signature:

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Carlo Giaquinto
FD40022BFEDB4D2...

Date: **07-October-2021**

GENERAL INFORMATION

This document was constructed using the Medical Research Council (MRC) Clinical Trials Unit (CTU) at University College London (UCL) Protocol Template Version 7.0. The MRC CTU at UCL endorses the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) initiative. It describes the D3 trial, coordinated by MRC CTU at UCL, and provides information about procedures for entering participants into it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but sites entering participants for the first time are advised to contact the relevant CTU (MRC CTU at UCL or, for the sites in Thailand, the Program for HIV Prevention and Treatment (PHPT) CTU) to confirm they have the most up-to-date version.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2013 (seventh revision) and the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2).

The sites will comply with the principles of GCP as laid down by the ICH topic E6 (R2), the Declaration of Helsinki 2013 and applicable national regulations.

SPONSOR

Fondazione Penta Onlus (Penta) is the trial Sponsor and has delegated responsibility for the management of the D3 trial to the MRC CTU at UCL. The details of delegation of roles and responsibilities are outlined in a separate agreement for Collaborative Research between Penta Fondazione Onlus and MRC CTU at UCL. Queries relating to Penta sponsorship of this trial should be addressed to Professor Carlo Giaquinto, Chair of the Fondazione Penta Onlus, Torre della Ricerca Pediatrica Corso Stati Uniti 4, Padova, 35127 or via the trial team.

FUNDING

The trial is funded by ViiV Healthcare (Study 207742). The MRC Clinical Trials Unit at UCL receives core support from the UK Medical Research Council (grant number MC_UU_12023/26).

AUTHORISATIONS AND APPROVALS

This trial will be submitted for approval by Research Ethics Committees/Institutional Review Boards and by all required regulatory authorities in each of the participating countries: South Africa, Spain, Thailand, Uganda and the UK.

TRIAL REGISTRATION

This trial has been registered with the International Standard Randomised Clinical Trial Number Register (as the trial identifier ISRCTN17157458), the European Clinical Trials Database (EudraCT; 2020-001426-57) and ClinicalTrials.gov (NCT04337450).

RANDOMISATIONS

Training will be provided for DIRECT RANDOMISATION ONLINE as part of the site initiation and database training. Individual passwords will be provided.

SAE REPORTING

Within 24 hours of becoming aware of a SAE or notable event, the Adverse Event Log and SAE and/or Notable Adverse Event information should be completed on the trial database. Pregnancies should also be reported within 24 hours on the trial database.

As back-up, if it is not possible to enter the data within the timeframe stated above, please send completed worksheets for the event(s) to the relevant CTU within 24 hours of becoming aware of the event(s). Any worksheets sent by email must be encrypted or transferred using other secure methods. Please ensure that an acknowledgement of receipt by the CTU is received.

MRC CTU email: mrcctu.d3safety@ucl.ac.uk

For the sites in Thailand, worksheets should be sent to the PHPT CTU:
Fax: +66 53 240 913 or email: PHPTCTU.trial-d3@phpt.org

TRIAL SPONSOR

SPONSOR

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TRIAL ADMINISTRATION

Please direct all queries to the D3 Trial Manager at the appropriate CTU. Queries from PHPT sites in Thailand should be sent to the D3 Trial Manager at PHPT CTU. All other queries should be sent to the D3 Trial Manager at MRC CTU at UCL. Clinical queries will be passed to the Medical Experts.

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For full details of all trial committees, please see **Section 14**.

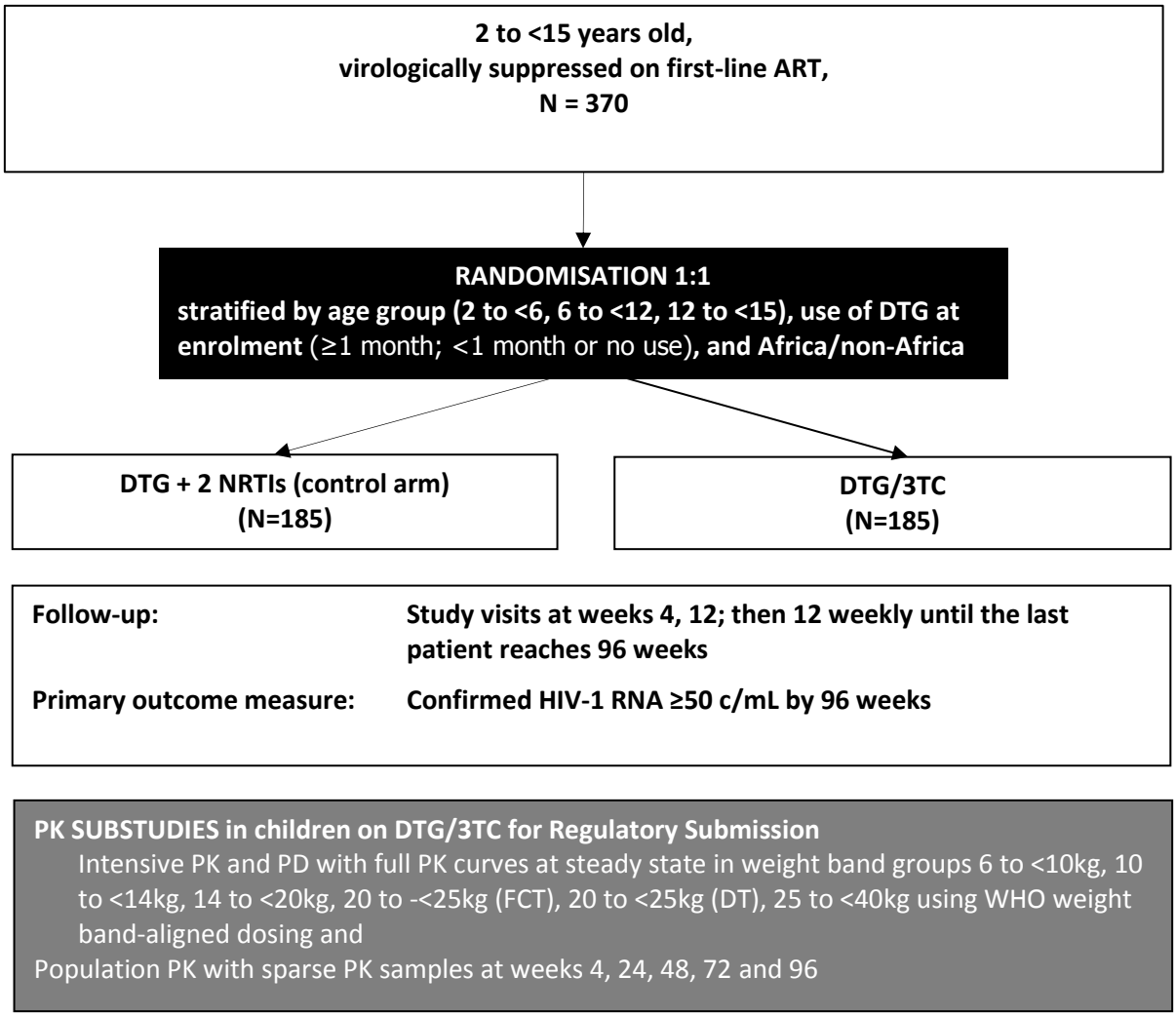
SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym	D3
Long Title of Trial	A randomised non-inferiority trial with nested PK to assess DTG/3TC fixed dose formulations for the maintenance of virological suppression in children with HIV infection aged 2 to <15 years old
Version	2.0
Date	04-Oct-2021
ISRCTN #	ISRCTN17157458
EudraCT #	2020-001426-57
NCT #	NCT04337450
Study Design	An open-label randomised (1:1) multicentre non-inferiority trial
Type of Participants to be Studied	HIV-infected children aged 2 to <15 years old weighing 6kg or more and virologically suppressed on antiretroviral treatment for at least the last 6 months
Setting	South Africa, Spain, Thailand, Uganda, United Kingdom
Interventions to be Compared	Dolutegravir (DTG) and lamivudine (3TC) (known as DTG/3TC) vs. DTG plus 2 nucleos(t)ide reverse transcriptase inhibitors (NRTIs)
Study Hypothesis	DTG/3TC arm will provide non-inferior virological efficacy compared with DTG + 2 NRTIs
Primary Outcome Measure	Proportion of children with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50c/mL) by week 96
Secondary Efficacy Outcome Measures	• Proportion of children with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50c/mL) by week 48 • Proportion of children with confirmed HIV-1 RNA ≥50c/mL at weeks 48 and 96 (modified FDA snapshot) • Proportion of children with HIV-1 RNA ≥50c/mL at weeks 24, 48 and 96 (including blips and confirmed measures ≥50c/mL) • New resistance-associated mutations in those with confirmed HIV-1 RNA ≥50c/mL • Time to any new or recurrent WHO 3 or WHO 4 event or death • Change in CD4 (absolute and percentage) from baseline to weeks 24, 48 and 96

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Secondary Safety Outcome Measures	• Incidence of serious adverse events, grade ≥3 clinical and laboratory adverse events • Incidence of adverse events leading to discontinuation or modification of the treatment regimen • Proportion of children with a change in ART for toxicity or switch to second-line • Change in blood lipids from baseline to weeks 48 and 96 • Change in creatinine clearance estimated using bedside-Schwartz formula to weeks 48 and 96
Patient-reported outcome measures	• Adherence as assessed by participant/care-giver questionnaires • Acceptability, sleep and mood, suicidal ideation and health-related quality of life as assessed by participant/care-giver completed questionnaires
Randomisation	Participants will be allocated 1:1 to DTG/3TC or DTG + 2 NRTIs
Number of Participants to be Studied	370
Duration of follow-up in the trial	At least 96 weeks
Nested Pharmacokinetics and Safety Study	An open-label single arm steady-state intensive pharmacokinetics and pharmacodynamics substudy to assess the pharmacokinetics, safety, tolerability and antiviral activity of the fixed-dose combination of DTG/3TC in virologically-suppressed HIV-1 infected children aged ≥2 years and weighing 6-<40kg using WHO weight band-aligned dosing. This study will be used for regulatory filing.
Ancillary Studies	Pharmacogenomics and population PK modelling; TB-PK substudy; Virology substudy; Health economics.
Sponsor	Fondazione Penta Onlus
Funder	ViiV Healthcare; core funding support from the UK Medical Research Council
Chief Investigator and MRC CTU at UCL Project Leader	Dr Anna Turkova

TRIAL SCHEMA

Figure 1: Trial Entry, Randomisation and Treatment



TRIAL ASSESSMENT SCHEDULE

Table 1: Trial Assessment Schedule

STUDY WEEK NUMBER#	SCREEN W-12 TO W0*	W0	W4	W12	W24	W36	W48	W60	W72	W84	W96	FURTHER FOLLOW-UP	END OF STUDY VISIT
Clinical Assessments and dispensing requirements													
Signed Informed consent	X	Confirm											
Clinical assessment [1]	X	X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Dispense ARVs		X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Laboratory Assessments													
Pregnancy test (urine) [2]	X	X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
HBsAg(1.5mL) [3]	X												X
HIV-1 RNA viral load (1.5mL) [4]	X	(X)	(X)	(X)	(X)	(X)	X	(X)	(X)	(X)	X	As per local practice but at least every 48 weeks	X
Haematology (2mL) [5]	X	X*	X	X	X	(X)	X	(X)	(X)	(X)	X	As per local practice	X
Biochemistry (2mL) [6]	X	X*	X	X	X	(X)	X	(X)	(X)	(X)	X	As per local practice	X
Lipase (same draw as biochemistry) [7]		X	X	X	X								
Lipids (same draw as biochemistry) [8]		X					X				X	As per local practice	(X)
Lactate (1mL) [9]		X	X	X	X								
HbA1c (1mL) [10]		X			X		X		X		X	As per local practice	(X)
T cell lymphocyte subsets (same draw as haematology) [11]		X	(X)	(X)	X	(X)	X	(X)	X	(X)	X	As per local practice or every 24 weeks	X
Urine dipstick [12]		X					X				X	Every 48 weeks	X

STUDY WEEK NUMBER	SCREEN W-12 TO W0*	W0	W4	W12	W24	W36	W48	W60	W72	W84	W96	FURTHER FOLLOW-UP	END OF STUDY VISIT
Other Assessments													
Adherence assessment [13]		X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Acceptability questionnaire [14]		X	X		X		X		X		X	Every 24 weeks	X
Sleep and mood questionnaires [14]		X	X		X		X		X		X	Every 24 weeks	X
Suicidal ideation and behaviour (children aged ≥6 years) [13]	X	X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
HRQoL questionnaire/assessment [14]		X	X		X		X		X		X	Every 24 weeks	X
Storage Samples													
Plasma storage (6-14mL) [15]		X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Buffy coat storage (same draw as plasma storage) [16]		X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Sparse PK samples storage (1mL EDTA) [17]			X		X		X		X		X		
Pharmacogenomics storage (1mL EDTA) [18]		X											
Total blood draw (mL) [19]	7	13-23	12-22	11-21	13-23	6-20	14-22	6-20	8-22	6-20	14-22	6-21	13-22
Intensive PK and PD substudy in the first DTG/3TC participants (7 to 14mL) [20]		≥7 days after switch from DTG-based ART and ≥21 days after switch from non-DTG-based ARTART											

*Randomisation visit should happen not later than 12 weeks after the most recent screening visit; Haematology [5] and biochemistry [6] should be repeated at randomisation if the time between screening tests and randomisation is more than 4 weeks.

#From week 4, sites are advised to schedule visits as close as possible to the target date and within +/-14 days.

( ) Optional if done in routine care.

[1] Including medical and ART history, clinical examination, weight, height, MUAC, waist circumference, paediatric WHO staging for HIV and adverse events (starting from week 0). The physician/medical officer will prescribe ART to the next visit and make decisions on any modifications of therapy as necessary.

[2] For girls who have reached menarche, pregnancy test should be repeated at every visit.

[3] Hepatitis B screening must be done at screening visit with HBsAg.

[4] Real-time/local viral load to be done at screening, weeks 48 and 96 and then every 48 weeks (with confirmatory viral loads for HIV RNA ≥50c/mL); more frequent viral loads may be done if site routine viral loads are more frequent than 12-monthly. An additional viral load must be done if treatment failure is suspected. Retrospective viral load testing will be performed using routine stored plasma [15] at the scheduled trial visits when a real-time VL is not done.

[5] Haematology: Hb, RBC, MCV, WBC, lymphocytes, neutrophils, platelets.

[6] Biochemistry: urea, creatinine, albumin, ALT, AST, ALP, bilirubin.

[7] Where possible, the same 2mL as biochemistry draw should be used to measure lipase at weeks 0, 4, 12 and 24. Please refer to the list for priority blood draw if it is necessary for an additional sample to be drawn so as not to exceed the maximum allowable blood draw volume for the child's weight.

[8] Where possible, the same 2mL as biochemistry draw should be used to measure lipids (TC, LDL, HDL, triglycerides) at weeks 0, 48 and 96 and thereafter as per local practice. Please refer to the list for priority blood draw if it is necessary for an additional sample to be drawn so as not to exceed the maximum allowable blood draw volume for the child's weight.

[9] Lactate can be measured in the same biochemistry draw or an additional sample in a fluoride oxalate tube (1 mL) should be collected depending on local laboratory processing; at weeks 0, 4, 12 and 24. Please refer to the list for priority blood draw if it is necessary for an additional sample to be drawn so as not to exceed the maximum allowable blood draw volume for the child's weight.

[10] Glycosylated haemoglobin A1c (HbA1c) can be measured in the same haematology draw or an additional sample in EDTA tube (1mL) should be collected depending on local laboratory processing; at weeks 0, 24, 48, 72 and 96. Please refer to the list for priority blood draw if it is necessary for an additional sample to be drawn so as not to exceed the maximum allowable blood draw volume for the child's weight.

[11] Where possible, the same 2mL as the haematology draw should also be used to measure CD3, CD4, CD8 percentage and absolute, total lymphocyte count. Please refer to the list for priority blood draw if it is necessary for an additional sample to be drawn so as not to exceed the maximum allowable blood draw volume for the child's weight.

[12] Urine dipstick for proteinuria at weeks 0, 48, 96 and then every 48 weeks

[13] Pill count (except week 0), adherence questionnaire and suicidal ideation and behaviour questionnaire (C-SSRS) at each scheduled visit.

[14] At weeks 0, 4, 24, 48, 72, 96 and then every 24 weeks, acceptability, sleep, mood and health-related quality of life (plus smiley faces scale) questionnaires will be collected. At screening/enrolment, questions will relate to adherence/acceptability of the pre-enrolment regimen

[15] 2-5 x 1.5mL plasma stored from 6-14mL EDTA blood for future batch testing retrospective VL, including low-level viraemia and resistance testing in a subset of samples. Additionally, plasma from EDTA blood sample must be stored at unscheduled visits if treatment failure is suspected.

[16] HIV-1 DNA and resistance tests on HIV-1 proviral DNA with the next generation sequencing (NGS) will be assessed on buffy coat in all participants at weeks 0, 24, 48 (Intensive PK participants only), and at the time points when HIV-1 RNA≥50c/mL is identified on the retrospective viral load testing and in baseline samples (all participants). Additional buffy coat from EDTA blood sample must be stored at unscheduled visits if treatment failure is suspected.

[17] Children at sites in South Africa, Thailand and Uganda: 1 plasma sample (plasma from 1mL whole blood) collected for children on DTG-based ART who are not undergoing intensive PK at this visit will be stored for population PK modelling. For sparse PK sample collection, there are no requirements for the timing of study drug administration or PK sampling on the day of sparse PK visit. However, if the participant's usual timing of study drug administration falls during the visit, the sparse PK sample should preferably be collected prior to study drug administration. The date and time of the last dose of study drug taken prior to collection of this sparse PK sample must also be documented along with PK sampling time.

[18] Children at sites in South Africa, Thailand and Uganda: Whole blood sample for pharmacogenomics; may be taken after week 0 if missed at week 0.

[19] The total blood volume differs due to the saved plasma volume which in turn depends on the child's weight – heavier children will have more plasma saved – and also whether non-mandatory tests are performed as part of routine care. Total blood volumes must be within the maximum allowable for the child's weight.

[20] 7 plasma PK samples (1-2mL blood for each) taken over 24 hours in the first children per weight band recruited at the PK sites and randomised to DTG/3TC arm. The visit should be scheduled ≥21 days after switching to DTG/3TC from non-DTG-based ART and could coincide with the week 4 or 12 visit if blood volumes for the planned blood tests are within the maximum allowable for the child's weight. The PK visit could be scheduled earlier for participants switching to DTG/3TC from DTG-based ART or changing DTG dose but must be at least ≥7 days after change and ≥21 days after starting on DTG.

Priority for blood draw in case of blood sampling difficulties is:

(1) VL if at a timepoint where real-time VL is requested
(2) 1.5ml plasma for storage for VL testing where real time VL is not being done
(3) Biochemistry, lipase
(4) Haematology (and HbA1C)
(5) Lactate
(6) Additional plasma storage
(7) CD4 cell count (if required)
(8) Lipids
(9) HbA1C (if not measured in the haematology sample)
(10) Sparse PK sample storage

A total of 13-23mL of blood to be collected at the visits when most study tests are scheduled (7-9mL of blood for virology tests, safety blood tests and sparse PK sample plus an additional 6-14mL blood for storage). Total amounts drawn will depend upon the weight of the child and their health and should not exceed the maximum allowable blood-draw volumes for children (see **Appendix I**).

LAY SUMMARY

This study aims to find out whether treating children and young people living with HIV with two anti-HIV medicines, dolutegravir and lamivudine, is safe and as effective as dolutegravir-based treatment with three anti-HIV medicines.

When medicines need to be taken for life, as for HIV infection, it is important that they not only work well, but also that they continue to be safe, with a low chance of long-term side effects, and that they are easy to take every day.

Dolutegravir (DTG) is one kind of anti-HIV medicine that works very well and has few side effects. In international treatment guidelines it is one of the most highly recommended medicines for adults and young people who need to start anti-HIV medicines for the first time. Lamivudine (also known as 3TC) is another anti-HIV medicine that is used in many HIV treatment regimens and has been shown to be very safe. Both of these medicines are taken once a day. Anti-HIV treatment using a two-medicine regimen including DTG and 3TC may offer treatment which is as safe and effective as a three-medicine regimen.

This study will include 370 children and young people aged 2 to less than 15 years old who are living with HIV and are being treated with anti-HIV medicines for the first time. They will be split into two groups, by chance, by a process called “randomisation”. One group will receive DTG-based three-medicine treatment. The second group will change to the combination of two medicines, dolutegravir and lamivudine (with the combination written usually as “DTG/3TC”). Depending on their weight, those in the second group will be able take the new medicine either as one tablet a day or as a small number of dispersible tablets that are also taken once a day. All children and young people in the study will have regular clinic assessments that are at a similar frequency to the clinic visits that they would have outside of the study. Blood tests will be performed to check that the medicine is safe and, at some visits, participants and their carers will also be asked to answer some questions on how they feel about taking their medicine. We will follow all children and young people until the last participant who joins the study has been in the study for 96 weeks.

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ABBREVIATIONS

ABBREVIATION	EXPANSION
3TC	Lamivudine
ADME	Absorption, distribution, metabolism, excretion
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APDU at UCLH	Advanced Pathogen Diagnostics Unit at University College London Hospitals NHS Foundation Trust
AR	Adverse reaction
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV/r	Atazanavir/ritonavir
AUC	Area under the curve
BD	Bis in die (twice a day)
bPI	Boosted protease inhibitor
BSA	Body surface area
CAB	Community Advisory Board
CI	Confidence interval
CL	Clearance
Cmax	Maximum concentration
CMV	Cytomegalovirus
CrCl	Creatinine Clearance
CRF	Case Report Form (paper or electronic case report forms)
C-SSRS	Columbia Suicide Severity Rating Scale
CTU	Clinical Trials Unit
DAIDS	Division of AIDS
DALY	Disability adjusted life-year
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DT	Dispersible tablet
DTG	Dolutegravir
DRESS	Drug rash with eosinophilia and systemic symptoms
EACS	European AIDS Clinical Society
EBV	Epstein-Barr virus
EDTA	Ethylenediaminetetraacetic Acid

ABBREVIATION	EXPANSION
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EQ-5D-Youth	EQ-5D-Youth is a standardized child-friendly version of the instrument for measuring health status, developed by EuroQol group
EU	European Union
FBC	Full blood count
FCT	Film-coated tablet
FDA	Food and Drug Administration
FDC	Fixed dose combination
FTC	Emtricitabine
GCP	Good Clinical Practice
HbA1c	Glycosylated haemoglobin A1c
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B
HDL	High density lipoprotein
HIV	Human Immunodeficiency Virus
HSR	Hypersensitivity reaction
IAS-USA	International Antiviral Society–USA
IB	Investigator Brochure
ICER	Incremental cost-effectiveness ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational medicinal product
INR	International Normalised Ratio
INSTI	Integrase inhibitor
IRB	Institutional Review Board
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention-to-treat
LDL	Low density lipoprotein
LFTs	Liver function tests
LMIC	Low- and middle-income countries
LPV/r	Lopinavir/ritonavir
LTFU	Lost to follow-up
MedDRA	Medical Dictionary for Regulatory Activities

ABBREVIATION	EXPANSION
MOP	Manual of Operations
MRC	Medical Research Council
MRC CTU at UCL	Medical Research Council Clinical Trials Unit at University College London
MUAC	Mid-upper arm circumference
NE	Notable event
NGS	Next generation sequencing
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NTD	Neural tube defect
OD	Once daily
OI	Opportunistic infection
PHPT	Program for HIV Prevention and Treatment
PI	Principal Investigator
PIS	Patient Information Sheet
PK	Pharmacokinetics
PSRAE	Possible suicidality-related adverse event
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RT	Reverse transcriptase
SAE	Serious adverse event
SAR	Serious adverse reaction
SJS	Stevens–Johnson syndrome
SOC	Standard of care
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TAF	Tenofovir-alafenamide
TB	Tuberculosis
TC	Total cholesterol
TDF	Tenofovir disoproxil-fumarate
TEN	Toxic epidermal necrolysis
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
UAR	Unexpected adverse reaction

ABBREVIATION	EXPANSION
UK	United Kingdom
ULN	Upper limit of normal range
Vd	Volume of distribution
VL	Viral load
WHO	World Health Organization
YTB	Youth Trials Board
ZDV	Zidovudine

1 BACKGROUND

1.1 IMPORTANCE AND RATIONALE

1.1.1 SCIENTIFIC RATIONALE FOR STUDY

HIV has shifted from a deadly disease to a chronic infection with improved survival dependent upon life-long antiretroviral therapy (ART). Current HIV treatment guidelines recommend first-line ART regimens consisting of three antiretroviral drugs: two nucleoside/nucleotide analogue reverse-transcriptase inhibitors (NRTIs) as a backbone combined with an integrase strand transfer inhibitor (INSTI) as the third agent or 'anchor' drug. Dolutegravir (DTG) is currently recommended as a preferred third agent for treatment of children and adolescents in countries adopting WHO, Penta or DHHS guidelines.[1-3] Bictegravir is another INSTI antiretroviral, structurally similar to dolutegravir, which is recommended as preferred third agent for children ≥25kg in high-income countries, but it is not yet licensed outside the US, and it is not widely available.[3] Low- and middle-income countries are currently implementing programmatic transition of adults and children to DTG due to individual and programmatic benefits associated with DTG-based ART.[4,5]
The WHO-convened Paediatric ARV Working Group strongly endorsed rapid transition to DTG-based regimens for all children and infants (older than 4 weeks and weighting at least 3 kg) established on first- and second-line ART irrespective of their current regimen.[5] Children in high income countries who are established on ART are also increasingly being switched to DTG-based three-drug ART for simplification of their treatment.

Life-long ART presents new challenges of treatment fatigue and long-term toxicities, and the growing population in need of ART pose critical public health questions over the long-term financial sustainability of continued ART scale-up. In response to this, research interest has shifted beyond survival and viral suppression to optimising treatment safety and health-related quality of life[6] with focus on regimens that are easier to take, offer less risk of toxicity and are more affordable, while remaining highly effective. Dual therapy, using two antiretrovirals instead of three, with at least one anchor drug, is one of these approaches for initial and maintenance therapy.[7-11]

The D3 trial aims to compare DTG/3TC dual therapy in children to DTG-based three-drug ART as the best recommended and widely scaled-up standard of care for first-line treatment.

1.1.2 DOLUTEGRAVIR (DTG) –BASED DUAL THERAPY

A dolutegravir-based two drug regimen is one of the promising dual therapy strategies. Dolutegravir is a potent INSTI, with a higher probability of virological suppression than other third agents and a high barrier to resistance. It is taken once daily and is generally well-tolerated, with lower discontinuation rates compared to standard-dose efavirenz (600mg in adults) or PIs. Adult formulations are already widely available for adults and older children, who can take an adult tablet. Paediatric dispersible DTG (5mg tablets produced by ViiV Healthcare and 10mg scored tablets produced by Mylan/Viatris and Macleods) have been recently approved by stringent regulatory authorities. Paediatric dispersible formulations from generic companies are expected to become available for younger children in most lower middle income countries (LMIC) in 2021-2022. Dolutegravir-based ART is quickly adopted by most countries for first- and second-line therapy.[1-5] By 2020, it had gained the highest share of the third-agent market in low and middle income countries (LMIC).[12] For dual therapy, dolutegravir can be combined with antiretrovirals from other classes, including NRTI (e.g. lamivudine, tenofovir), NNRTI (e.g. rilpivirine) or PI (e.g. boosted darunavir or atazanavir). A recent systematic review and meta-analysis summarised the currently available results of randomised controlled trials (RCTs) and observational studies on virological failure and HIV drug resistance for dolutegravir-based dual maintenance therapy: of 1670 adult participants in 14 studies,

10 (0.7%, 95% CI 0.4-1.3) experienced virological failure (VL ≥50 copies/mL) by 48 weeks. Only one participant developed a new resistance mutation to NNRTI (a participant on dolutegravir and rilpivirine in one of the SWORD trials) and none developed resistance to dolutegravir.[10] The authors concluded that dolutegravir-based dual therapy is a promising simplification strategy for people with stable HIV suppression. In the switch studies where an interventional group switches to a new regimen and a control group continues on their stable and well-tolerated treatment, more participants in the switch arms are anticipated to develop adverse events. Thus in the SWORD trials (513 in the dolutegravir-rilpivirine group and 511 in the current ART group) more participants taking dolutegravir-rilpivirine compared to participants continuing on their current ART reported any adverse events (77% vs 71%), drug-related adverse events (19% vs 2%) and events leading to study drug discontinuation (3% vs 1%) at 48 weeks.[13]

1.1.3 Dolutegravir (DTG) and lamivudine (3TC) dual therapy

Lamivudine is a NRTI with a well-known safety profile and no major side effects which is also taken once-daily. It is already widely used in LMIC. There are a number of completed and ongoing adult trials evaluating dual therapy with dolutegravir and lamivudine, given as separate formulations (DTC+3TC) or using a fixed dose combination tablet (DTG/3TC), in virologically suppressed and naïve adults (**Table 2**).

Overall the trial results show high level of virological suppression after a switch to DTG+3TC **in virologically suppressed adults**.

The ANRS 167 LAMIDOL trial is an ongoing open-label, single-arm, French trial assessing the efficacy and tolerance of DTG+3TC in selected **virologically suppressed** adult participants on first-line ART; 101/104 (97%) were suppressed at week 48.[14,15]

The ASPIRE study in the US randomised 89 **virologically suppressed** adults on first-line ART to switch to DTG+3TC or to remain on current treatment with follow-up to 48 weeks; at week 48 using the FDA snapshot algorithm, VL was <50 copies/mL in 90.9% of participants in the DTG+3TC arm versus 88.9% of participants in the standard of care arm; only 1 participant had confirmed VL≥50 copies/mL and they were in the DTG+3TC arm.[16] Post-hoc analysis of residual viraemia in ASPIRE (with a cut-off of HIV-1 detection of 0.5c/mL) showed no difference in ultra-low viral loads in DTG and SOC arms (difference in mean residual viraemia (DTG-SOC) at week 24, 1.3 c/mL, (95%CI: –2.1 to +4.7, p=0.45) and at week 48, 0.5 copies/mL (95% CI: –2.9 to +3.9, p=0.77).[17]

Another ongoing adult open-label non-inferiority RCT in Spain, DOLAM, randomised 90 **virologically suppressed** participants to three arms (monotherapy with dolutegravir, dual therapy with DTG+3TC and triple therapy). The monotherapy arm was discontinued at 24 weeks as two participants who failed treatment developed integrase associated mutations. In the DTG+3TC arm, 29/30 (97%) participants remained suppressed at 24 weeks; a participant who had viral rebound had no resistance. A further 120 participants per arm are being recruited in the remaining two arms in the continuing phase of the trial.[18]

TANGO, an open-label phase III RCT, sponsored by ViiV Healthcare, compared a switch to DTG/3TC versus continuing on tenofovir alafenamide (TAF)-containing triple ART in 741 **virologically suppressed** adults who were followed up for 96 weeks as per randomised allocation. The trial showed that virological efficacy of switching to DTG/3TC was non-inferior to continuing 3- or 4-drug TAF-based ART at 48 and 96 weeks. The overall rate of adverse events was similar between arms, but the rate of grade 2-5 drug-related adverse events was numerically higher in the DTG/3TC arm compared to the TAF-based regimen arm (6% vs 2%, respectively). [19,20] A higher adverse event rate is

often seen in the switch arm, where participants are exposed to new drugs, while those in the control arm continue their pre-study treatment.

Observational studies confirm the results of the trials and report high maintenance of virological suppression in adults on DTG and 3TC over 24-96 weeks (97% to 100%) in real life settings.[21-24]

A few trials have investigated DTG and 3TC in **ART-naive adults**. In a proof-of-concept single-arm study, PADDLE assigned 20 **ART-naïve** adults with VL below 100,000 copies/mL and no resistance mutations to DTG+3TC; at 96 weeks 18/20 had VL<50 copies/mL with one participant with confirmed virological failure at week 36 and one participant committing suicide.[25,26]

The AIDS Clinical Trials Group enrolled 120 **ART-naïve** participants in the US and Puerto Rico with VL up to 500,000 copies/mL in the ACTG A5353 single-arm phase II trial; at 24 weeks 90% were suppressed.[27] Viral decay in participants on 2-drug therapy with dolutegravir and lamivudine in the ACTG A5353 trial was compared to DTG-triple therapy in the SPRING-1 and SINGLE trials. There were no significant differences between dual and triple ART groups.[28]

The ViiV Gemini-1 and Gemini-2 phase III trials randomised 1433 **ART-naïve adults** to 2-drug therapy with DTG+3TC versus 3-drug therapy with dolutegravir and a fixed dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) (DTG+TDF/FTC); the trials demonstrated non inferior virological efficacy for the dual therapy vs the triple therapy at weeks 48, 96 and 144.[29-31] The trials showed fewer drug-related adverse events with DTG+3TC and change in renal and bone biomarkers favoured DTG+3TC.There were no treatment-emergent INSTI or NRTI mutations among participants with protocol-defined confirmed virological failure. One participant in the DTG+3TC group with reported non-adherence had viral rebound followed by low-level viraemia (<200c/mL) and developed NRTI (M184V) and INSTI (R263R/K) mutations at ≥132 weeks. The results of these phase III studies support DTG+3TC dual therapy as an effective option for ART initiation and provide reassuring evidence that similar approach will work for maintenance therapy.[29,30]

Table 2: Available results from adult studies evaluating a two-drug regimen with DTG and 3TC

STUDY	OUTCOME MEASURE	SUPPRESSION/FAILURE RATES AS REPORTED
Virologically suppressed participants		
ANRS 167 LAMIDOL: single arm study in adults on first-line ART[14,15]	Therapeutic success (therapeutic failure included: confirmed VL>50c/mL, interruption of treatment, loss to follow-up, death)	101/104 (97%) at week 48 (therapeutic failures included 1 confirmed VL>50c/mL, 1 interruption of therapeutic strategy, 1 LTFU by week 48).
ASPIRE: RCT comparing DTG+3TC versus SOC in adults on first-line ART[16]	Treatment failure including confirmed VL≥50c/mL, interruption of treatment, loss to follow-up	3/44 (6.8%) at week 24 in the DTG+3TC arm (failures included 1 confirmed VL>50c/mL, 1 treatment discontinuation, 1 LTFU by week 24) versus 3/45 (6.7%) in the SOC arm (failures included 2 regimen simplifications, 1 LTFU by week 24). FDA snapshot algorithm for VL<50c/mL at 48 weeks: 40/44 (91%) were suppressed in the DTG+3TC arm versus 40/45 (89%) in the SOC arm. In the as-treated analysis 95% in the DTG+3TC arm versus 95%.
DOLAM: RCT comparing DTG versus DTG+3TC versus SOC in adults on first-line ART[18]	Virological failure (confirmed VL>50c/mL) or interruption of treatment	1/30 at week 24 (confirmed VL>50c/mL) in DTG+3TC arm, none in the SOC arm. I blip (single VL≥50 c/mL) in DTG+3TC arm.
TANGO: RCT comparing DTG/3TC	Virological failure (VL≥50c/mL) at week 48 and 96 (ITT-E snapshot))	Week 48: 1/369 (0.3%) on DTG/3TC vs 2/372 (0.5%) on TAF-ART; adjusted difference -0.3 (95% CI -1.2 to 0.7)

versus TAF-based triple ART[19,20]		Week 96: 1/369 (0.3%) on DTG/3TC vs 4/372 (1.1%) on TAF-ART; adjusted difference -0.8 (95% CI -0.2 to 0.4)
ART-naïve participants		
PADDLE: single arm study in ART-naïve adults[25,26]	FDA snapshot algorithm: proportion with VL<50c/mL (therapeutic failure included VL≥50c/mL, missing VL or interruption of treatment)	18/20 (90%) at week 48: therapeutic failures included 1 suicide and 1 participant who had confirmed VL≥50c/mL and discontinued study. 18/20 (90%) at week 96 (no new failures).
ACTG A5353: single arm study in ART-naïve adults[27]	FDA snapshot algorithm: proportion with VL<50c/mL (therapeutic failure included VL≥50c/mL, missing VL or interruption of treatment) Protocol defined virological failure: confirmed VL>400c/mL at week 16 or 20 or confirmed VL>200c/mL at or after week 24	108/120 (90%) at week 24; therapeutic failures included 6 participants who had discontinued study/LTFU, 1 with missing VL, 5 with VL≥50c/mL 3 participants had protocol defined virological failure prior to or at 24 weeks
GEMINI-1,2: phase III RCT in ART-naïve adults[29,31]	FDA snapshot algorithm: proportion with VL<50 c/mL at weeks 48, 96 and 144 (ITT-E snapshot)	Pooled GEMINI 1 and 2 at week 48: 655/716 (91%) on DTG+3TC vs 669/717 (93%) on DTG+TDF/FTC; adjusted difference -1.7% (95% CI -4.4 to 1.1) Pooled GEMINI 1 and 2 at week 96: 616/716 (86%) on DTG+3TC vs 642/717 (90%) on DTG+TDF/FTC; adjusted difference -3.4 (95% CI -6.7 to 0) Pooled GEMINI 1 and 2 at week 144 584/716 (82%) on DTG+3TC vs 599/717 (84%) on DTG+TDF/FTC; adjusted difference -1.8 (95% CI -5.8 to 2.1)

LTFU = lost to follow-up

Children and adolescents are arguably the most important population to benefit from dual therapy as they stay on life-long ART longer than adults and are at higher risk of accumulating long-term toxicities, treatment fatigue and care attrition. Children are undergoing fast growth, pubertal and neurodevelopmental maturation and may experience different side effects to adults of long-term exposure to antiretroviral drugs and therefore may benefit more from maintenance therapy with reduced number of drugs. Conversely, adolescents are known to have worse adherence than adults and with dual therapy they may be at higher risk of virological failure and acquisition of new resistance compromising their future treatment options. HIV still remains one of the leading causes of deaths among adolescents.[32] In resource limited settings, limited virological monitoring, lack of resistance testing, frequent need for co-treatment for TB and hepatitis B and a more frequent occurrence of unplanned pregnancies influence the choice of treatment regimen and should be accounted for in the design of any trial.

1.1.4 DOLUTEGRAVIR DOSING FOR CHILDREN

Dolutegravir is licensed by the EMA and the US FDA for HIV-infected children from 4 weeks of age, weighing at least 3kg based on the results of a paediatric dose-finding Phase I/II study for dolutegravir (IMPAACT P1093)[33] and PK and safety studies nested in the ODYSSEY randomised controlled trial.[34] The results of PK studies in ODYSSEY showed that adult DTG 50mg film-coated tablets (FCT) could offer a practical and accessible dosing strategy for children ≥20kg allowing rapid alignment of WHO-preferred ART regimens for adults and children ≥20kg in low- and middle-income countries.[35] The ODYSSEY trial results, recently presented, demonstrated superiority of DTG-based three-drug ART compared to SOC in children aged ≥4 weeks and weighing 3kg, starting first- or second-line treatment.[36,37] The dose of lamivudine is already established for children, including infants. An adult single tablet of DTG/3TC 50/300mg is licensed for adults and adolescents weighing at least 40kg by the EMA and for adults by the FDA.

A paediatric fixed dose combination (FDC) dispersible tablet, containing 5mg of DTG and 30mg of 3TC has been developed. Its bioavailability was assessed in a phase I, single-dose, three-period crossover study in healthy volunteers (ViiV Healthcare study number 205894), comparing adult film-coated DTG and 3TC tablets with paediatric DTG/3TC dispersible tablets administered as dispersion (comparison 1) and direct-to-mouth (comparison 2) and comparing dispersible DTG/3TC administered as dispersion and direct-to-mouth (comparison 3). Geometric mean peak and overall exposures (Cmax, AUC) of DTG were between 1.3-fold to 2.0-fold higher with paediatric dispersible DTG/3TC tablets compared to adult DTG tablet. For paediatric dispersible formulations, GM Cmax and AUC were 1.3 to 1.5-fold higher when dispersed compared to when given direct-to-mouth. The geometric mean systemic exposure of 3TC (Cmax, AUC) was equivalent to the adult formulation in all three comparisons (**Table 3**).[38]

Table 3: Relative bioavailability assessment of DTG/3TC paediatric dispersible

PK PARAMETER	RATIO OF GLS MEANS [90% CI]		
	D (n=18) vs. A (n=18)	M (n=18) vs. A (n=18)	D (n=18) vs. M (n=18)
	DTG PK Parameters		
AUC (0-∞)	1.64 [1.47, 1.85]	1.27 [1.13, 1.43]	1.30 [1.15, 1.45]
AUC(0-t)	1.66 [1.47, 1.87]	1.28 [1.13, 1.44]	1.30 [1.15, 1.47]
Cmax	1.98 [1.76, 2.22]	1.29 [1.15, 1.45]	1.54 [1.37, 1.73]
	3TC PK Parameters		
AUC (0-∞)	0.98 [0.92, 1.04]	0.96 [0.91, 1.02]	1.02 [0.96, 1.08]
AUC(0-t)	0.98 [0.92, 1.05]	0.97 [0.91, 1.03]	1.01 [0.95, 1.08]
Cmax	0.91 [0.82, 1.01]	0.92 [0.83, 1.02]	0.99 [0.89 1.10]

Treatment A = adult DTG (50 mg, 1 conventional tablet) and adult 3TC (300 mg, 1 conventional tablet) administered as direct-to-mouth (reference); treatment D = paediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as a dispersion and taken immediately (comparison 1); treatment M = paediatric DTG/3TC (DTG 5 mg/3TC 30 mg, 10 dispersible tablets) administered as direct-to-mouth (comparison 2).

1.1.5 DOLUTEGRAVIR WITH ANTI-TUBERCULOSIS (TB) THERAPY

A PK study of co-administration of dolutegravir with rifampicin in healthy adult volunteers showed that BD dolutegravir overcomes the induction effect of rifampicin [39] and therefore can be used in HIV and TB co-infection. A study in HIV-infected adults with TB treated confirmed that increasing dolutegravir dose to 50mg BD co-administered with rifampicin results in a similar dolutegravir exposure to DTG 50mg OD without rifampicin.[40] The study showed dolutegravir was effective and well-tolerated in HIV/TB co-infected adults receiving rifampicin-based TB treatment. The ODYSSEY trial is evaluating dolutegravir PK in children on ART who require anti-TB treatment with rifampicin; preliminary results show that doubling the DTG weight-appropriate daily dose (given twice daily) in children with HIV and TB co-infection aged 6-<18 years is safe and sufficient to reach acceptable drug exposures .[41] More PK and safety data are required on doubling the adult DTG dose when it is given with rifampicin in children weighing 20 to <25kg.

1.1.6 DOLUTEGRAVIR AND PREGNANCY

Reproductive toxicology animal studies, including embryofetal development studies in rats and rabbits, showed no evidence of adverse developmental outcomes with DTG exposure. [42] In May 2018, a National Institutes of Health (NIH)-funded observational surveillance study in Botswana (TSEPAMO) evaluating the safety of ART regimens in pregnancy identified an increased risk of neural tube defects (NTD) amongst infants of women who initiated dolutegravir-based regimens prior to pregnancy. The study reported 4 cases of NTD out of 426 infants born to women who conceived on dolutegravir (0.9%); this compared to 14 out of 11,173 infants born to women receiving non-dolutegravir based regimens (0.13%).[43] In a recent report including all data from August 2014

through to March 2021 there were 9 cases of NTD in 5860 deliveries where the mother was taking DTG at conception (0.15%), compared to 22 NTDs in infants of 22,475 women conceiving on non-dolutegravir regiments (0.11%), resulting in a non-significant estimated difference in NTD prevalence of 0.06% (95% CI -0.03 to 0.20).[44-46]

In the same study, there were two reported NTDs among 4581 deliveries in which the mother started dolutegravir during pregnancy (0.04%), compared to 87 NTDs among 119,630 deliveries (0.07%) in HIV-uninfected mothers,[44] showing no increased risk of NTDs if dolutegravir was started post conception. The TSEPAMO study and other surveillance and reproductive studies are ongoing and more data on safety of dolutegravir for women of childbearing age and their infants are expected in the future.

1.1.7 DUAL THERAPY WITH DTG/3TC FIXED DOSE FORMULATION FOR CHILDREN LIVING IN DIFFERENT SETTINGS

Inclusion of trial participants from low-, middle and high-income countries using large Penta network sites in Europe, Thailand and partner sites in Africa will ensure the results are generalisable and applicable not only in high-resource countries where frequent viral loads and real-time resistance testing are part of routine care, but also in the settings where most children and adolescents with HIV live. We anticipate that the majority of the participants will come from sub -Saharan Africa. In view of differences in prevalence of coinfections and healthcare context in high- and low-income countries, we will stratify randomisation by region (African countries vs other countries).

Nested in this trial at the African sites, the intensive PK and safety study will evaluate PK, safety and tolerability of the paediatric DTG/3TC dispersible and adult film-coated tablets in children dosed according to WHO weight bands. The results of this study will be used for regulatory submission.

1.2 OBJECTIVES AND HYPOTHESES

The overall aim is to evaluate two-drug therapy with DTG/3TC FDC given once daily in comparison with DTG-based triple-drug ART in HIV-1 infected children and adolescents who are virologically-suppressed on their ART regimen.

1.2.1 PRIMARY OBJECTIVE

To assess whether DTG/3TC is non-inferior to DTG + 2 NRTIs in terms of virological suppression

1.2.2 HYPOTHESIS

DTG/3TC will provide non-inferior virological suppression compared with DTG + 2 NRTIs over 96 weeks.

1.2.3 SECONDARY OBJECTIVES

- To evaluate clinical and laboratory adverse events (AEs) associated with the trial antiretrovirals
- To evaluate new resistance mutations in participants with virological rebound (confirmed VL≥50 copies/mL)
- To assess low level viraemia and virological reservoirs
- To evaluate adherence, tolerability, acceptability, sleep and health-related quality of life
- To evaluate and model the pharmacokinetics and pharmacodynamics of dispersible and film-coated fixed-dose DTG/3TC formulations in children weighing 6-<40kg using WHO weight band-aligned dosing
- To evaluate cost-effectiveness of treatment maintenance with DTG/3TC FDC if DTG/3TC is shown to be non-inferior to DTG + 2 NRTIs

1.3 STUDY DESIGN

The D3 study is an open-label multicentre randomized non-inferiority trial in HIV-1 infected children (aged 2 to <15 years old) who have been virologically suppressed (<50c/mL) for at least 6 months and have no history of treatment failure. Previous antiretroviral drug substitutions for toxicity, simplification, changes in national guidelines or drug availability are allowed. Children will be randomized 1:1 receive DTG/3TC or DTG + 2 NRTIs (control arm).

A total of 370 children will be enrolled over approximately 18 months. Randomization will be stratified by age (2-<6; 6-<12; 12-<15), use of DTG at enrolment (≥1 month; <1 month or no use), and region (Africa; non Africa). At least half the children enrolled will be below age 12 to ensure sufficient numbers of younger children receive DTG/3TC FDC for safety evaluation. The primary outcome measure is the proportion of participants with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50 c/mL) **by week 96.**

Secondary outcome measures include the proportion of participants with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50 c/mL) **by week 48** and the FDA snapshot analysis of the proportion of participants with confirmed HIV-1 RNA ≥50 c/mL at weeks 48 and 96. All children will be followed -up for a minimum of 96 weeks.

1.4 STUDY POPULATION

HIV-1 infected children aged 2 to <15 years old will be recruited from sites in UK, Spain, Thailand, South Africa and Uganda.

2 SELECTION OF SITES AND CLINICIANS

The trial Sponsor has delegated overall responsibility for site and investigator selection in Europe, South Africa, Uganda and UK to the MRC CTU at UCL and in Thailand to the PHPT CTU.

Sites will be chosen on the basis of criteria below.

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

To participate in the D3 trial, investigators and clinical trial sites must fulfil a set of basic criteria that have been agreed by the D3 Trial Management Group (TMG) and are defined below.

Sites where a previous serious protocol breach is known to have occurred within the last 3 years will be visited and thoroughly reviewed before allowing participants to enter the trial.

Once a site has been identified as being compliant with the criteria below, the trial team will provide the site with a copy of this protocol, a trial summary and the Summary of Product Characteristics (SPC) or Investigator Brochure.

Those centres that meet the criteria will be issued with the D3 master file documentation for their site-specific approval and CTU accreditation documents. Centres must complete the D3 Accreditation Form at the same time as applying for their site-specific approval

2.1.1 SITE PI'S QUALIFICATIONS & AGREEMENTS

1. The Site (and Country) PI must have an MD degree (or equivalent) and be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial at their site and should provide evidence of such qualifications through an up-to-date curriculum vitae and/or other relevant documentation requested by the Sponsor, the Institutional Review Board (IRB) (sometimes denoted a Research Ethics Committee; REC), and/or the regulatory authorities.

2. The Site PI must be thoroughly familiar with the appropriate use of the Investigational Medicinal Products (IMP), as described in the protocol, in the current Investigator Brochure, in the Summary of Product Characteristics (SPC) and in other information sources provided by the Sponsor.

3. The Site PI must be aware of, and must comply with, the principles of GCP and the applicable regulatory requirements. GCP training must be completed by the PI and active site staff prior to site initiation and a record of GCP training must be accessible.

4. The Site PI and site must permit monitoring and auditing by the Sponsor and delegated individuals, and inspection by the appropriate regulatory authorities.

5. The Site PI is responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

6. If the Site PI/site retains the services of any individual or party to perform trial-related duties and functions, the Site PI/site should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the

integrity of the trial-related duties and functions performed and any data generated.

7. The Site PI must maintain a delegation log of appropriately-qualified persons to whom they have delegated significant trial-related duties.

8. The Site PI must sign an investigator statement, which verifies that the site is willing and able to comply with the requirements of the trial.

2.1.2 ADEQUATE RESOURCES

1. The Site PI must be able to demonstrate a potential for recruiting the required number of suitable participants within the agreed recruitment period (that is, the investigator regularly treats the target population).

2. The Site PI must have sufficient time to properly conduct and complete the trial within the agreed trial period.

3. The Site PI must have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4. The Site PI must ensure that all persons assisting with the trial are adequately informed about the protocol, the IMPs, and their trial-related duties and functions.

5. The site must have sufficient data management resources to allow prompt data entry/data return to the relevant CTU. Sites that have previously participated in CTU-coordinated trials should have a track record of good data return.

2.1.3 SITE ASSESSMENT

Each selected clinical trial site must complete the D3 Site Accreditation Form, which includes the Investigator Statement, Signature and Delegation of Responsibilities Log, and staff contact details. The Investigator Statement verifies that the site is willing, and able to comply with the requirements of the trial. This will be signed by the Site PI. In addition, and in compliance with the principles of GCP, all site staff participating in the trial must complete the Signature and Delegation of Responsibilities Log and forward this to the relevant CTU. The CTU must be notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the Trial Master File (TMF) at the site and also at the CTU.

2.2 SITE TRAINING

Site training will be carried out prior to site activation. This may be performed as face-to-face (on-site training or at a central Investigator's Meeting) or via teleconference/webinar (where on-site/central training is not possible and the site has previous experience in paediatric HIV trials and the PI is known to the relevant CTU). Training will include the following list of items, but this list is not exhaustive:

- The study protocol and other trial reference documents
- Informed consent process
- Data management
- Investigational Medicinal Product
- Adverse event reporting procedures
- Randomisation procedures including back-up (if applicable)

- Laboratory samples
- Storage, accessibility and archiving of study documents
- Frequency of and expectations for any monitoring visits.

A log of attendees will be kept in the TMF and Investigator Site File (ISF) as a record of participants present at all types of training event.

2.3 APPROVAL AND ACTIVATION

On receipt of the documents outlined in **Section 2.1.3** at the relevant CTU, confirmation that all necessary essential documentation is in place, completion of site training, and confirmation of study drug at site, written confirmation of site activation will be sent to the PI that the site is open to enrolment. The site's pharmacist/designee will be consulted prior to site activation so that the initial drug order can be dispatched to the named pharmacist/nurse in the Site Accreditation form documents.

1. The site should conduct the trial in compliance with the protocol as agreed by the Sponsor and which was given favourable opinion by the REC and/or IRB.
2. The Site PI or delegate should document and explain any required deviation from the approved protocol (e.g. due to local/regional ethics/regulatory requirements) and communicate this with the trial team at the relevant CTU.

A list of activated sites may be obtained from the CTU Trial Manager.

2.4 SITE MANAGEMENT

Sites in Spain, South Africa, Uganda and UK will be managed by the MRC CTU at UCL together with national co-ordinators and local monitors. The sites in Thailand will be managed directly by the PHPT CTU.

3 SELECTION OF PARTICIPANTS

There will be **no exceptions** to eligibility requirements at the time of randomisation**.** Questions about eligibility criteria must be addressed prior to attempting to randomise the participant.

The eligibility criteria are the standards used to ensure that only medically appropriate patients are considered for this study. Patients not meeting the criteria should not join the study. For the safety of the participants, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the trial.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

3.1 PARTICIPANT INCLUSION CRITERIA

1. HIV-1 infected children who are virologically suppressed for at least the last 6 months prior to enrolment[a,b]
2. Aged 2 to <15 years old
3. Weight 6 kg or higher
4. Girls who have reached menarche must have a negative pregnancy test at screening and randomisation
5. Girls who are sexually active must be willing to adhere to highly effective methods of contraception[c]
6. A parent or legal guardian is willing and able to give informed consent on behalf of the child as per national legislation and willing to adhere to the protocol
7. Participant is willing to give informed assent if the trial site clinician deems them old enough and able to understand the age-appropriate information about participation in the study

[a]Children will be considered virologically suppressed if they meet either of the following 2 scenarios (A or B) AND any additional viral loads between the first viral load (used for eligibility) and the screening viral load are <50c/mL[b]:

A. At least two HIV-1 RNA viral loads <50c/mL: a screening viral load <50c/mL and one in >6 to <12 months prior to screening[b].
OR
B. At least three HIV-1 RNA viral loads <50c/mL: a screening viral load <50c/mL, one in the <6 months prior to screening[b] plus one in the >12 to <18 months prior to screening[b].

[b] Viral load <200 c/ml is allowed for diluted samples following approved dilution protocols for validated HIV-1RNA assays. Any dry blood spot viral loads used for eligibility should be below the limit of detection for the used assay. The screening sample VL must always be <50 c/ml and cannot be done using a dry blood spot.

[c] Highly effective contraception methods are injectable, implantable, oral and intrauterine contraceptives which have an expected failure rate <1% per year (see **Section 6.6**)

3.2 PARTICIPANT EXCLUSION CRITERIA

1. Any previous switch in ART regimen for virological, immunological or clinical treatment failure
2. Evidence of previous resistance to 3TC or INSTI[a]
3. Any prior use of regimens consisting of single or dual NRTIs with the exception of a course of zidovudine for prevention of mother to child transmission
4. Known allergy or contraindications to dolutegravir or lamivudine
5. Diagnosis of tuberculosis and on anti-tuberculosis treatment; children can be enrolled after successful tuberculosis treatment[b]
6. Treatment of co-morbidities with drugs which have significant interactions with antiretroviral treatment, requiring dose adjustment of the study drugs (children can be enrolled after the illness resolves)
7. Randomisation visit more than 12 weeks after the most recent screening visit
8. Positive HBsAg [c]
9. Screening ALT equal to 3 or more times the upper limit of normal AND bilirubin equal to 2 or more times the upper limit of normal (ALT ≥3xULN AND bilirubin ≥2xULN)
10. Screening ALT equal to 5 or more times the upper limit of normal ALT (≥5xULN)
11. Patients with severe hepatic impairment or unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice), or known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
12. Screening creatinine clearance <30 mL/min/1.73m^2 [d]
13. Patients aged ≥6 years at moderate or high risk of suicide as determined by Columbia-Suicide Severity Rating Scale (C-SSRS) [e]
14. Girls who are pregnant or breastfeeding
15. Children who are in the legal custody of the state and do not have a parent or guardian able to provide informed consent on their behalf.

[a] Resistance testing is not required at trial entry

[b] Successful tuberculosis treatment is defined as completed anti-tuberculosis treatment, free of tuberculosis-associated symptoms and not known to be smear- or culture-positive in the last month of treatment.[47]

[c] Screening ALT of more than 2xULN should be further assessed for HBsAg-negative HBV infection and include testing for HBcAb and HBsAb; participants positive for HBcAb and negative for HBsAb should be excluded; participants negative for HBsAg and positive for both HBcAb and HBsAb can be included as they have immunity against hepatitis B.

[d] For calculation of creatinine clearance or estimated glomerular filtration rate in children an updated bedside Schwartz equation should be used eGFR (mL/min/1.73m^2)=41.3 x height (m)/serum creatinine (mg/dL)

[e] See **Section 5.8.1.C** for categorisation of risk of suicide determined by C-SSRS

3.3 NUMBER OF PARTICIPANTS

370 children will be enrolled over a planned duration of 18 months. At least half the children enrolled will be below age 12 to ensure sufficient numbers receive the new DTG/3TC FDC to evaluate safety in younger children.

3.4 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in **Section 4.3**.

3.5 SCREENING PROCEDURES

At or prior to the screening visit, carers of HIV-infected children and adolescents will be provided with an information sheet about the D3 trial and given the opportunity to discuss with family and friends. Upon their return for the screening visit they should be given the opportunity to ask any questions and it should be ensured that they feel they have had adequate time to consider trial participation before being asked to give written consent for the trial (see Patient Information Sheet (PIS) and Consent Form). Carers must confirm that they have read the relevant patient information sheets.

Written informed consent to enter into the trial and be randomised must be obtained from parents/guardians/persons with legal responsibility for children/adolescents, after explanation of the aims, methods, benefits and potential hazards of the trial and **before** any trial-specific procedures are performed or any blood is taken for the trial. Children deemed able to understand the trial should give assent according to national regulations/guidelines; if they refuse to assent they cannot participate. Signed trial consent and assent forms must be kept by the investigator in the ISF, a copy in the child's medical records and a copy given to the participant or family.

It must be made completely and unambiguously clear that the participant (or parent or guardian of a child) is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment (or that of their child).

For all children and adolescents (aged <15 years based on eligibility criteria), the primary carer providing consent will be asked to nominate another one or two carers (depending upon local practice) who will be responsible for the child's welfare in the event that the carer is unable to continue caring for them. Whilst the carer who consented is alive, counselling of any other person who brings the child to the clinic is necessary to explain the trial, but re-consent is not needed. If the carer who originally gave consent dies, it will be necessary to obtain re-consent from the next nominated primary carer.

After consenting to participation in the trial, the HIV-infected adolescent or child will have clinical information including medical and ART history recorded, an examination including WHO staging of HIV infection (1, 2, 3 or 4; **Appendix II**) and weight, height, MUAC and waist circumference performed, and blood taken for a real-time VL test, haematology, biochemistry and hepatitis B (HBsAg) (See **Table 1: Trial Assessment Schedule**). A pregnancy test will be performed in any girl who has reached menarche (Tanner Stage 4). Plasma will be saved.

Carers and children will be given an appointment for a randomisation visit. Ideally randomisation should take place as soon as the screening test results are available but not later than 12 weeks after the screening visit.

Re-screening is allowed if the time between original screening and randomisation visits exceeds 12 weeks. Re-screening is also permitted if a participant's intercurrent clinical condition preventing them from enrolling in the trial in the first instance has resolved or improved and the participant is deemed to meet the inclusion and exclusion criteria at the time of re-screening.

Children who are screened will be allocated a trial ID number. The screening form should be entered on the database as soon as all required information is available and before the randomisation visit.

The trial register will record all persons who are screened to join the trial. The register will be kept in a secure place in each clinical site and must be available for monitoring, audit and inspection. The management of the register will be the responsibility of the Principal Investigator at that site.

4 REGISTRATION & RANDOMISATION

4.1 RANDOMISATION VISIT

The randomisation visit may be scheduled at any time between 1 day and 12 weeks after the screening visit; ideally as soon as all laboratory test results from the screening visit are available.

The participant's eligibility, including the results of screening laboratory tests, and the consent (and assent where applicable) for enrolment will be confirmed.

After confirming consent to trial participation, enrolment assessments will be performed as summarised in the Trial Assessment Schedule (**Table 1:**)**.** Blood samples will be taken to measure T-cell subsets (CD4, CD8, CD3 and total lymphocyte count), lipids, lipase, lactate and HbA1c. Plasma, buffy coat, and, for participants at sites in South Africa, Thailand and Uganda, an EDTA sample for pharmacogenomics, will be saved. If the interval between screening and randomisation is longer than 4 weeks, haematology and biochemistry blood tests should be repeated at randomisation (see **Table 1:**). When possible, and particularly if there is doubt about the place of residence of a child and his/her family, a study nurse/field worker, preferably the same nurse who gave information about the trial to the carer/child, will accompany the trial participant to their home and record details such as a map indicating the place of residence.

4.2 RANDOMISATION PRACTICALITIES

The child/adolescent and the carer should be physically present together with a study clinician in either the site clinic or a hospital ward at the time of randomisation.

Further details on the process of randomisation can be found in **Section 9.1**. To randomise a participant, the appropriate eCRFs must be completed in the online trial database, accessible from the local clinical sites, which will automatically check for eligibility. Only those with completed and verified screening and randomisation forms on the database will be able to be randomised. More details on this process are included in the trial MOP. The generated randomisation lists will be securely incorporated within this web-enabled trial database, and allocation concealed until the point of the current randomisation. The details of the participant's treatment allocation will be notified to clinical staff, and the trial number and allocation cross checked between those randomising and those managing the participant clinically.

If the main electronic randomisation system is not working, randomisations will not take place and the randomisation visit will need to be rescheduled.

The participant's open-label treatment allocations and the date of randomisation will be entered into the Trial Register at the site. The clinician should complete a prescription with the participant's details and trial medications as allocated. The prescription will be for 4 weeks. The pharmacist or pharmacy technician should ensure that the participant and the caregiver know how to take the different drugs before they leave the clinic.

4.2.1 ENROLMENT OF DIFFERENT MEMBERS OF THE SAME FAMILY OR HOUSEHOLD INTO THE TRIAL

If more than one child from a family or household is to be enrolled at the same time and meet the inclusion criteria they will be allocated to the same arm to facilitate their care (please refer to Manual of Operations). Based on previous trials at these study sites we expect this to happen rarely.

Participants should all be counselled that they should on no account share their ART with anyone.

4.3 CO-ENROLMENT GUIDELINES

Participants will not ordinarily be permitted to take part in any other clinical intervention study whilst participating in the D3 trial. Participation in other studies that do not involve an intervention may be acceptable but should be discussed with the D3 TMG via the MRC CTU at UCL. The D3 TMG will consider co-enrolment of D3 participants onto other trials where the interventions do not conflict with the trial objectives on a case-by-case basis.

5 TREATMENT OF PARTICIPANTS

5.1 INTRODUCTION

Treatment selected for the control arm in the D3 trial is DTG plus 2 NRTIs, in line with WHO, Penta and DHHS preferred first-line ART for children and adolescents. The D3 trial will test a reduced ART regimen consisting of two antiretroviral drugs, dolutegravir and lamivudine, given as fixed dose combination tablets.

All randomisations will be open-label because of the complexities of the number of pills required for blinding. Therefore, all participants will know what regimens they are taking. All doses will be based on WHO weight bands to ensure that results of the trial are generalisable to ART programmes.

DTG/3TC formulations for children randomised to the DTG/3TC arm will be provided by ViiV Healthcare. DTG formulations will be provided by ViiV Healthcare for children randomised to DTG + 2 NRTIs, where they are not yet available in the national programmes.

Further details on unregistered products supplied for the trial by ViiV Healthcare can found in **Appendix III**.

5.2 DTG/3TC ARM

Children randomised to the DTG/3TC arm will receive once daily DTG/3TC fixed dose combination dispersible or film-coated tablets dosed using WHO weight bands as per the table below.

Table 4: WHO weight band-based dosing

WHO WEIGHT BANDS	DTG* EVALUATED IN ODYSSEY ONCE DAILY DOSE, MG	3TC WHO-RECOMMENDED ONCE DAILY DOSE, MG	DTG/3TC ONCE DAILY DOSE, MG		DTG DOSING, MG/KG
			5/30MG, DISPERSIBLE TABLETS	50/300MG, FILM-COATED TABLETS	
6-<10 kg	15 DT	90	15/90 DT		1.5-2.5 (DT)
10-<14 kg	20 DT	120	20/120 DT	-	1.4-2.0 (DT)
14-<20 kg	25 DT	150	25/150 DT	-	1.3-1.8 (DT)
20-<25 kg	30 DT or 50 FCT	180*	30/180 DT**	50/300 FCT**	1.2-1.5 (DT) 2.0-2.5 (FCT)
≥25 kg	50 FCT	300	-	50/300 FCT	≤2 .0(FCT)

DT = dispersible tablets, FCT = film coated tablets

* EMA and FDA-recommended 3TC dose is 225mg for children 20-<25kg.

** Children 20-<25kg in PK sites will be taking DTG/3TC as either six 5/30mg DT or one 50/300mg FCT depending on the formulation allocated to their site for this weight band; participants in non-PK sites will be taking DTG/3TC 50/300mg.

Children 20-<25kg in PK sites will take DTG/3TC as either six 5/30mg DT or one 50/300mg FCT depending on the formulation allocated to their site for this weight band. Participants in non-PK sites will take DTG/3TC 50/300mg. The 3TC dose of 300mg in children 20-<25 kg taking 50/300mg FCTs exceeds the currently recommended dose. This dose is being investigated based on an acceptable safety profile of 3TC in children[48] and potential patient preference for one FCT. Clinical and laboratory monitoring at scheduled visits will be carried out to confirm the safety of this approach.

Doses should be recalculated at every visit based on current weight until the adult dose is reached when it would usually be maintained.

5.3 CONTROL ARM (DTG + 2 NRTIS)

All participants in the control arm will receive DTG + 2 NRTIs. Participants will stay on their current ART, where they are already receiving DTG + 2 NRTIs, or will move to DTG + 2NRTIs from randomisation. Antiretroviral drugs for the control arm will be sourced through national programmes where possible. ViiV Healthcare will provide the following formulations where they are not available through national programmes: DTG 5mg dispersible tablets for children <20kg; DTG 50mg film-coated tablets for children in Thailand. DTG 50mg film-coated tablets may also be provided for sites in South Africa and Uganda, if requested, in order to avoid stockouts. Subject to local patents, Kivexa (ABC/3TC 600/300mg) may also be provided for sites in Uganda, and Kivexa, Ziagen (ABC 300mg) and Epivir (3TC 150mg) for sites in South Africa, if requested, in order to avoid stockouts.

The doses of antiretrovirals should be in accordance with those recommended in the product information or according to international (WHO)/national guidelines in use in the country. Doses should be recalculated at every visit (until the adult dose is reached after which the same dose is usually maintained).

5.4 DISPENSING OF ALL TRIAL MEDICATION AND ACCOUNTABILITY

Throughout the trial, children and adolescents, or their carers, will be provided with a supply of all antiretroviral drugs sufficient to last until their next clinic visit and will be requested to return all empty bottles and to bring any bottles in use or unused to the follow-up clinic.

On no account should any drug assigned to a participant be used by anyone else. Unused drug must be returned to the site if a participant withdraws from treatment.

All antiretrovirals dispensed to D3 participants and returned to the site should be documented on a participant specific drug accountability log. At each site, a named person (trial pharmacist or research nurse) will be required to maintain complete records of all study medication dispensed.

For all D3 trial drugs supplied by ViiV Healthcare, the designated trial pharmacist or designated nurse will, on receipt of supplies prior to the commencement of the trial, conduct an inventory and complete a receipt of drug form which should then be returned to the relevant CTU. A cumulative accountability log should also be kept for all trial drugs supplied by ViiV Healthcare, with a separate log completed for each batch of drug. Inventories will be conducted monthly, and logs returned to MRC CTU at UCL.

Procedures for drug shipping, labelling, accountability and destruction will be detailed in the D3 Pharmacy Manual of Operations and must be in compliance with applicable local regulations, GCP and the protocol. Staff from the relevant CTU and local trial monitors will monitor drug accountability at site visits.

5.5 ART MODIFICATION, INTERRUPTION AND DISCONTINUATION

5.5.1 PERMITTED ART CHANGES

For secondary outcome measures using the (modified) FDA snapshot algorithm, the following ART changes will be treated as 'permitted' and unrelated to treatment failure:

In **the DTG/3TC arm**:

- Dose changes for weight gain or weight loss, which should be made as per the dosing table above (**Table 4:**)
- DTG dose change for TB treatment or other concomitant medications (i.e. BD dosing of DTG for concomitant use of rifampicin or certain anticonvulsants, such as carbamazepine, phenobarbital)
- Dose adjustment of 3TC unrelated to toxicity (e.g. reduction of creatinine clearance)

In **the control arm:**

- Dose changes and changes of ART components due to treatment simplification
- Dose changes and changes of ART components due to child's growth
- Changes of ART components due to change in country guidelines or stock-out at clinic
- Dose changes and changes of ART components unrelated to toxicity (e.g. due to TB treatment, other concomitant medications or reduction of creatinine clearance)

In the control arm ART changes should be in line with the national or international guidelines. Changes related to child's growth in the control arm include ART changes as children become eligible for different preferred antiretroviral drugs and usually result in a simplified regimen. In addition, simplification may include changes related to emerging availability of antiretroviral drugs administered once daily or as part of fixed dose combination. Sites may use the same antiretrovirals produced by different manufacturers, e.g. move from branded to generic products.

Examples of permitted changes during the trial in the control arm include:

- Change of ABC or ZDV to TDF for children reaching eligible age or weight cut off for TDF
- Change of ABC, ZDV or TDF to TAF if TAF-containing formulations become available for corresponding age/weight bands
- Changes of daily dose of DTG due to concomitant use of rifampicin for TB treatment or certain anticonvulsants (e.g. DTG is given twice daily (i.e. total dose is doubled))

5.5.2 OTHER ART DRUG SUBSTITUTIONS

If a participant does not tolerate an individual drug, an alternative drug may be substituted as considered appropriate by the investigator (see **Section 5.8** The choice of substitution will depend upon other drugs being taken now or in the past, and available age-appropriate formulations.

ART substitutions may be required if female participants are identified to be pregnant during the trial (see **Section 6.6**).

5.5.3 STOPPING DRUG EARLY

Discontinuation criteria are considered in **Section 5.10**.

5.6 MANAGEMENT OF PARTICIPANTS WITH CONFIRMED VIRAL LOAD ≥50 C/ML

Real-time VLs will be measured according to local guidelines (see **Section 6.2**). Mandated turn-around of VL results in the trial at weeks 48 and 96 (and 48-weekly thereafter) will be within 2-3

weeks. Participants with VL≥50 c/mL will be recalled back within the week 48 analysis window (42-54 weeks), week 96 analysis window (90-102 weeks), then 48 weekly (±6 weeks) and at the end of trial visit (+6 weeks) to confirm their VL results. In addition, confirmatory real-time VL testing may be done in line with national guidelines at other visits and targeted real-time VL testing will be done in participants with suspected treatment failure, and before any treatment change for suspected lack of efficacy. At the time of repeat viral load a plasma sample and buffy coat will be saved for retrospective resistance testing. Resistance tests can be done in real-time if these are routinely available at the site and VL is sufficiently high for viral amplification (standard resistance tests require VL ≥500 c/mL but can be attempted at VL ≥200c/mL).

At the time of repeat VL the participant should complete an unscheduled follow-up visit, including a medical review, adherence assessment, medical history on intercurrent illnesses, immunisations and treatment interruptions (see **Section 6.0**)

Participants on DTG/3TC who have 2 consecutive real time VL≥50c/mL should be switched off DTG/3TC to a 3-drug ART regimen at their next scheduled trial visit or earlier and within 12 weeks of the second viral load above 50c/mL. The choice of the 3-drug regimen is at the discretion of the site clinician and may depend on the results of resistance tests (if available) and the availability of age-appropriate antiretroviral formulations. A switch to a DTG-based 3-drug regimen could be considered. A repeat viral load at the next scheduled trial visit after the switch should be considered. The management of the participant and the choice of the new ART regimen should be discussed with the trial physician.

Participants in the control arm with 2 consecutive real time VL≥50c/mL should be managed as per national guidelines.

5.7 OVERDOSE OF TRIAL MEDICATION

All participants should be counselled about the importance of taking the medications as prescribed. Participants must be told to come to the clinic immediately if they take too many pills. As no specific adverse consequences of overdose with any of the trial medications have yet been described, participants will be managed on a case-by-case basis by site clinicians in discussion with the trial physician.

5.8 MANAGEMENT OF ADVERSE REACTIONS

Toxicity will be managed in both randomised groups according to standard clinical practice. The Division of AIDS (DAIDS) tables (version 2.1, July 2017) will be used for grading the severity of adverse events (see **Appendix IV**). Neutrophil grading is based on NIH Paediatric toxicity tables[49] and WHO 2010 recommendations for antiretroviral therapy in infants and children,[50] recognising the lower normal levels in African populations.
Blood tests additional to those described in the trial schedule may be requested at any time for clinical management of the participant. Wherever possible, any side effects will initially be managed by symptomatic measures and administration of appropriate (non-contraindicated) medication. In particular, grade 1-2 gastrointestinal side effects such as nausea (with or without vomiting), and diarrhoea will be managed by anti-emetics and or anti-diarrhoeal agents in the first instance. Interruption of or changes in ART will be avoided except in the events of toxicity that is considered at least possibly related to one or more of the antiretroviral drugs. Alternate explanations for clinical or laboratory abnormalities that may at first appear to be related to a specific drug should be sought.

Management of adverse events/toxicity should generally follow the criteria below, but clinicians should use their clinical judgement as to the best management for the individual participant.

- Grade 1:
  - Continue ART
  - Routine monitoring
  - Manage using symptomatic measures and other concomitant medication, if appropriate

- Grade 2:
  - Continue ART
  - Manage using symptomatic measures and other concomitant medication, if appropriate
  - Work-up to exclude other causes

Raised ALT ≥2xULN should be assessed for HBV infection and include testing for HBsAg, HBcAb and HBsAb; participants with confirmed HBV infection should be started on tenofovir-containing ART. If paediatric age-appropriate tenofovir formulations are not available in the country, the need for HBV treatment should be assessed and further management should be discussed with the MRC CTU.

Raised serum aminotransferase ≥3xULN *and* total serum bilirubin level ≥2xULN or raised serum aminotransferase ≥3xULN and coagulopathy (INR >1.5)may indicate idiosyncratic drug induced liver injury [51] and recommendations for Grade 3 or 4 toxicity events as outlined below should be followed.

- Grade 3 or 4:
  - Request laboratory investigations if relevant, obtain repeat confirmatory laboratory results within 72 hours
  - If child is well, continue ART pending receipt of the confirmatory laboratory tests/repeat observations, unless there is an immediate need to substitute due to clinical concern
  - Work-up to exclude other causes
  - Following confirmation of toxicity, and if there is no other obvious cause:
    - if not too sick, substitute immediately
    - otherwise, stop all drugs and restart with substituted drugs when better

For severe reactions where the cause may be attributed to one or more drugs, all drugs should be stopped temporarily and may be restarted if the symptoms resolve and this is appropriate.

5.8.1 Information on specific ART drug toxicities

For the complete list of possible ARV-related adverse effects refer to the table of adverse effects listed in the current approved IB for DTG/3TC, dispersible DTG tablets and film-coated DTG 50mg tablets and SPCs for other ARVs used for children in the control arm.

5.8.1.A Liver toxicity

Liver toxicities can occur for multiple reasons. It may be necessary to discontinue or substitute drugs with an appropriate alternative if drug induced liver injury is suspected.

Liver stopping criteria:

- ALT ≥3xULN and bilirubin ≥2xULN
- ALT ≥3xULN and symptoms of acute hepatitis or hypersensitivity (fatigue, nausea, vomiting, right upper quadrant pain, fever, rash or eosinophilia (>5%))

- ALT ≥ 5xULN and <8xULN for more than 2 weeks with bilirubin <2xULN and no symptoms of acute hepatitis or hypersensitivity
- ALT ≥8xULN

If liver toxicity stopping criteria are met:[52]

- Immediately stop DTG and/or other suspected ARVs with known risk of hepatotoxicity
- An increase of ALT to ≥3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual liver serum measures (ALT, AST, ALP, and total and direct bilirubin) to confirm the abnormalities
- Initiate close observation with repeating liver enzyme and serum bilirubin tests two or three times weekly
- Frequency of retesting can decrease to once a week or less if abnormalities stabilize

Follow-up assessments and additional investigations:

- Obtain a detailed history of symptoms and prior or concurrent diseases
- Obtain a history of concomitant drug use (including paracetamol (acetaminophen) and other non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, and exposure to chemical agents
- Obtain additional tests to evaluate liver function, as appropriate (e.g., INR or prothrombin time and direct bilirubin if it has not been done)
- Arrange additional investigations as available to rule out acute viral hepatitis (including hepatitis A, B, C, and E, EBV, CMV)
    - Hepatitis A immunoglobulin M (IgM) antibody
    - HBsAg, HBcAb (total and IgM)
    - Hepatitis C total antibody
    - Hepatitis E IgM antibody
    - Cytomegalovirus IgM antibody
    - EBV capsid antigen IgM antibody or EBV DNA PCR
- Add screening for syphilis in adolescents
- Obtain complete blood count with differential to assess eosinophilia
- Obtain paracetamol (acetaminophen) level if paracetamol intake cannot be excluded
- Consider testing for illicit drugs and alcohol as applicable
- Consider liver ultrasound
- Consider testing for other local infectious causes based on investigator discretion

If no cause found and transaminitis persists:

- Consider further investigations to exclude autoimmune hepatitis:
    - Anti-nuclear antibody, anti-smooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (or gamma globulins)
- Consider tests to exclude metabolic liver disease
    - Ferritin and transferrin saturation, alpha-1-antitrypsin level and caeruloplasmin
- Arrange liver ultrasound and consider further imaging (magnetic resonance or computerised tomography) and liver biopsy to evaluate liver disease
- In participants with obesity, diabetes, insulin resistance (pre-diabetes) or hyperlipidaemia non-alcoholic steatohepatitis (NASH) should be considered as one of differential diagnoses (to confirm NASH, the demonstration of hepatic steatosis by imaging or biopsy is required as well as the exclusion of other coexisting chronic liver conditions manifesting with hepatosteatosis)
- Consider gastroenterology or hepatology consultations for persistent transaminitis.

Considerations for study treatment re-challenge and restart:

- If a **causal relationship** between the liver event and suspected ARVs cannot be ruled out, then **DTG/other ARVs must be permanently discontinued** and the participant not re-challenged due to the risk of a recurrent reaction
- If the liver event has a clear underlying alternative cause, other than drug-induced liver injury, restarting of the ARV may be permitted but the investigator **must discuss this first with the MRC CTU at UCL**. See **Appendix V** for Liver Safety – Checklist for Drug Restart Criteria.

5.8.1.B Allergic reaction or rash

Participants may continue drugs for grade 1 or 2 allergic reactions or rash at the discretion of the investigator. Consideration should be made as to which ARV or other drug may be causing the reaction. The carer/participant should be advised to contact the investigator immediately if there is any worsening of symptoms, if mucosal involvement develops or if further systemic signs or symptoms develop. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed.

Participants with grade ≥2 rash that is associated with an increase in ALT OR grade ≥3 allergic reactions or rash that are considered to be possibly or probably related to drug should permanently discontinue that specific drug and substitute with an appropriate alternative; the participant will remain in the study. Investigators should contact MRC CTU at UCL to discuss cases if there is any uncertainty about the course of action. Participants should be treated as clinically appropriate and the AE log should be completed or updated as necessary.

Severe skin reactions, such as Stevens Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported with the use of many antiretrovirals, including dolutegravir. Abacavir is associated with a risk for hypersensitivity reactions (HSR); HSR have been also reported with dolutegravir. Participants, who develop rash of any grade, and/or any other symptom suggestive of allergic reaction, will be evaluated for the possibility of a clinically suspected HSR or a serious skin reaction, and managed appropriately as outlined in the local prescribing information. In the event of discontinuation of ARVs, health care providers will obtain a complete history of the events surrounding the discontinuation. If there are any symptoms consistent with a hypersensitivity reaction, ARVs that are suspected to cause this reaction, in particular abacavir or dolutegravir should not be reinitiated, because of the possibility of a rapid-onset hypersensitivity reaction upon re-initiation of abacavir or dolutegravir, which may be life-threatening.

5.8.1.C Suicidal Ideation Behaviours and Sleep Disorders

Participants with HIV infection may occasionally present with symptoms of depression and/or suicidality (suicidal ideation or behaviour). In addition, insomnia and depression have been reported with the use of several antiretroviral drugs including all integrase inhibitors. Post-marketing real-life studies report relatively high rates of neuropsychiatric side effects and sleep disorders associated with dolutegravir-based ART.[53,54] Suicidal ideation has been associated with integrase inhibitors, primarily in patients with pre-existing depression or psychiatric conditions.

Therefore, all participants in the trial should be monitored appropriately for neuropsychiatric adverse events, suicidal ideation and behaviour, self-injurious behaviours or any other unusual changes in behaviour. Suicidal ideation and behaviour will be monitored and rated using Columbia Suicide Severity Rating Scale (C-SSRS) in children aged 6 years and above. The estimation of suicide risk is based on C-SSRS results and clinical judgment. It is recommended that subjects who experience signs of suicidal ideation or behaviour have prompt clinical and behavioural evaluation

and timely mental health consultation (see **Table 5**). Discontinuation of the antiretroviral drugs associated with suicidal ideation and/or behaviour should be considered and discussed with the trial physician.

Table 5: Suicide risk evaluation based on C-SSRS and recommended interventions

RISK STRATIFICATION	CORRESPONDING C-SSRS POINTS	INTERVENTIONS
Low Suicide Risk	Suicidal ideation **WITHOUT method, intent, plan or behaviour** (C-SSRS Suicidal Ideation #1 or #2)	Clinical and behavioural evaluation Outpatient mental health referral
Moderate Suicide Risk	Suicidal ideation with method, **WITHOUT plan, intent or behaviour in the past month** (C-SSRS Suicidal Ideation #3) Or Suicidal behaviour more than 3 months ago (C-SSRS Suicidal Behaviour Lifetime)	Clinical and behavioural evaluation Arrange urgent mental health referral Develop safety plan Consider suicide precautions Review HIV treatment
High Suicide Risk	Suicidal ideation with intent or intent with plan **in past month** (C-SSRS Suicidal Ideation #4 or #5) Or Suicidal behaviour **within past 3 months** (C-SSRS Suicidal Behaviour)	Initiate local psychiatric admission Immediate suicide precautions: arrange a responsible adult to stay with participant until transfer to higher level of care is complete Follow-up and document outcome of mental health evaluation Review HIV treatment

5.8.1.D Decline in renal function

DTG inhibits the renal organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter 1 (MATE-1). Due to this inhibition, the tubular uptake of creatinine from the blood is decreased (creatinine secretory fraction dependent on OCT2 and MATE-1 transport), leading to increases in serum creatinine and decreased eGFR or CrCl, without changing true GFR. A 10-14% decrease of creatinine clearance was observed in adult studies .[42] These changes are not considered to be clinically relevant since they do not reflect a change in true GFR.

In children, who develop renal impairment and creatinine clearance of <30mL/min /1.73m^2, to reduce the risk of increased exposure to 3TC and the potential for any associated toxicities, treatment with DTG/3TC and any other fixed dose combination medications containing 3TC should be switched to the individual components and the 3TC dose adjusted for renal dysfunction, according to EACS 2019 recommendations [55] or approved local prescribing information. In children on TDF who develop decreased creatinine clearance <50mL/min, TDF must be switched to an alternative nucleoside at the discretion of the Investigator. For calculation of creatinine clearance or estimated glomerular filtration rate in children, an updated Schwartz equation should be used (eGFR=CrCl (mL/min/1.73m^2)=41.3 x height (m)/serum creatinine (mg/dL).[56]

5.8.1.E Haematological disorders

Haematological disorders can frequently occur in children with HIV for a number of reasons including concurrent infections, malnutrition, malignancies and adverse reactions to ARVs or treatment of comorbidities. Clinicians should always be alert to clinical signs of anaemia,

neutropenia, and thrombocytopenia, and participants should receive education or counselling about the associated symptoms. Of all ARVs, zidovudine (ZDV) is most commonly associated with development or deterioration of anaemia and/or neutropenia. Of frequently used concomitant medications, co-trimoxazole is rarely associated with leukopenia, neutropenia and anaemia. Non-drug related causes for anaemia and/or neutropenia, such as concurrent bacterial, mycobacterial or fungal infection, malaria, helminthiasis, malignancy, and malnutrition, and, for anaemia, iron deficiency, haemoglobinopathy and G6PD deficiency should be investigated and treated as appropriate.

5.9 TB MANAGEMENT STRATEGIES

Participants, exposed to a case of TB, should have symptom screening for TB and chest X-ray and, if available, immune sensitisation tests (tuberculin skin test, interferon-gamma releasing assays). Children exposed to TB who do not report any of the symptoms of current cough, fever, weight loss or night sweats (the latter is included in symptom screening for adolescents) and have a normal chest X-ray are unlikely to have active TB and should be offered preventive treatment as per WHO or national recommendations for management of latent TB infection.[57] Current WHO recommendations for preventive therapy for latent TB infection in children and adolescents living with HIV include: 6-9 months daily isoniazid monotherapy or 3 months weekly regimen of rifapentine plus isoniazid or 3–4 months of daily isoniazid plus rifampicin or 3–4 months of rifampicin alone. Rifampicin interacts with many antiretroviral drugs (see **Section 5.5.1** and **Section 5.5.2**), and therefore for TB prevention should be used only in children on efavirenz-based ART regimens which have minimal interactions with rifampicin or when other preventive regimens cannot be used (e.g. isoniazid resistance or toxicity). In the latter cases, ART modification maybe required to overcome rifampicin inducing effect on liver enzymes.

Participants with symptoms suggestive of TB, should be investigated for TB as per WHO 2016 algorithm.[58] See **Appendix VI** for management of participants with suspected TB.

Participants who develop TB during the trial (or are likely to have TB according to the algorithm above) should receive TB treatment following national guidelines (usually rifampicin, isoniazid, pyrazinamide, and ethambutol). Respiratory samples should be collected for GeneXpert (or alternative molecular tests) and sent for TB culture prior to start of TB treatment. Where available, drug sensitivity tests to first-line anti-TB drugs should be performed on positive cultures and regimens modified on the basis of these results. Rifampicin is the cornerstone of TB treatment but interacts with many HIV medications. To overcome drug interaction and ensure adequate exposure of antiretroviral drugs (ARVs) ART modifications will be required for all children on DTG (see below).

Participants may need to be referred to the national TB treatment programme in order to access anti-tuberculosis medication, and close liaison between the trial team and the TB treatment providers will be required.

5.9.1 MANAGEMENT OF CHILDREN WITH TUBERCULOSIS INFECTION

Dolutegravir pharmacokinetics is influenced by concomitant treatment with rifampicin. This interaction can be overcome by giving the daily weight-appropriate dose of dolutegravir twice daily (daily dose is doubled).[34,40] Twice daily administration of DTG should remain until 2 weeks after the last dose of rifampicin has been given to allow the enzyme inducing effect of rifampicin to fade away after its discontinuation.

All NRTIs, except tenofovir alafenamide (TAF) can be co-administered with rifampicin-containing anti-TB treatment. There is currently a lack of data about the co-administration of tenofovir alafenamide (TAF) with rifampicin in children, therefore TAF should be switched to an alternative NRTI (tenofovir disoproxil fumarate, abacavir or zidovudine). CTUs should be notified and will provide advice (See **Appendix VI**).

5.10 HEPATITIS-B (HBV) COINFECTION

Participants will be screened for HBV infection at the screening visit as per WHO recommendations.[59] Children with HBV infection determined by presence of HBsAg will not be included in the trial.

5.11 PROTOCOL TREATMENT DISCONTINUATION

In consenting to the trial, participants are consenting to the allocated ART, trial follow-up and data collection. However, an individual participant may stop treatment early or be stopped early for any of the following reasons:

- Unacceptable toxicity or adverse event
- Intercurrent illness that prevents further treatment
- Any change in the participant's condition that justifies the discontinuation of treatment in the clinician's opinion
- Inadequate compliance with the protocol treatment in the judgement of the treating physician
- Withdrawal of consent for treatment by the carer or withdrawal of consent or assent by the participant

As the patient's participation in the trial is entirely voluntary, they may choose to discontinue the trial treatment at any time without penalty or loss of benefits to which they are otherwise entitled. Although the participant is not required to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason while fully respecting the participant's rights.

See **Section 6.7** for details on early stopping of follow-up.

5.12 COMPLIANCE & ADHERENCE

Most older children will already be receiving DTG-based ART (usually with 3TC). Similar proportions of younger children are likely to start DTG in DTG/3TC and control arms immediately following randomisation; suitable patient information and fully informed consent procedures will ensure that participants understand the trial requirements. There are no specific aspects of the DTG/3TC regimen or DTG-based triple ART that pose major challenges, so we would anticipate low rates of non-compliance with randomised allocation.

All the clinical centres will provide adherence support as per standard of care, and participants will be asked about missed doses and pill counts conducted at every visit to monitor this. See **Section 6.4** for further details. From previous trials, all the centres have experience in supporting families with complex adherence challenges.

5.13 TREATMENT DATA COLLECTION

Information about all ART received, including formulation, frequency, dose, start and stop dates, and reasons for change will be collected on the ART Log.

5.14 NON-TRIAL TREATMENT

5.14.1 PROPHYLAXIS

HIV-infected children/adolescents should remain on co-trimoxazole prophylaxis as per WHO [59] or national guidelines. Children exposed to tuberculosis (TB), should be assessed for TB and if active TB is excluded they should receive TB prevention treatment as per current WHO [57] or country guidelines (see **Section 5.8**).

5.14.2 OTHER CONCOMITANT MEDICATIONS

Children with comorbidities at the time of enrolment who require treatment that has significant drug interactions with DTG or 3TC should not be enrolled in the trial (See **Section 3.2**). The site investigator should check for potential drug interactions between concomitant medications and dolutegravir and lamivudine using the Interaction Checker at the University of Liverpool Drug Interaction Site (https://www.hiv-druginteractions.org/checker). Children can be enrolled after the illness resolves.

For children already enrolled in the trial, who are diagnosed with an intercurrent illness, all necessary concomitant medications are allowed. If a medication with a known drug interaction to one of the antiretrovirals that the child is receiving is essential for the participant's management, and if appropriate dose adjustment is not possible, the respective antiretroviral should be stopped and the concomitant medication used. (See **Section 5.8** for specific issues relating to tuberculosis.)

6 ASSESSMENTS & FOLLOW-UP

All participants will be seen in clinic at screening, enrolment (randomisation, week 0) and then at weeks 4, 12, 24, 36, 48, 60, 72, 84 and 96 and then every 12 weeks until the last participant enrolled reaches week 96. Visits will include evaluations from both physician/medical officers and nurses.

Trial visit schedules will be prepared for each participant at randomisation, and participants should be followed on the same schedule even if their ART is changed or discontinued. The target dates for trial visits are determined by the date of randomisation and are not affected by subsequent events. Clinics may choose to re-schedule visits to allow for public holidays or other unavoidable circumstances that affect the scheduled visit date, but the re-scheduled visit should be ideally no more than 14 days from the originally scheduled visit date (either before or after).

Participants will be expected to attend on the scheduled day unless agreed in advance with the clinic. Participants will be given a card with the contact details for the trial research team so they can contact them if needed to re-arrange a visit. If they are unable to attend on the day, every effort should be made to complete the visit within 14 days of the scheduled date. If a scheduled visit is missed without notice then the clinic should endeavour to contact the participant by phone or by home visit.

If a participant is more than 14 days late for a scheduled study visit, the visit should be performed as soon as possible, including the appropriate assessments that were specified in the trial schedule for the visit week that was missed.

The schedule defines visit dates necessary for data collection, but the participant may be seen more frequently for clinical care as needed, for example if the participant develops drug toxicity or other clinical events; in addition a participant will be recalled when their real-time VL≥50c/mL. At any such unscheduled visits, routine assessments as for a standard clinician and nurse visit will be performed (as for week 12), including pregnancy testing as recommended. Other laboratory tests will be performed as clinically indicated.

Young people who reach the age of consent whilst in the trial must re-confirm their continued participation by signing the informed consent form. The signed consent form must be kept by the investigator in the ISF, a copy in the child's clinical records and a copy given to the participant for their records.

6.1 TRIAL ASSESSMENT SCHEDULE

See **Table 1:** for a tabular summary of all assessments and procedures. Participants will have an end of trial visit within ±6 weeks of the last recruited participant reaching 96 weeks follow-up (with return for confirmatory viral load if their real-time viral load is ≥50c/mL).

AT EACH ASSESSMENT (weeks 0, 4, 12, 24, 36, 48, 60, 72, 84, 96 and then every 12 weeks until the end of the trial visit), the following will be undertaken:

- Symptom check by a nurse or physician to detect intercurrent illness, HIV disease progression or adverse events to ART.
- Medical history since last visit including intercurrent illnesses, adverse events, signs and symptoms of HIV disease and WHO stage. Adverse events as well as inpatient and outpatient

attendances outside trial visits should be recorded in the child's notes. If adverse events meet the reporting criteria, they should be reported using the AE log (See **Section 7**).

- Weight, height, mid-upper arm circumference (MUAC) and waist circumference.
- Assessment of adherence to ART by pill counts (except week 0) and a brief adherence questionnaire.
- Assessment of suicidal ideation and behaviour by completion of a C-SSRS questionnaire.
- Urine pregnancy test in all girls who have reached menarche.
- Plasma storage (stored plasma samples will be used subsequently for HIV RNA viral load measurements and resistance tests where appropriate).
- A buffy coat (from the same blood draw as for plasma storage) will be stored for total HIV-1 DNA for NGS testing (where required) and total HIV-1 DNA as a surrogate measure of HIV reservoir.
- Changes in ART, opportunistic infections (OI) prophylaxis and other concomitant medication.
- The next supply of drugs to last until the next clinic visit. Prescriptions of new antiretrovirals and any alterations to prescribed doses should be recorded on the ART Log. Doses should be checked at every visit and adjusted for body surface area (BSA), or weight as appropriate.

AT SPECIFIC VISITS, THE FOLLOWING WILL BE UNDERTAKEN:

- At weeks 0, 4, 24, 48, 72, 96, then every 24 weeks and at the end of trial visit, acceptability of trial medications will be assessed
- At weeks 0, 4, 24, 48, 72, 96 then every 24 weeks and at the end of trial visit, sleep and mood, and health-related quality of life questionnaires (EQ-5D-Youth plus smiley faces scale) will be performed.
- At screening and weeks 48 and 96, then every 48 weeks and at the end of trial visit, HIV VL will be measured in real-time at all sites; if a real-time VL≥50 copies/mL after screening, participants will be recalled back for a repeat viral load within 6 weeks of the scheduled visit date. (Some sites may do HIV VL at other study visits as part of routine care; in this case, recall will be as per routine care).
- At screening, weeks 4, 12, 24, 48, 96, full blood count (FBC) will be performed. FBC must be repeated prior to randomisation at week 0 if screening bloods are not done within 4 weeks of randomisation. FBC after week 96 will be performed as per local practice and at the end of trial visit. Other haematology tests may be performed if clinically indicated, but are not required by the protocol.
- At weeks 0, 24, 48, 72 and 96, CD3, CD4, CD8 percentage and absolute, total lymphocyte count will be measured (using the same blood draw as for haematology at weeks 24, 48 and 96). After week 96, T-cell lymphocyte subsets will be done every 24 weeks and at the end of trial visit.
- At screening, weeks 4, 12, 24, 48, 96, urea, creatinine, albumin, AST, ALT, ALP and bilirubin will be measured. Biochemistry tests must be repeated at enrolment if screening bloods are not done within 4 weeks of randomisation. After week 96, biochemistry tests will be done as per local practice and at the end of trial visit. Other biochemistry tests may be performed if clinically indicated, but are not required by the protocol.
- At weeks 0, 4, 12 and 24, lipase and lactate will be measured (using the same blood draw as for biochemistry at weeks 4, 12 and 24).
- At weeks 0, 48 and 96, lipids (total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides)) will be measured (using the same blood draw as for biochemistry tests at weeks 48 and 96). After week 96, lipids tests will be done as per local practice and at the end of trial visit.
- At weeks 0, 24, 48, 72 and 96, HbA1c will be measured (using the same blood draw as for haematology, where possible). After week 96, and at the end of trial visit, HbA1c tests will be done as per local practice.
- At weeks 0, 48, 96, then every 48 weeks and at the end of trial visit, urine dipstick for proteinuria will be done.

- At week 0, a whole blood EDTA sample will be taken from participants in South Africa, Thailand and Uganda for pharmacogenomic testing. If missed, this sample may be taken later in the trial since it does not depend on the specific time point.
- At weeks 4 (if not undergoing intensive PK), 24, 48, 72 and 96, a blood sample for sparse PK will be taken (plasma sample from 1mL whole blood) from participants in South Africa, Thailand and Uganda to assay drug levels (see **Section 10.2**)
- At each visit, all girls who reached menarche and continue receiving dolutegravir-containing ART should receive repeat counselling on highly effective contraception and the risk of neural tube defects associated with conceiving on dolutegravir (see **Section 6.6**).

For children randomised to DTG/3TC and enrolled in the intensive PK study:
- 7 plasma PK samples (1-2mL each) taken over 24 hours at an intensive PK visit.
- A questionnaire evaluating experience with dispersible tablets and dosing systems will be administered on the PK day.

Children who were not exposed to DTG prior to enrolment or who were exposed <3 weeks to DTG, should have their PK visit scheduled at least 3 weeks after they switch from non-DTG based ART to allow sufficient time for a wash-out period of the previously used third agents. Children who were exposed to DTG for ≥3 weeks prior to enrolment should have their PK visit scheduled at least 7 days after starting DTG/3TC. The PK visit could coincide with a trial scheduled visit if blood volumes for the planned blood tests are within the maximum allowable for the child's weight and health status (See **Appendix I** – Safe Limits of Blood Sample Volume in Children).

Unscheduled visits, for example if the child develops drug toxicity or other clinical events or they are recalled for repeat VL, should be recorded using the appropriate eCRFs. At such visits, laboratory tests should be performed as clinically indicated. Participants in all groups may undergo all necessary diagnostic tests for clinical management of an illness. Pregnancy tests in girls who reached menarche should be also done.
For suspected treatment failure, VL must be done and plasma and buffy coat saved prior to any ART regimen change.

6.2 PROCEDURES FOR ASSESSING EFFICACY

6.2.1 HIV-1 VIRAL LOAD TESTING

For all participants, real-time plasma HIV-1 VL will be measured at the screening visit to confirm eligibility for the trial. Otherwise, real-time VL will be measured according to local guidelines to ensure the trial results are relevant and generalizable to a wide range of settings. Provision of more frequent than routinely done viral loads would likely alter patient management and subsequent behaviour, particularly within a trial (e.g. recall of participants for confirmed viral load or provision of adherence counselling following a single raised viral load would likely result in improved adherence); this would mean trial results would not apply to most of sub-Saharan Africa where the majority of HIV-infected children reside. Routine annual viral load testing will be aligned to week 48 and 96 visits and continue 48-weekly. Mandated turn-around of VL results in the trial at weeks 48 and 96 (and 48-weekly thereafter) will be within 2-3 weeks. Participants with VL≥50 c/mL will be recalled back within the week 48 window (42-54 weeks), week 96 window (90-102 weeks) and 48 weekly (±6 weeks) thereafter to confirm their VL results. Week 48 and 96 visits (and 48 weekly thereafter) should be arranged as close to the scheduled visit as possible (to allow for recall within the window if necessary). A real-time viral load will also be performed at the end of trial visit, with prompt recall for participants with VL≥50 c/mL.

In addition, targeted real-time VL testing will be done and plasma sample and buffy coat saved in participants with suspected treatment failure, and before any treatment change for suspected lack of efficacy.
EDTA-plasma samples will be stored at weeks 0, 4, 12, 24, and then 12 weekly for retrospective viral load testing and/or resistance testing. All batched VL measurements will be performed using validated assay platforms within each country (lower limit of detection of ≤50 copies/ml) in one or more designated laboratories. The selection of laboratories will be made based on the availability of an appropriate VL assay, and the presence of adequate quality assurance procedures. Results will be reviewed regularly by the Data Monitoring Committee (DMC) to ensure participant safety (see **Section 14.4** -for further details on DMC reviews).

A combination of retrospective batched viral loads and routine viral load test results are being used to monitor efficacy in the ODYSSEY trial [34] and completeness of viral load test results is very high (94% at the last DMC, December 2019, Dr Debbie Ford, personal communication).

6.2.2 Resistance testing

Similar to viral load monitoring, real-time resistance testing will be done locally as per routine practice in participants with virological failure using validated methods where available. Batched genotypic resistance testing will be performed retrospectively on stored buffy coat samples from all participants who have confirmed VL ≥50 copies/mL by Next Generation Sequencing (NGS) testing on the saved buffy coat samples using in-house assay. Drug resistance mutations will be classified using the latest IAS-USA definitions and drug susceptibility predicted using the latest version of the Stanford database algorithm. Development of new resistance mutations will be described and compared between arms.[64] The results will be made available to treating clinicians at the trial closure.

The impact of archived reverse transcriptase (RT) resistance mutations, in particular the most commonly occurring M184V/I mutation, on maintenance of virological suppression remains unclear; children with pre-treatment drug resistance receiving partially-active ART may be at higher risk of experiencing virological failure.[65] Prevalence of NRTI mutations in treatment-naïve patients in eastern Africa is estimated at 3.2% (95%CI 1.6-5.7).[66] Frequency of M184V/I in nationally representative surveys of infants <18 months diagnosed through early infant diagnosis (EID) varied widely from 2.6% in Uganda and 9.5% in South Africa.[67] Considering the theoretical possibility of impairing treatment efficacy, the impact of the archived RT resistance at baseline on the rate of virological failure and viral blips and whether archived RT resistance disproportionally affects the performance of DTG/3TC dual therapy will be evaluated. Archived resistance on the stored buffy coat samples at baseline will be assessed by NGS testing of HIV-1 DNA using in house developed methods of pol/RT in the APDU at UCLH.[68]

6.2.3 CD4+ T-cell counts

Blood will be collected at weeks 0, 24, 48, 72, 96, then 24 weekly and at the end of trial visit for determination of total and percentage CD4 T-cell counts. The CD4 count will be measured using the standard assay in the laboratory operating at each site according to quality-assured procedures.

6.2.4 Clinical events

A symptom check and targeted physical examination (to evaluate any reported symptoms) will be performed at each visit. Hospital admissions will be solicited at all visits. Where there is any clinical suspicion of a WHO Stage 3 or 4 disease event, sites will endeavour to investigate the participant to the fullest extent possible given local availability of imaging and laboratory investigations (including

microbiology) in order to establish a clear diagnosis of the event. The list of HIV-related conditions for each WHO stage and their diagnostic criteria are provided in **Appendix II**.

6.3 PROCEDURES FOR ASSESSING SAFETY

A symptom check performed at each visit will explicitly prompt for symptoms relating to possible drug toxicities. Blood will be drawn at trial visits to assess laboratory safety parameters as indicated in the schedule of trial assessments; this includes full blood count, tests of renal and liver function and lipid profiles. All required blood tests including any confirmatory tests should be recorded on the database. Additional safety blood tests or investigations may be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

Adverse events (clinical and laboratory) will be graded using the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1 – July 2017. [69] Neutrophil grading is based on NIH Paediatric toxicity tables[49] and WHO 2010 recommendations for antiretroviral therapy in infants and children,[50] recognising the lower normal levels in African populations (see **Appendix IV**).

Serious adverse events (SAEs) will be defined according to ICH GCP (see **Section 7**). Suspected cases of drug induced liver injury, possible suicidality-related adverse events (PSRAE), ABC hypersensitivity and pregnancies constitute notable events (NEs, see **Section 7.2**). Both SAEs and NEs will be reported to the relevant CTU according to standard timelines (see **Section 7**).

Clinical and clinically significant laboratory events of all grades will be reported on the AE log. In addition, information on SAEs and NEs will be reported with clinical narrative and investigations that support the diagnosis in order to enable an evaluation of the event.

6.4 PATIENT-REPORTED OUTCOMES

6.4.1 PROCEDURES FOR ASSESSING ADHERENCE AND ACCEPTABILITY

Adherence to ART will be assessed in all participants at each visit by pill counts for tablets, and short nurse-administered adherence questions. At 0, 4, 24, 48, 72, 96 weeks and then every 24 weeks a more detailed acceptability questionnaire will be administered. This will elicit understanding of drug dosing regimens and reasons for non-adherence, and participant opinions about the different regimens, particularly with regard to pill burden and complexity.

6.4.2 ASSESSMENT OF SLEEP AND MOOD

Sleep disturbance will be assessed in all participants using participant/carer questionnaires at 0, 4, 24 weeks and then every 24 weeks. Anxiety and depression will be assessed in participants aged ≥6 years using participant/carer questionnaires at 0, 4, 24 weeks and then every 24 weeks. Questionnaires will be translated into local languages. The language in which the questionnaires are administered and the method (child-reported, parent-reported or administered by clinic staff) will be recorded on the appropriate eCRF.

6.4.3 ASSESSMENT OF SUICIDAL IDEATION

Suicidal ideation and behaviour will be assessed at every trial visit for children aged 6 years and above. Appropriately trained site staff will conduct the evaluation with the participant using questionnaires translated into local languages. The language in which the evaluation is conducted will be recorded on the appropriate eCRF.

6.5 OTHER ASSESSMENTS

6.5.1 HEALTH ECONOMICS AND HEALTH-RELATED QUALITY OF LIFE ASSESSMENT

Policymakers require information on the costs and health effects of alternative interventions when considering how to allocate limited resources to meet the population's health needs. We will estimate costs and cost-effectiveness of the dual DTG/3TC ART versus DTG + 2 NRTIs evaluated using generic health measures (QALYs, DALYs-averted) to allow comparison with other interventions. Resource use and total costs will be estimated using trial data and other sources (e.g. unit costs/prices) to be representative of general roll-out in LMIC.

The trial will measure healthcare-related costs in trial participants, starting at randomisation and continuing for the duration of follow-up. Information on each non-elective hospitalisation (including reason and duration of stay) will be recorded.

A simple health-related quality of life instrument (EQ-5D-Youth), plus smiley faces scale, will be used to inform the cost-effectiveness analysis. The EQ-5D-Youth is very similar to the validated EQ-5D used in adults but has simplified language to make it more appropriate for children. The self-completed version is recommended for children aged ≥8 years. For children aged 4 to <8 years, and those aged ≥8 years unable to complete the EQ-5D-Y themselves, a proxy version 1 will be used. Translations of the questionnaire will be made into appropriate local languages and verified. The questionnaire will be administered in the participant's own language. The language in which the questionnaire was administered and the method (self-completed or by proxy) will be recorded on the eCRF.

6.6 PREVENTION AND MANAGEMENT OF PREGNANCY

Pregnancy testing will be undertaken at screening and randomisation in girls who have reached menses. Pregnant girls will be ineligible for the trial. Pregnancy tests will be undertaken in girls who have reached menarche at all trial follow-up visits and at other time-points as required. Females will be encouraged to disclose missed menses as soon as possible; if this happens, a pregnancy test should be done.

If a girl who has reached menarche chooses to enter the trial, she will need to agree to use highly effective contraception if she becomes sexually active and to report to the study site staff as soon as possible if there is a possibility of pregnancy. Condom use should be recommended in addition to highly effective contraception. Teenage girls should receive sexual and reproductive health education as per WHO[70] and national recommendations; if an adolescent girl becomes sexually active during the lifespan of the trial, she should be counselled about the potential risks associated with pregnancy during the trial, including the possible increased risk of neural tube defects associated with dolutegravir use at conception, the importance of using highly effective contraception and the need to report to the study site staff as soon as possible if she believes that pregnancy has occurred. It must be explained to female participants who discontinue dolutegravir during the trial that they need to follow the same precautions for a month after dolutegravir is discontinued because dolutegravir levels are decreasing slowly and low levels may still have an adverse effect on the baby at the very early stages of pregnancy. At the end of trial visit, all girls who have reached menarche and continue receiving dolutegravir-containing ART should receive repeat counselling on effective contraception and the risk of neural tube defects associated with conceiving on dolutegravir.

Highly effective contraception with an expected failure rate <1% per year includes:[71]

1. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    a. oral
    b. intravaginal
    c. transdermal
2. Progestogen-only hormonal contraception associated with inhibition of ovulation
    a. oral (e.g. containing 75 micrograms desogestrel)
    b. injectable
    c. implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)

Dolutegravir has no interaction with hormonal contraceptives, and therefore any hormonal contraceptives inhibiting ovulation can be used in female participants on DTG. Please refer to **Appendix VII** for guidance on prescribing hormonal contraceptives for participants on different ART regimens.

A National Institutes of Health (NIH)-funded observational surveillance study in Botswana (TSEPAMO) evaluating the safety of ART regimens in pregnancy has reported a small possible increased risk of neural tube defects (NTD) in women conceiving on dolutegravir. The updated results suggest the difference between DTG- and non-DTG-based ART is no longer significant (see **Section 1.1.6).** Based on new evidence, the WHO and other international HIV treatment guidelines recommend the use of DTG-based ART as the preferred treatment for all populations, including pregnant women and those of childbearing potential.[72-74] Female participants taking dolutegravir, who decide during the trial that they would like to become pregnant or are identified to be pregnant, need to discuss the risks and benefits of continuing dolutegravir with their health care providers. Women conceiving on dolutegravir are recommended to start folic acid (5 mg/d) before pregnancy and continue during the first trimester of pregnancy.[74]

Women who are on DTG/3TC will need to switch to triple ART for the duration of pregnancy and breastfeeding. Women on triple ART including DTG who are pregnant may continue dolutegravir-based regimens. Discontinuing dolutegravir-based regimens is unlikely to confer any benefits particularly after the neural tube has formed, and medication changes during pregnancy could increase the risk of viremia and transmission of HIV to the infant. Pregnant participants should be encouraged to remain in the study whether or not their ART regimen is changed at this time.

Pregnant participants should receive counselling and receive support to make decisions about continuing pregnancy. Folic acid should be provided to pregnant participants throughout the first trimester. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child.

Advice on breast-feeding should be given according to local or national guidelines. All infants will receive infant prophylaxis according to the current local standard-of-care.

Reporting of pregnancy and pregnancy-related events is outlined in **Section 7.2.1**.

6.6.1 SUMMARY OF CURRENT DRUG SAFETY PROFILES IN PREGNANCY

Reproductive toxicology animal studies, including embryofoetal development studies in rats and rabbits, showed no evidence of adverse developmental outcomes for dolutegravir.[42] In May 2018, the TSEPAMO study reported an increased risk of NTDs among women who had conceived on

dolutegravir (see **Section 1.1.6**). Although the NTD risk difference between DTG or non-DTG ART at conception is no longer statistically significant with the updated results of TSEPAMO study,[45] further data collection on safety of dolutegravir for women of childbearing age and their infants is ongoing and updated results will continue to become available during this trial. In view of this alert, all eligible girls with childbearing potential will be counselled about the potential risks associated with pregnancy during the trial and the potential risks of antiretroviral therapy for the infant.

The NRTIs emtricitabine, lamivudine, zidovudine, abacavir are generally considered to be safe in pregnancy and are widely used. The previous formulation of tenofovir, TDF, is also considered safe in pregnancy and widely used. Modifications to the NRTI combination may be made by the treating physician based on the assessment of risks of particular drugs in pregnancy and their likely antiretroviral efficacy. At present there are inadequate data regarding the use of TAF in pregnant women. Animal studies indicate no direct or indirect harmful effects with respect to reproductive toxicity [75].

If a female participant receiving dolutegravir, darunavir or tenofovir alafenamide becomes pregnant during the study, a determination regarding study drug discontinuation must be made by the investigator after discussion with the participant. Continuation of study drug can be considered if the potential benefit justifies the potential risk.

6.7 EARLY STOPPING OF FOLLOW-UP

In consenting to the trial, participants and their carers are consenting to treatment according to the allocated treatment strategy as well as to trial follow-up visits and data collection. If a participant or their carer later chooses to discontinue participation in the trial it is important to be aware that there are various degrees to which they can discontinue participation:

1. Discontinue DTG/3TC or DTG+2NRTIs early and permanently
2. Discontinue scheduled D3 trial visits
3. Object to being contacted in the future
4. Object to data being collected as part of the participant's routine care
5. Object to storage of existing blood samples (the participant must make the request in writing in order to withdraw consent for storage of existing blood samples)

If a participant chooses to discontinue their trial treatment, the clinician or nurse will explain the importance of remaining on trial follow-up or, failing this, of allowing routine clinic follow-up data to be used for trial purposes. The participant should continue to attend trial follow-up visits providing they are willing; that is, they should be encouraged to not leave trial follow-up even if they no longer wish to take trial treatment.

If the participant does not wish to remain on trial follow-up, their decision must be respected. Prior to transferring to routine clinic follow-up, the participant will be asked to have assessments performed as appropriate for an end of trial visit although they would be at liberty to refuse any or all individual components of the assessment. It should be discussed with the participant and their carer whether they are willing to be contacted in the future, in order to collect routine data for the trial, or, if not, whether data may be collected from their medical notes. Even if a participant stops trial participation early, the medical data already collected during their participation in the trial will be kept and used in analysis, as consent cannot be withdrawn for data already collected. Consent for stored samples already collected to be used in future research, outside of the study protocol, can be

withdrawn when stopping trial follow-up early (but this should be discouraged and should follow a discussion with the participant).

The MRC CTU at UCL should be informed of all participants stopping participation in the trial early, regardless of the degree, using the Visit Checklist eCRF. The reason for the participant stopping participation and the degree of the requested withdrawal should be ascertained wherever possible and documented in the participant's notes. Participants stopping trial participation early have a negative impact on a trial's data.

Participants may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial.

Participants who stop trial follow-up early will not be replaced; their data will be used up until the point of lost to follow-up and allowance has been made for loss to follow-up in the sample size calculations.

6.8 PARTICIPANT TRANSFERS

If a participant moves away from the area, every effort should be made for the participant to be seen at another participating trial site. A copy of the participant's medical record (the source documentation, including any trial worksheets) should be provided to the new site and the participant's parent/carer will need to sign a new consent form. The participant must also sign a new assent/consent form, if applicable. Once this has been done, the new site will take over responsibility for the participant; until this has been done, responsibility for the participant lies with the original site.

If transfer to another participating site is not possible (e.g. if the participant moves to a different country), then the participant should be considered as lost to follow-up.

6.9 LOSS TO FOLLOW-UP

Every effort will be made to see participants at 48 and 96 weeks. For operational management in the clinic, a participant will be classified as 'lost to follow-up' (i.e. no further efforts to trace the participant are being made) when they have missed 2 consecutive scheduled clinic visits. During this time period attempts should be made to contact the participant via phone (if available) and to follow-up with home visits, if at all possible. Subsequently, if the participant attends clinic and an eCRF is entered on the database, the "lost to follow-up" status will be reversed.

At analysis, a participant who does not attend their end of trial visit will be classified as "lost to follow-up" if they are not known to have died and the clinic has confirmed that they are unable to contact them.

6.10 COMPLETION OF PROTOCOL FOLLOW-UP

Participants will have an end of trial visit within ±6 weeks of the last recruited participant reaching 96 weeks follow-up (with return for confirmatory viral load if viral load is ≥50c/mL at the end of trial visit). The trial will end when all participants have completed their end of trial visit and any extra

visits for repeat viral loads, all retrospective viral load data have been obtained and the database has been locked.

Post end of trial, ViiV Healthcare will supply DTG/3TC formulations to the trial participants on the DTG/3TC arm until age-appropriate DTG/3TC formulations are available through the local national-local HIV treatment programme, if:

- In the opinion of the treating physician, the participant is continuing to derive benefit from the study drug AND
- There are provisions in place to collect and report safety data to ViiV Healthcare under an approved clinical study protocol

7 SAFETY REPORTING

The principles of GCP require that both investigators and Sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials. These procedures are described in this section of the protocol. **Section 7.1** lists definitions, **Section 7.3** gives details of the investigator responsibilities and **Section 7.4** provides information on MRC CTU at UCL responsibilities.

7.1 DEFINITIONS OF ADVERSE EVENTS

The definitions of the EU Directive 2001/20/EC Article 2 based on the principles of GCP apply to this trial protocol. These definitions are given in **Table 6:**.

Table 6: Definitions of Adverse Events

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Is another important medical condition***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

7.1.1 Medicinal Products

An investigational medicinal product (IMP) is defined as the tested investigational medicinal product and the comparators used in the study (EU guidance ENTR/CT 3, April 2006 revision). This therefore includes DTG/3TC and, in the control arm, DTG-based triple ART (including DTG and NRTI backbone).

Adverse reactions include any untoward or unintended response to drugs. Reactions to an IMP should be reported appropriately.

7.1.2 Adverse Events

Adverse Events include:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after enrolment in the trial
- Continuous persistent disease or a symptom present at baseline that worsens following the enrolment in the trial

Adverse Events do not include:

- Medical or surgical procedures (the condition that leads to the procedure is the adverse event)
- Pre-existing disease or a condition present before treatment that does not worsen
- Hospitalisations where no untoward or unintended response has occurred, e.g., elective cosmetic surgery, social admissions
- Unintentional overdose of medication without signs or symptoms

7.1.3 Disease-related Events

Disease-related events are those considered to be related to HIV infection and are categorised according to WHO staging of HIV infection. All adverse events meeting the definitions above should be reported, regardless of their relationship to HIV. All deaths should be reported as fatal SAEs.

7.2 NOTABLE EVENTS

7.2.1 Pregnancy

Pregnancy occurring during participation in D3 should be reported as a notable event by completing the Pregnancy Notable Event eCRF on the trial database within 24 hours of the site becoming aware. Pregnancy complications and elective terminations for medical reasons must be reported as an adverse event. Spontaneous abortions, congenital abnormality or birth defect are SAEs and, as any event fulfilling the criteria of an SAE, should be reported within 24 hours of the site becoming aware of the event. Any SAE occurring in association with a pregnancy which occurred during the trial and is brought to the investigator´s attention after the participant has completed the study and considered by the investigator as possibly related to the investigational product, should also be reported as an SAE. All pregnancies and their outcomes will be reported to ViiV Healthcare and to the Antiretroviral Pregnancy Register.

Any pregnancy that occurs in a trial participant will be followed-up to determine outcome (including premature termination) and status of mother and child up to 30 days of age, which must also be reported to MRC CTU at UCL on the Outcome of Pregnancy eCRF. The clinical team responsible will be informed of the mother's participation in the trial and will be asked to inform the MRC CTU at UCL if there is any suspicion of any adverse effect of the trial medication.

Babies born to participants who become pregnant during the study will be reviewed at 6-8 weeks of age. Adverse events occurring in an infant born to female trial participants within 30 days of delivery should be reported on the Outcome of Pregnancy eCRF in order to evaluate for a possible adverse reaction related to *in utero* exposure to the study drugs.[76] At the end of pregnancy and when the newborn reaches 30 days of age the investigator will complete the Outcome of Pregnancy eCRF.

All infants will receive infant prophylaxis according to the current local standard of care. Follow-up of a child born to the partner of a male participant (who was taking trial treatment at the time of conception) will be according to local practice.

7.2.2 LIVER EVENTS

Any suspected case of drug induced liver injury (regardless of drug received) should be entered on the AE Log and reported as a notable event on the trial database within 24 hours of the site becoming aware. The usual criteria should be used to assess the severity grading of the event and whether the event meets the criteria of SAE or ART-modifying AE. If the event meets stopping criteria (see **Section 5.7.1.A**), the event should be reported as an SAE and additional information (on Liver Toxicity eCRF) will be requested from the sites. The Liver Toxicity eCRF should be completed within a week of the site becoming aware of the event. Any results of liver investigations, including liver biopsy and/or imaging should be reported.

7.2.3 SUICIDAL IDEATION OR BEHAVIOUR

A possible suicidality-related adverse event (PSRAE) should be entered on the AE log and reported as a notable event on the trial database within 24 hours of the site becoming aware. A PSRAE may include, but is not limited to, an event that involves suicidal ideation, a preparatory act toward imminent suicidal behaviour, a suicide attempt, or a completed suicide. The investigator will exercise his or her medical and scientific judgment in deciding whether an event is possibly suicide-related. The usual criteria should be used to assess the severity grade of the event and whether the event additionally meets the criteria of an SAE. If the event meets SAE criteria, the Investigator will be requested to collect additional information (on PSRAE eCRF) which should be completed within one week of the investigator diagnosing a possible suicidality-related SAE

7.2.4 ABC HYPERSENSITIVITY REACTION (HSR)

Clinically suspected ABC HSR should be reported as a notable event. The event should be entered on the AE log and reported as a notable event on the trial database within 24 hours of the site becoming aware. The usual criteria should be used to assess the severity grade of the event and whether the event meets the criteria of an SAE. If the event meets SAE criteria, additional information (on Abacavir Hypersensitivity Reaction eCRF) will be requested from the sites and should be completed within one week of the onset of the hypersensitivity reaction.

7.3 INVESTIGATOR RESPONSIBILITIES

Clinical and laboratory AEs of all grades should be recorded in the participant's medical notes and reported on the AE log. In addition, within 24 hours of the investigator becoming aware of an SAE or a notable event, the Adverse Event log, and the SAE and/or notable event information should be completed on the trial database Pregnancies are classified as notable events, and these should also be reported within 24 hours. Where it is not possible for site staff to enter the data onto the database within the timeframes, for SAEs, and/or notable events, the completed AE event log, SAE and/or Pregnancy Notable Event worksheets should be sent to the CTU within 24 hours of becoming aware

of the event. All events that are not SAEs or notable events should be entered on the AE log on the trial database within 7 days of the site becoming aware of the event.

7.3.1 Investigator Assessment

7.3.1.A Seriousness

When an AE or AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in **Table 6:**. If the event is serious, then it must be entered on the AE log, with SAE information completed, on the trial database within 24 hours.

7.3.1.B Severity or Grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be categorised using the DAIDS table, corrected Version 2.1 - July 2017, with minor modifications (see **Appendix IV)**.

7.3.1.C Causality

The investigator must assess the causality of all clinically significant AEs (i.e. excluding asymptomatic lab AEs) in relation to ART received in the trial using the definitions in **Table 7:**. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality of adverse event is assessed as possible, probable or definitely related, then the event is classified as an AR; if the adverse event is serious, it is classified as SAR.

Table 7: Assigning Type of Adverse Events Through Causality

Relatedness	Description	AE Type	SAE Type
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	AR	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	AR	SAR
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition, other concomitant treatments).	AR	SAR
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient's clinical condition, other concomitant treatment).	Unrelated AE	Unrelated SAE
Unrelated	There is no evidence of any causal relationship	Unrelated AE	Unrelated SAE

If an AE is considered to be related to trial treatment and drug is stopped or the dose modified, this should be recorded on the ART Log.

7.3.1.D Expectedness

For SAEs, if there is at least a possible involvement of IMP given during the trial, the trial physician at MRC CTU (to whom responsibility is delegated by the Sponsor) will assess the expectedness of the event. An unexpected adverse reaction is one not previously reported in the current approved Reference Safety Information, that should be accessed through the D3 reserved area on the Penta website (https://penta-id.org/reserved-area/d3), or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in **Table 6:**. If a SAR is assessed as being unexpected, it becomes a SUSAR.

7.3.1.E Notification

The relevant CTU should be notified of all SAEs and notable events within the timeframes outlined in **Section 7.3**.

Investigators should notify the relevant CTU of all reportable AEs occurring from the time of randomisation until 30 days after the participant exits the trial. Any subsequent events that may be attributed to IMP received in the trial should also be reported to national reporting schemes where relevant.

7.3.2 Notification Procedure

1. For SAE and notable events, the AE Log and SAE worksheets, or for pregnancy, the Pregnancy Notable Event worksheet, must be completed by an investigator (named on the Signature List and Delegation of Responsibilities Log, who is responsible for the participant's care; this will be either the Principal Investigator or another medically qualified person with delegated authority for event reporting). Due care should be paid to the grading and causality of the event as outlined above.

2. In the absence of the responsible investigator, the worksheets should be completed and signed by a member of the site trial team. The responsible investigator should subsequently check the AE log, SAE and Pregnancy Notable Event worksheets as applicable, make changes as appropriate and sign. The initial report must be followed by detailed, written reports as appropriate.

3. The minimum criteria required for reporting a SAE are the trial number and month and year of birth, name of investigator reporting, the event, and why it is considered serious.

4. An AE should be entered on the AE log on the trial database, and marked as being a SAE and/or a notable event. The additional questions required for SAEs (as per the SAE worksheet) should be completed. Pregnancy should be reported on a Pregnancy Notable Event eCRF.

5. As back-up, if it is not possible for the event information to be entered on the database within 24 hours of the site becoming aware of the event, completed AE log, SAE and/or Pregnancy Notable Event worksheets as applicable must be sent securely to the relevant CTU.

   <u>For sites co-ordinated by MRC CTU:</u>
   Email information to **mrcctu.d3safety@ucl.ac.uk**

For sites co-ordinated by PHPT:
Fax: **+66 53 240 913** or email information to **PHPTCTU.trial-d3@phpt.org**
PHPT will send an onward notification to the MRC CTU.

6. Updated information should be recorded on the study worksheets and entered on the database as information becomes available. The relatedness to the received medications should be updated based on new available information and the course of the event should be updated. Extra, annotated information and/or copies of test results may be provided separately. For the notable liver events, possible suicidality-related adverse events (PSRAEs) and ABC hypersensitivity events (see **Section 7.2**) meeting the seriousness criteria, additional eCRFs (Liver Toxicity eCRF, PSRAE eCRF and ABC HSR eCRF, respectively) should also be completed within 7 days of first becoming aware of the event. The participant must be identified by trial number (and random check letters) and month and year of birth. The participant's name should not be used on any correspondence and should be deleted from any test results.

7. Staff should follow their institution's procedure for local notification requirements.

SAE REPORTING

Within 24 hours of becoming aware of a SAE or notable event, the Adverse Event Log and SAE and/or Notable Adverse Event information should be completed on the trial database. Pregnancies should also be reported within 24 hours on the trial database.

As back-up, if it is not possible to enter the data within the timeframe stated above, please send completed worksheets for the event(s) to the relevant CTU within 24 hours of becoming aware of the event(s). Any worksheets sent by email must be encrypted or transferred using other secure methods. Please ensure that an acknowledgement of receipt by the CTU is received.

MRC CTU: email: mrcctu.d3safety@ucl.ac.uk

For the sites in Thailand, worksheets should be sent to the PHPT CTU:
Fax: +66 53 240 913 or email: PHPTCTU.trial-d3@phpt.org

7.4 CTU RESPONSIBILITIES

Medically qualified staff at the MRC CTU and/or the Chief Investigator will review all SAE reports received and, for any reported as SARs, this will include making an assessment of expectedness.

The CTUs are undertaking the duties of trial Sponsor and are responsible for the reporting of SUSARs and other SARs to the regulatory authorities and the research ethics committees, as appropriate. This responsibility is delegated to Country PIs, and Site PIs where appropriate, for relevant reporting requirements in individual countries. The relevant CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

MRC CTU at UCL will prepare Annual Safety Reports in the form of a Developmental Safety Update Report (DSUR) on behalf of the Sponsor which will be submitted to the Competent Authorities and Ethics Committees in each country participating in the trial.

Pharmaceutical companies will also be notified of SAEs and notable events according to the agreed contractual arrangements.

8 QUALITY ASSURANCE & CONTROL

8.1 RISK ASSESSMENT

The Quality Assurance (QA) and Quality Control (QC) considerations have been based on a formal Risk Assessment, which acknowledges the risks associated with the conduct of the trial and how to address them with QA and QC processes. QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of GCP and applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. This Risk Assessment has been reviewed by the MRC CTU at UCL's Research Governance Committee and has led to the development of a data management plan, safety management plan and monitoring plan which will be separately reviewed by the MRC CTU at UCL's Quality Management Advisory Group

8.2 SOURCE DATA

The investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's participants. Source data are contained in source documents and are defined by EU guidelines as all information in original records that are used for the reconstruction and evaluation of the clinical trial. Source documents are the first place where the source data are recorded. These can include hospital records, clinical and office charts, participant/care-giver completed questionnaires, laboratory notes, x-rays, and pharmacy dispensing records.

Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). Each data element should only have one source.

A source data plan will be put in place as part of the green light process with each site. This plan will define the source documents and the data therein, together with location of these source documents and any applicable plans for transmission of source data between the site and the Sponsor (or the delegated institution).

The following data are examples of that which should all be verifiable from source documents, which may include paper notes and electronic health records:

- Signed consent and (where applicable) assent forms
- Dates of visits including dates any trial specimens were taken and processed in the laboratory
- Eligibility and baseline values
- SAEs, NEs and adverse events of any grade
- Dates IMP were dispensed and returned
- Pharmacy/clinic IMP accountability and prescription logs.

8.3 CENTRAL MONITORING AT MRC CTU AT UCL AND PHPT CTU

Local staff will be trained on the trial database before being given access to enter data into the database. Data stored on the trial database will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, the site will be asked to check against the source data and to verify or correct the entry on the database. MRC CTU at UCL will also raise reminders for any overdue and/or missing data with regular inconsistency reports of errors.

Other essential trial issues, events and outputs will be detailed in the Monitoring Plan that is based on the trial-specific Risk Assessment.

8.4 ON-SITE MONITORING

The frequency, type and intensity for routine monitoring and the requirements for triggered monitoring will be detailed in the monitoring plan. This plan will also detail the procedures for review and sign-off.

8.4.1 DIRECT ACCESS TO PATIENT RECORDS

Participating investigators must agree to allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participant/carer consent for this must be obtained. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

8.4.2 CONFIDENTIALITY

We plan to follow the principles of the UK Data Protection Act 2018 regardless of the countries where the trial is being conducted. In particular, the investigator must assure that participants' anonymity will be maintained and that their identities are protected from unauthorised parties. Participants will be assigned a trial identification number and this will be used on eCRFs; participants will not be identified by their name. The investigator will keep securely a participant trial register showing identification numbers, names and date of birth. This unique trial number will identify all laboratory specimens, eCRFs, and other records and no names will be used, in order to maintain confidentiality. All records will be kept in locked locations. Clinical information will not be released without written permission, except as necessary for monitoring by the trial monitors.

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Children will be randomised 1:1 to DTG + 2 NRTIs (control arm) or DTG/3TC. Randomisation will be stratified by age (2 to <6, 6 to <12, 12 to <15 years), use of DTG at enrolment (≥1 month; <1 month or no use), and region (Africa; non Africa). At least half the children enrolled will be below age 12.

The randomisation list will be prepared by staff at the MRC CTU at UCL under the direction of the Trial Statistician using permuted blocks with variable size; this ensures that if a site opens early or recruitment is slow in an age band, clinical staff are unable to predict the next allocated treatment. These computer-generated sequentially numbered lists will be incorporated securely into the trial database (accessed over the web at each site), concealed from local staff. Allocation will be made after eligibility has been confirmed by local site staff through the web-enabled database. Only the next randomisation will be provided, the remainder of the list will be concealed (ensuring allocation concealment). Delegated member(s) of staff at each site will be responsible for carrying out the randomisation process using a secure electronic system within the trial database. Randomisation will not take place until after informed consent has been given and the participant is ready to receive therapy.

9.2 OUTCOME MEASURES

9.2.1 PRIMARY OUTCOME MEASURE

Proportion of children with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50c/mL) **by week 96.**

9.2.2 SECONDARY EFFICACY OUTCOME MEASURES

- Proportion of children with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50c/mL) by week 48.
- Proportion of children with confirmed HIV-1 RNA ≥50c/mL at weeks 48 and 96 (modified FDA snapshot)
- Proportion of children with HIV-1 RNA ≥50c/mL at weeks 24, 48 and 96 (including blips and confirmed measures ≥50c/mL)
- New resistance-associated mutations in those with confirmed HIV-1 RNA ≥50c/mL
- Time to any new or recurrent WHO 3 or WHO 4 event or death
- Change in CD4 (absolute and percentage) from baseline to weeks 24, 48 and 96

9.2.3 SECONDARY SAFETY OUTCOME MEASURES

- Incidence of serious adverse events, grade ≥3 clinical and laboratory adverse events
- Incidence of adverse events leading to discontinuation or modification of the treatment regimen
- Proportion of children with a change in ART for toxicity or switch to second-line
- Change in blood lipids from baseline to weeks 48 and 96
- Change in creatinine clearance estimated using bedside-Schwartz to weeks 48 and 96

9.2.4 PATIENT-REPORTED OUTCOME MEASURES

- Adherence as assessed by participant/care-giver questionnaires

- Acceptability, sleep and mood, suicidality ideation and health-related quality of life as assessed by participant/care-giver completed questionnaires

9.2.5 PROTECTION FROM BIAS

It is not practical to use placebos for the multi-drug regimens included in the control arm in this trial with variable formulations used across the different weight bands, as the number of tablets may diverge substantially. Further, the tablets in the control arm vary in size, colour, and taste. Introduction of placebo would increase the pill burden substantially and be logistically infeasible. As improved adherence may be an important benefit for once daily drugs and regimens with fewer tablets, providing matching placebos would negate this potential benefit.

Therefore, to counter the possibility of bias, objective outcome measures have been chosen as much as possible. The primary outcome measure (virological rebound) will be measured by laboratory staff blinded to randomised allocation, as will other secondary outcomes based on laboratory tests (HIV resistance, CD4, tests of renal function, bone profiles and lipids). Pharmacokinetic assays will only be run for the relevant drug (i.e. we will only assay dolutegravir on samples from children receiving dolutegravir) but the assay is an objective measure of drug levels and cannot be manipulated by knowledge of treatment received.

For clinical secondary outcome measures (WHO 3 or 4 events or death; SAEs), events will be assessed against WHO criteria for WHO events and ICH criteria for SAEs.

For drug modification for adverse events (AEs), bias will be minimised by setting clear criteria in the protocol for management of AEs of different grades and acuteness of onset (**Section 5.5**), and by discussion of complex cases on teleconferences with the sites.

Every effort will be made to minimise loss to follow-up and to ascertain outcomes completely thus avoiding bias from differential ascertainment between the randomised groups. Children lost to follow-up will be traced using home visits and mobile phone contact numbers taken on recruitment.

Anthropometric measurements will be analysed as z-scores normalised to age and sex.

9.3 SAMPLE SIZE

Non-inferiority of once daily DTG/3TC will be assessed by the difference between the DTG/3TC treatment group and the DTG-based triple ART group (control) in the estimated proportion of participants with confirmed viral rebound (defined as the first of two consecutive HIV-1 RNA ≥50c/mL) **by week 96.** Non-inferiority will be inferred if the upper bound of the two-sided 95% confidence interval (CI) for the difference between the two groups (DTG/3TC minus control) is less than 10% (the non-inferiority margin).

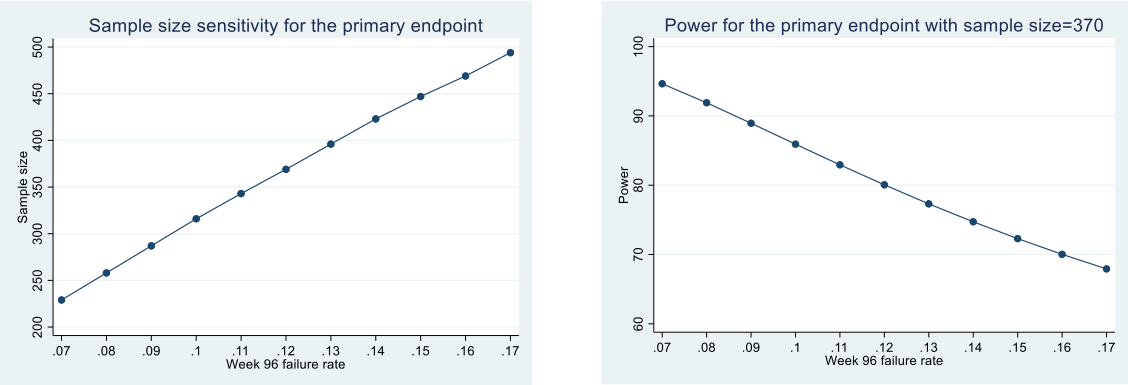
In BREATHER (PENTA16), comparing continuous with short-cycle (5 days on, 2 days off) EFV-based ART, proportions with viral rebound (confirmed HIV RNA ≥50c/mL) by 96 weeks were 10% in the short cycle therapy arm and 11% in the continuous treatment arm. [77] [78] Adult studies of DTG/3TC in ART-experienced and ART-naïve patients (which have mostly looked at HIV RNA<50c/mL with some requiring confirmatory HIV RNA≥50c/mL for failure) are consistent with ~90% suppression at 48 weeks and in studies with longer follow-up few new failures between 48-96 weeks (**Table 2**).

In BREATHER 12/199 (6%) participants were lost-to-follow-up by 144 weeks; [77,79] however this population was mostly in high income settings where patients may be more easily traced if they miss a clinic visit.

A total of 370 participants (185 per arm) will provide 80% power to exclude a non-inferiority margin of 10% for the difference in the proportion of participants reaching the primary endpoint assuming 12% have had confirmed viral rebound (2 consecutive HIV RNA ≥ 50 c/mL) by 96 weeks in both arms, 10% loss to follow-up and a two-sided α of 0.05 (with failure and loss to follow-up assumptions conservative given the BREATHER/PENTA 16 results).

Figure 2 shows the sensitivity of the required sample size to the true failure rate (assuming the same failure rate in both arms), holding the proportion lost to follow-up and α fixed. On the left-hand side the power is fixed at 80% and on the right hand side the total sample size is fixed at n=370.

Figure 2: Sensitivity to the assumed probability of virological rebound by 96 weeks



Should the failure rate by 96 weeks in the control group be substantially different to 12% by 96 weeks (e.g. <7% or >17%) we will consider modifying the non-inferiority margin (currently set at 10%) without reference to the accumulating comparative data.

9.4 INTERIM MONITORING & ANALYSES

A Data Monitoring Committee (DMC) Charter will be drawn up that describes the membership of the DMC, relationships with other committees, terms of reference, decision-making processes, and the timing and frequency of interim analyses (with a description of stopping rules and/or guidelines). The DMC can recommend premature closure or reporting of the trial, or that recruitment be discontinued or modified. See **Section 14.4** (DMC) for further details on interim assessments.

9.5 ANALYSIS PLAN (BRIEF)

The analyses will be described in detail in a full Statistical Analysis Plan. This section summarises the main issues.

For the primary analysis, the two treatment groups (DTG/3TC and control) will be compared in the intention-to-treat population, defined as all randomised participants excluding those demonstrably randomised in error; where randomisation in error will be judged by the participant meeting a major violation of the eligibility criteria. The comparison will be of the cumulative probability of virological rebound by week 96 (as defined above); imputation will be used where a child has one HIV RNA

≥50c/mL with no subsequent viral load measurement. To allow for censoring, the survival curve for each combination of strata and randomised group will be calculated using a Cox model adjusting for stratification factors and randomised group. The average cumulative failure function (1-survival curve) for each randomised group will be estimated as a weighted average of the corresponding stratum-specific cumulative failure functions. Similarly, the average difference between the cumulative failure functions at week 96 is the point estimate for the difference in overall probability of virological rebound between the DTG/3TC and control arm. A 2-sided bias-corrected 95% CI for the difference in the probability of virological rebound by week 96 (DTG/3TC – control) will be calculated with bootstrap standard errors. The bootstrapping will sample 1000 times and be stratified by stratification factors. DTG/3TC will be considered non-inferior to DTG-based triple ART if the upper limit of the 95% confidence interval of the difference DTG/3TC-control is less than the non-inferiority margin of 0.10. If non-inferiority is demonstrated, we will test for superiority of DTG/3TC versus DTG-based triple ART.

A sensitivity analysis will be done with the per protocol population, censoring follow-up after a participant makes a non-permitted treatment change to ART (see 5.5.1 for permitted changes)

The cumulative probability of virological rebound **by** week 48 (secondary outcome measure) will be estimated similarly.

Participants with VL≥50 c/mL at weeks 24, 48 and 96 will be compared between arms using a modified version of the FDA snapshot algorithm (see **Appendix VIII**).

Other endpoints will be analysed using the following statistical methods:

- Descriptive statistics for the summary of baseline characteristics
- Fishers Exact test and logistic regression for the analysis of binary variables
- Analysis of variance and linear regression models for the analysis of continuous variables, adjusting for baseline
- Poisson regression for the analysis of incidence of clinical/adverse events
- Log-rank test and Cox proportional hazard model for the analysis of time to event variables.

Clinical and adverse events will be summarised by System Organ Class using the Medical Dictionary for Regulatory Activities (MedDRA) coding.

No adjustment will be made for testing multiple secondary outcomes; secondary efficacy outcomes are very closely related to the primary outcome and it is appropriate to test secondary safety outcomes independently since it is important to identify any risks associated with DTG/3TC. If we fail to demonstrate non-inferiority of DTG/3TC versus DTG-based triple ART for the primary outcome, patient-reported outcomes will not be used to conclude superiority of DTG/3TC.

The primary analysis is based on 96 week data but data from the nested Intensive Pharmacokinetics and Safety Study and sparse PK samples on the Intensive PK and Safety Study participants up to 48 weeks will be provided to ViiV Healthcare in confidence for the purposes of regulatory filing. (See **Section 10.1**).

9.5.1 SUBGROUP ANALYSIS

Subgroup analyses will be planned by the randomisation stratification factors (age groups (2 to <6, 6 to <12, 12 to <15), use of DTG at enrolment (≥1 month; <1 month or no use), and region (Africa; non Africa)).

10 ANCILLARY STUDIES

10.1 INTENSIVE 24H PK AND PD STUDY OF DTG/3TC

To support regulatory approvals of the DTG/3TC paediatric formulation and to ensure timely access to this formulation for children, an intensive PK study will be nested in the trial.

AIM: to evaluate the pharmacokinetics, safety, tolerability and exploratory antiviral activity of the fixed-dose combination of DTG/3TC in virologically suppressed HIV-1 infected children aged at least 2 years and weighing <40kg using WHO weight band-aligned dosing.

STUDY DESIGN: an open-label, single arm steady-state intensive PK and safety study

STUDY POPULATION:

- Participants enrolled on the DTG/3TC arm in the main trial and therefore meeting all inclusion and exclusion criteria as per the main trial.
- Participants weighing <40kg
- Participating sites: sites in Uganda and South Africa with prior experience of conducting paediatric PK studies.

Additional inclusion criteria:

- A parent or legal guardian willing and able to give informed consent for participation in the intensive PK study

Additional exclusion criteria:

- Illnesses that could influence drug pharmacokinetics, i.e. severe diarrhoea, vomiting, renal disease or liver disease
- Participant is receiving concomitant medications that have significant drug interactions with dolutegravir
- Severe malnutrition defined as weight for height less than 3 standard deviations below the median WHO growth standards

PRIMARY ENDPOINTS:

- Steady State AUC0-24 and C24 for DTG
- Steady State AUC0-24 for 3TC

SECONDARY ENDPOINTS:

- Pharmacokinetic assessments: t_{max}, C_{max} for DTG and 3TC and C_{24} for 3TC based on intensive PK sampling
- Clinical and laboratory adverse events over 24 and 48 weeks
- Serum creatinine at weeks 24 and 48
- Body weight and height at 24 and 48 weeks
- The proportion of subjects with plasma HIV-1 RNA <50c/mL at weeks 24 and 48 using the FDA snapshot algorithm
- The proportion of subjects with plasma HIV-1 RNA ≥50c/mL at weeks 24 and 48 using the FDA snapshot algorithm
- Time to loss of viral response, defined as the first of two consecutive HIV-1 RNA ≥50c/mL (survival analysis)

- HIV-1 RNA viral loads at baseline and weeks 4, 12, 24 and 48
- HIV-1 resistance mutations in all participants at baseline and in participants with confirmed HIV-1 RNA ≥50 copies/mL at any visit after day 1 using next generation sequencing on proviral DNA for HIV-1 RNA ≥50c/ml to 200 c/mL and standard Sanger plasma-based sequencing for HIV-1 RNA ≥200 c/mL
- Retrospective proviral DNA analyses on stored buffy coat samples using next generation sequencing at baseline, week 24, week 48, and study drugs discontinuation
- CD4+ cell count at weeks 24 and 48
- Acceptability and palatability of dispersible and film-coated DTG/3TC FDC formulations

Children enrolled at PK sites who are randomised to DTG/3TC and weighing 6-<40kg will be asked for additional consent to participate in the intensive PK study.

The dosing will be weight band based as in the main trial (**Table 4**:). For children 20-<25kg, the PK sites will be allocated to use either DT or FCT; allocation will be done by MRC CTU who will aim to balance use of both formulations in each participating country.

We plan to recruit at least eight children per weight band and formulation (6 to <10kg DT, 10 to <14kg DT, 14 to <20kg DT, 20 to <25kg DT, 20 to <25kg FCT, 25 to <40kg FCT).

In 20 to <25kg weight band ≥8 children will be enrolled to receive DTG/3TC dispersible tablets and ≥8 children to receive DTG/3TC film-coated tablets; participating PK sites will be allocated to use either dispersible or film-coated tablets in this weight band. Across 5 weight bands (with 2 formulations tested in the 20 to <25kg weight band) this totals 48 children with evaluable PK curves for dolutegravir and lamivudine. We also require at least 14 children per age group (2 to <6 years (cohort 2) and ≥6 years (cohort 1)) and we will monitor recruitment by weight band to achieve this.

The pharmacokinetic variability (CV) of the C_{max} and AUC0-24 in the ODYSSEY trial were observed to be around 30% in all weight bands. With a sample size of 14 subjects per age cohort, there is >80% power to achieve 95% CIs for apparent clearance within 60% and 140% of the geometric mean parameter estimates, even when assuming a higher variability (%CV) of 53%. [80] Larger variations were seen for C_{trough} in ODYSSEY in children in 6 to <10kg weight band.[81]

Table 8: Number of children planned for recruitment in the intensive PK study per WHO weight band groups

AGE GROUP (MINIMUM N PER AGE GROUP)	WHO WEIGHT BANDS (KG)/ MINIMUM N PER WEIGHT BAND				
	6 TO <10 KG	10 TO <14 KG	14 TO <20 KG	20 TO <25 KG[1]	≥25 KG
2 to <6 years (n≥14)	n=8 (DT)	n=8 (DT)	n=8 (DT)	n=8 (DT) n=8 (FCT)	n=8 (FCT)
≥6 years (n≥14)					

DT = dispersible tablets, FCT = film coated tablets
[1]For 20-<25kg weight band PK sites will be allocated to use either DT or FCT.

At the PK visit all children must have been exposed to DTG for at least 3 weeks and to DTG/3TC for at least 7 days.. The PK visit could coincide with a trial scheduled visit if blood volumes for the planned blood tests are within the maximum allowable for the child's weight and health status (See

Appendix I – Safe Limits of Blood Sample Volume in Children). Children in the PK substudy will be part of the main trial and will have the same assessments as in the main trial (See **Table 1**). Seven plasma samples (1-2mL blood for each) will be taken at least 7 days after initiating DTG/3TC regimen (and ≥21 days after starting DTG) over 24 hours in the first children per weight band recruited at the PK sites and randomised to DTG/3TC arm (t=0 (prior to observed dosing), 1, 2, 3, 4, 6 and 24h post-dosing). In total, 14mL of blood will be drawn from children weighing ≥10kg (2mL per sample), and 7mL from children weighing <10kg (1 mL per sample). Food increases absorption of DTG and decreases 3TC C_{max}, increasing intersubject variability. Therefore children weighing ≥10kg will preferably be fasted overnight (at least 3 hrs predose) and remain fasted until 2 hours post-dosing to minimize intersubject variability and reflecting the worst case scenario for dolutegravir absorption. Children in the 6 to <10kg weight-band will be asked to remain fasted 2hrs predose until 1hr post-dose. The procedure details will be outlined in the Intensive PK Manual of Operations (MOP).

The plasma concentrations for dolutegravir and lamivudine will be determined with validated highly-sensitive LC-MS/MS methods at the department of Pharmacy of the Radboud University Medical Center in Nijmegen, the Netherlands. Pharmacokinetic parameters (AUC_{0-24}, Vd, CL, t1/2) will be evaluated using WinNonlin/Phoenix (Pharsight Corporation, CA, USA) from observed concentration time data. Plasma exposures will be summarised using standard measures (including AUC_{0-24}, C_{max} or C_{min} and T_{max}), and geometric means will be compared with adult reference values.

Adverse events and treatment discontinuations in children in the PK sub study will be described in detail and summarised using descriptive statistics. Comparisons will be made with adult reference PK data and paediatric data from P1093 and ODYSSEY using descriptive statistics.[82-84]

Retrospective viral load testing will be done at weeks 0, 4, 12, 24 and 36 on saved plasma and real time viral load testing at week 48 or more often if part of routine care. Participants with VL ≥50 after week 0 will have their saved plasma sample tested at the subsequent scheduled study visit for confirmatory VL, except at visits when a real-time confirmatory viral load will be done. Testing for possible resistance mutations in all participants at baseline and in the participants with confirmed VL≥50 c/mL will be performed using next generation sequencing on proviral DNA. The results of the virological tests in PK participants up to and including 48 weeks will be used for regulatory purposes and will be kept confidential until the trial's primary endpoint is reported.
Sparse PK results on Intensive PK study participants will also be used to support regulatory submission (see **Section 10.2** for description of sparse PK study).

10.2 EXPLORATORY POPULATION PK AND PK/PD ANALYSES

One disadvantage of intensive PK studies is the relatively small population set and possible selection bias because standardization around drug intake is high. It has been observed that dolutegravir concentrations are highly variable in children, with no single factor known to be responsible for this. In this large study we have the opportunity to study this in more detail. All participants on DTG-based ART (DTG/3TC and control arms) at sites in South Africa, Thailand and Uganda will have a sample stored for pharmacogenomics at baseline and sparse PK sampling for modelling of dolutegravir and lamivudine.

AIMS:

1. To conduct exploratory population PK analyses of dolutegravir and lamivudine exposures in children

2. To conduct exploratory population PK/PD analysis

Five blood samples (1ml for each) will be taken to assay drug levels, at week 4, 24, 48, 72 and 96 (**Table 1**) with the exact times of blood sampling recorded. These sparse data will be pooled with the intensive data to allow appropriate population pharmacokinetic analyses assessing paediatric DTG and 3TC exposures. These population pharmacokinetic analyses will be performed using appropriate software e.g. NONMEM version VII (or similar software). The analyses may also be used to determine if covariates, such as age, weight, sex, BSA, and concomitant medications alter DTG or 3TC pharmacokinetics in children.

Consent for analysis of pharmacogenetic determinants of PK as well as drug safety and efficacy will be requested for all children as part of trial enrolment. A 1mL whole blood sample will be drawn for this analysis and stored (See **Table 1:**). Genomic DNA extraction from whole blood and genetic analysis will be undertaken at the department of Molecular and Clinical Pharmacology, University of Liverpool. Analysis will be undertaken using a genome-wide association study (GWAS) using global SNP array which will include genes encoding enzymes previously implicated in metabolism and disposition of DTG and/or 3TC including (but not limited to) *UGT1A1* [85], *CYP3A4/CYP3A5* [86], *CYP1A1/1B1*[87] *and NR1I2.* Analysis will be undertaken to determine association of variant alleles with variability in PK-related outcomes (C_{min}, C_{max} and $AUC_{0\text{-}24h}$) for the sparse sampling protocol and identify novel associations with PD-linked genetic loci related to efficacy and toxicity in addition to those related to PK. Any significantly associated variants will be reported to Radboud University Medical Center Nijmegen for incorporation into PK/PD modelling analyses.

10.3 TB-PK SUBSTUDY

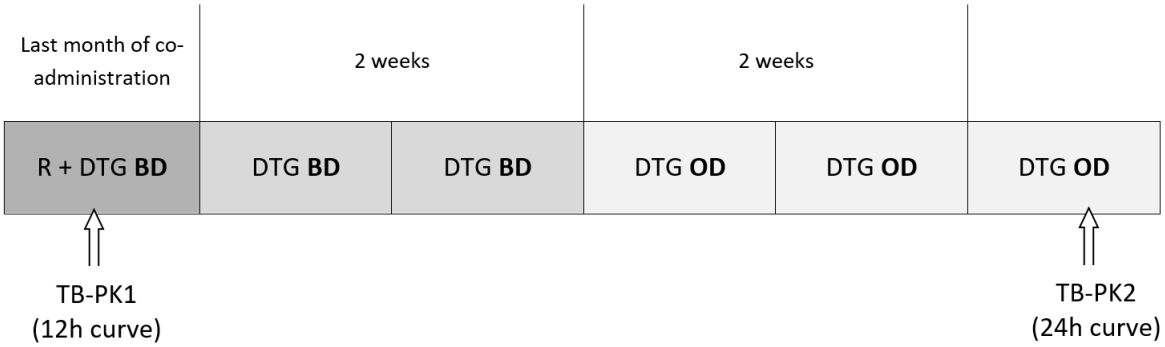
Rifampicin significantly lowers DTG plasma concentrations. The mechanism behind this interaction is increased enzyme activity of UDP-glucuronosyltransferase (UGT) caused by rifampicin resulting in increased metabolism and elimination of DTG. Increasing dolutegravir dose to 50 mg BD when using concomitant rifampicin resulted in a similar exposure compared to DTG 50mg OD without rifampicin in healthy adults.[88] The INSPIRING study reported that DTG BD also resulted in therapeutic plasma trough concentrations in HIV/TB co-infected adults on rifampicin-based TB treatment and that it was both effective and well-tolerated.[40] Furthermore, in adults with resistant HIV, who received dolutegravir 50mg BD without rifampicin, there was no added toxicity.[89] In the ODYSSEY trial, twice daily administration of the weight-appropriate dose of DTG (daily dose doubled) was evaluated in 13 HIV and TB co-infected children. The study showed that doubling DTG dose in children aged 6-<18 years was safe and sufficient to overcome rifampicin hepatic enzymes inducing effect and reach acceptable drug exposures.[41] More PK and safety data are required for younger children and on doubling the adult DTG dose currently recommended for children ≥20kg when it is co-administered with rifampicin.. There are no reports in the literature of 3TC PK data in HIV/TB co-infected patients using concomitant rifampicin.

Based on the above, all children receiving a DTG based ART regimen in the D3 trial (in DTG/3TC or control arms) who develop TB and subsequently receive rifampicin, will be given DTG BD during TB treatment. The DTG dose will need to remain BD for 2 weeks after the last dose of rifampicin has been given as the enzyme inducing effect of rifampicin slowly fades away after discontinuing the drug.[1]

AIM: to assess the pharmacokinetics of DTG and 3TC in HIV/TB co-infected children receiving dolutegravir BD and rifampicin-based TB treatment to substantiate the findings from the ODYSSEY TB-PK substudy.

STUDY DESIGN: an open-label cross-over study. A first 12h PK curve of DTG and 3TC with rifampicin co-administration (TB-PK1) and a second 24h PK-curve without rifampicin co-administration (TB-PK2) will be recorded for each child. TB-PK1 will take place within the last month of rifampicin co-administration. Rifampicin treatment will then be stopped at the completion of TB treatment; DTG BD dosing will be continued for another 2 weeks and then reduced to OD. At least 2 weeks after resuming OD dosing of DTG a 'steady-state' for DTG will be reached and a second PK-curve (TB-PK2) will be recorded in the same child (Figure 3:).

Figure 3: DTG dosing and timing of TB-PK1 and TB-PK2



R= rifampicin, BD= twice daily dosing, OD= once daily dosing.

STUDY POPULATION:

Inclusion criteria:

- Participants enrolled in the main trial and therefore meeting all inclusion and exclusion criteria as per the main trial.
- Participant is receiving rifampicin as part of TB treatment or TB prevention therapy
- Participant is receiving DTG as part of their ART
- A parent or legal guardian willing and able to give informed consent for participation in the PK study

Exclusion criteria:

- Illnesses that could influence drug pharmacokinetics, i.e. severe diarrhoea, vomiting, renal disease or liver disease
- Concomitant medications known to have interactions with dolutegravir, other than rifampicin for TB treatment
- Severe malnutrition defined as weight for height less than 3 standard deviations below the median WHO growth standards

PARTICIPATING SITES:

Sites in Uganda and South Africa with prior experience of conducting paediatric PK studies.

Before enrolling in the TB-PK substudy, parents/carers of HIV-infected children and adolescents will be given a PK information sheet and asked to give written consent before any substudy-specific procedures are performed.

NUMBER OF PARTICIPANTS: All participants receiving DTG-based ART and developing TB disease will be asked to participate in this PK substudy.

STUDY PROCEDURES:

Seven plasma samples (1-2mL blood each) will be drawn at t=0 (prior to the dose), and at t= 1, 2, 3, 4, 6, and 12h (after the dose) on PK day 1 for measurement of DTG. In addition, four plasma samples (1mL blood for each) at t=0 (prior to the dose), and at t= 2, 4, and 6h (after the dose) for measurement of rifampicin. Total blood volume drawn for the first PK curve will be between 11 to 18 ml depending on the weight of the child, including the rifampicin samples. For PK day 2, seven plasma samples (1-2mL blood each) will be drawn at t=0 (prior to the dose), and at t= 1, 2, 3, 4, 6, and 24h (after the dose) for measurement of DTG. No additional samples will be drawn. Hence, total blood volume drawn for the second PK curve will be between 7 to 14 mL depending on the weight of the child. The blood volumes will be within the limits of maximum allowable total blood draw volumes over 24 hours for children (see **Appendix I**). Food increases absorption of DTG and decreases 3TC C_{max}, increasing intersubject variability. Therefore children weighing ≥10kg will preferably be fasted overnight (at least 3 hrs predose) and remain fasted until 2 hours post-dosing to minimize intersubject variability and reflecting the worst case scenario for dolutegravir absorption. Children in the 6 to <10kg weight-band will be asked to remain fasted 2hrs predose until 1hr post-dose. The procedure details will be outlined in the Intensive PK Manual of Operations (MOP).

Safety Assessments will be performed as per the main trial protocol. Blood will be drawn at trial visits to assess laboratory safety parameters as per **Table 1:**.

The plasma concentrations of DTG and rifampicin will be assayed at the Department of Clinical Pharmacy of the Radboud University Medical Center in Nijmegen, The Netherlands. Pharmacokinetic parameters (AUC_{0-24}, Vd, CL, t1/2) will be evaluated using WinNonlin/Phoenix (Pharsight Corporation, CA, USA) from observed concentration time data. C_{max}, T_{max} and C_{min} will be determined from observed concentration time data. Geometric Means and 95% confidence intervals will be estimated for pharmacokinetic parameters (except for T_{max}) of DTG at TB PK1 and TB PK2 and rifampicin at TB PK1. BD DTG (with RIF) and OD DTG will be compared in all children with two evaluable PK curves. Within-patient ratios of AUC_{0-24}, C_{max} and C_{min} for BD DTG (with RIF) versus OD DTG will be calculated. Overall GMRs (geometric mean ratios) for BD DTG versus OD DTG daily will be calculated after log-transformation of the within-patient ratios and 95% CI for the GMR will be calculated using the t-distribution.
Adverse events and treatment discontinuations in all children who are treated for TB and receive double dose of DTG co-administered with rifampicin will be described in detail and summarised using descriptive statistics.

10.4 VIROLOGY SUBSTUDY

10.4.1 ULTRASENSITIVE VIRAL LOAD TESTING AND HIV RESERVOIR

Reduced ART may result in viral replicative activity below detection by routine viral load tests, which can contribute to increased viral reservoirs,[90,91] increased immune activation, inflammation and immune senescence.[92,93]

AIM: to compare low level viraemia and viral reservoirs in DTG/3TC and control arms.

Efficacy of DTG/3TC dual therapy will be further investigated by assessing its effect on very low level viraemia and the HIV reservoir. Total HIV-1 DNA will be used as a surrogate measure of HIV-1 reservoir size.[91] Low level viraemia (quantitation limit 1-5 copies/mL depending on the available plasma volume) and total HIV-1 DNA will be assessed retrospectively on stored plasma and buffy coat respectively. Plasma will be collected at baseline and each study visit according to the trial assessment schedule. Blood samples for buffy coat storage will be collected at enrolment, 4, 12 and then every 12 weeks using the same blood draw (**Table 1**). Samples will be stored locally and later transferred to the Advanced Pathogen Diagnostics Unit (APDU) at UCLH or the African Health Research Institute (AHRI) laboratory for analyses. The ultrasensitive quantitative HIV-1 RNA will be assessed by in house modified protocol using the HOLOGIC® APTIMA HIV-1QuantDx [94] and the HIV-1 DNA will be assessed by in-house quantitative PCR.[95]

10.5 HEALTH ECONOMICS

If dual therapy is shown to be safe and non-inferior to DTG-based triple ART in terms of virological efficacy it is likely that there will be substantial individual and societal cost savings associated with taking one less drug for the lifetime of an HIV-infected person.

Aim: to compare net health benefits and incremental cost-effectiveness ratios (ICERs) of DTG/3TC dual therapy and DTG-based triple ART.

Policy makers require information on the costs and health effects of alternative interventions to inform the allocation of limited health care resources to meet population's health needs. In this study, we will estimate the costs and cost-effectiveness of DTG/3TC versus DTG-based triple ART to help inform policy makers on whether dual DTG/3TC represents a valuable use of health care resources. Outcomes will be evaluated using generic health measures (quality-adjusted life years (QALYs) and disability-adjusted life years (DALYs) averted) to allow for comparison with other interventions. Costs will be estimated from a health care perspective. For the cost-effectiveness analysis, the cost of the treatment interventions will be related to their health outcomes (QALYs, DALYs). Cost-effectiveness will be summarised using both net health benefits - the health gain resulting from one treatment compared to another less the health opportunity cost forgone elsewhere as a result of the resources not being available for others - and incremental cost-effectiveness ratios (ICERs) – the cost per DALY-averted or QALY gained associated with more effective, but more costly alternatives. Determining cost-effectiveness requires comparison of the treatments to other claims on limited resources, which are captured using cost-effectiveness thresholds.

A health related quality of life (HRQoL) instrument (EQ-5D-Youth), plus smiley faces scale, will be used to estimate QALYs as part of the study. The self-completed version is recommended for children aged ≥8 years, and for children aged 4 to <8 years and those aged ≥8 years unable to complete EQ-5D-Y themselves, a proxy version 1 will be used. Translations of the questionnaire will

be made into appropriate local languages and verified. The questionnaire will be administered in the participant's own language. The language in which the questionnaire was administered and the method (self-completed or by proxy) will be recorded on the eCRF. The EQ-5D-Youth will be administered at weeks 0, 4, 24 and then every 24 weeks. The responses to the EQ-5D-Youth will be converted into HRQoL scores using adult tariff values elicited from members of the public where a score of 1 represents perfect health and 0 death. Given the study is across multiple countries, two analyses will be conducted, one where a common tariff is used (likely to be based on a survey in Zimbabwe) and another where the most relevant tariff based on the individual's country of residence is used (tariffs are not available for many LMIC countries). Once HRQoL scores are calculated, QALYs will be estimated using the area under the curve method with linear interpolation between time points. DALYs averted will be estimated by collecting information on comorbidities as part of the eCRFs and published DALY weights of these comorbidities will be applied to estimate DALYs averted. A cost-minimisation analysis will be performed if the EQ-5D-Y and other clinical parameters demonstrate no difference between randomised arms.

The trial will measure healthcare-related resource use in trial participants, starting at randomisation and continuing for the duration of follow-up. Information on ART received, concomitant medications, hospitalisations (number, reason, and duration of stay) and clinic visits will be recorded on eCRFs which will be collected at weeks 0, 4, 12 and then 12-weekly until the last participant reaches 96 weeks. Total costs will be estimated by applying appropriate unit costs and prices to resource use in trial participants. For unit costs / prices, two analyses will be conducted, one where a common set of unit costs / prices is used which is reflective of costs across LMIC and a second where country specific unit costs / prices are used.

The analysis will be conducted using appropriate statistical techniques to account for issues with economic data and to control for any important baseline variables (e.g. generalised linear models to account for non-normality of economic data). Missing data will be evaluated, and if appropriate, imputed using imputation by chained equations.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 TRIAL COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2013, and the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2).

11.1.2 SITE COMPLIANCE

The sites will comply with the principles of GCP as laid down by the ICH topic E6 (R2), the Declaration of Helsinki 2013 and applicable national regulations. The necessary agreements will be in place, setting out respective roles and responsibilities (see **Section 13**) of sites, Sponsor and CTUs.

The site will inform the relevant CTU as soon as they are aware of a possible serious breach of compliance, so that the MRC CTU at UCL can report this breach if necessary within 7 days as per the UK regulatory requirements. For the purposes of this regulation, a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the participants in the trial, or
- The scientific value of the trial.

11.1.3 DATA COLLECTION & RETENTION

Clinical notes, questionnaires, trial worksheets and administrative documentation should be kept in a secure location (for example, locked filing cabinets in a room with restricted access) and held for a minimum period as determined by the current clinical trial legislation in effect. Currently this will be for a minimum of 15 years after the end of the trial. The EU Clinical Trial Regulation 536/2014 is due to come into application and, following the transition period, the Sponsor and the investigator shall archive the content of the clinical trial master file for at least 25 years after the end of the clinical trial, unless other Union law requires archiving for a longer period. However, the medical files of subjects shall be archived in accordance with national law. During this period, all data should be accessible to the competent or equivalent authorities, the Sponsor and other relevant parties with suitable notice. The data may be subject to an audit by the competent authorities. Medical files of trial participants should be retained in accordance with the maximum period of time permitted by the hospital, institution or private practice.

11.2 ETHICAL CONDUCT OF THE STUDY

11.2.1 ETHICAL CONSIDERATIONS

Participation in a randomised controlled trial means that the participant and/or their carer as appropriate, agree to randomisation but neither the participant, carer nor clinician are able to choose all aspects of the participant's treatment. Participants will receive different treatments and expected toxicities will differ by arm; the common toxicities associated with antiretrovirals will be explained to children/families. The risk of HIV-1 viral load rebound due to a possibly less potent regimen and the risk of increased resistance in the DTG/3TC arm will be explained to children/families. Consent will be sought from parents/carers. Participants, deemed able to understand about the trial, will be asked to assent, according to national regulations/guidelines.

The trial will evaluate the net clinical and virological risk-benefit comparing 2-drug therapy DTG/3TC with DTG-based triple ART. The main risk to participants on DTG/3TC is viral load rebound and

potential increased resistance. Adult trial data have been reassuring in terms of non-inferior virological efficacy of DTG/3TC vs. 3-drug ART and no excess of resistance mutations (See **Section 1**). As described in **Section 9.4**, participants will have retrospective VL testing on saved plasma which will be monitored by DMC; in addition all participants will have VLs (at a minimum, as per SOC) at weeks 48 and 96, and 48-weekly thereafter, done in real-time, which will be available to clinicians.

The additional risk is potential toxicity from dolutegravir for participants who had a different third agent in their pre-trial ART. Overall, the risk of toxicity and intolerance possibly is higher after the switch to a new regimen compared to staying on the tolerated therapy. The possibility of additional toxicity needs to be balanced against the benefits of a reduced number of medications in the treatment regimen.

For female participants on dolutegravir in both arms, there is a possible risk of a baby with neural tube defect if a girl conceives on dolutegravir. As the trial enrols participants aged <15 years old, we expect very low rate of pregnancies in this age group. Access to highly effective contraception for sexually active participants will be provided in the study (See **Section 6.6**). Other dolutegravir-associated toxicities, including neuropsychiatric and liver toxicity are applicable for participants on dolutegravir in both arms (See **Section 5.7.1**).

Most study visits coincide with the usual 12-weekly frequency of visits for routine clinical care, except a visit at 4 weeks in both arms to provide information shortly after the switch to DTG/3TC formulation, with comparable information in the control arm. The amount of extra blood taken is modest for most participants, although those enrolled in intensive PK studies will also have a larger number of blood draws.

The trial will directly evaluate whether these potential risks are outweighed by improved VL suppression and overall risks of toxicity.

The goal of the trial is to obtain data to support licencing of DTG/3TC formulations for children to optimise their treatment options and to confirm efficacy and safety of DTG/3TC as a maintenance regimen over 96 weeks. The contract with supporting pharmaceutical companies will specify that the supply of study drugs is limited to the duration of the trial in each individual participant, however, the provision of DTG/3TC to participants randomised to the formulation may be extended in particular circumstances. Please see **Section 6.10** for details.

Participants will be informed fully of known risks and possible benefits by means of a patient information sheet for carers and older children/adolescents, and this will be reinforced by discussions with the trial research teams at the individual sites prior to enrolment.

Participants' confidentiality will be maintained throughout the trial. Data submitted to the CTUs, and samples sent to central testing facilities, will be identified only by the trial number (and random check letters to improve accuracy of identification) and month and year of birth, as well as date and time of sampling for PK samples).

11.2.2 Ethical Approvals

Before initiation of the trial at each clinical site, the protocol, all informed consent forms, and information materials to be given to the prospective participant will be submitted to each appropriate ethics committee for approval. Any further amendments will be submitted and approved by each ethics committee.

The study has been developed with Patient and Public Involvement (PPI) to ensure that its design is feasible and acceptable to potential participants, and to ensure its outcomes and potential impact are relevant to the population who may benefit from its results. PPI also helps to ensure transparency and accountability throughout this research. PPI activity will continue for the duration of the study, including dissemination of study results.

The rights of the participant to refuse to participate in the trial without giving a reason must be respected. After the participant has entered into the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, however, should be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated. Similarly, the caregiver/participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment.

11.3 COMPETENT AUTHORITY APPROVALS

This protocol will be submitted to the national competent or equivalent authority, as appropriate in each country where the trial will be run.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a Clinical Trial Authorisation is required in the UK and Spain. Local and national regulatory requirements will be followed in all participating countries.

The EudraCT number for the trial is 2020-001426-57.

The progress of the trial and safety issues will be reported to the regulatory agency or equivalent in accordance with local requirements and practices in a timely manner.

Safety reports, including expedited reporting and SUSARs, will be submitted to the competent authority in accordance with each authority's requirements in a timely manner.

11.3.1 OTHER APPROVALS

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the local R&D approval (or other relevant approval as above) and of the PIS and Consent Form) on local headed paper should be forwarded to the relevant CTU before any participants are screened for eligibility.

11.4 END OF TRIAL

The end of trial will be when all participants have completed follow-up, including extra visits for viral load, all data have been obtained and the database has been locked.

11.4.1 SAMPLE STORAGE AND DESTRUCTION

Specimens for which participants have consented will be stored and used for analyses as specified in the D3 protocol, patient information sheet and consent. Once analyses are complete, any of these samples that remain will be stored for a period of up to 5 years for future research, after which time they will be disposed of according to standard laboratory procedures and guidelines in the respective countries.

12 INDEMNITY

In consideration of the agreement by the Principal Investigator at each centre to supervise the trial, the Fondazione Penta Onlus undertakes to indemnify the Principal Investigator at each centre and the institutions which participate in the trial and their employees and agents in respect of any claims made against them by any third party which arise out of or as a result of the supervision or conduct of the trial (including any claim arising in respect of the technical procedures described in the protocol to which participants would not have been exposed but for their participation in the trial). Full details of the Indemnity agreement are given in a separate document. Cover against claims arising from medical negligence is not included.

Research facility/clinics selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees.

13 FINANCE

The trial is supported by grant funding from ViiV Healthcare (Ref 207742).

The trial will be co-ordinated by the MRC CTU at UCL, using core funding from MRC (grant number MC_UU_12023/26). Fondazione Penta Onlus is the Sponsor of the D3 trial. The necessary written agreements will be in place, outlining the funding arrangements to the sites.

Research support will be provided to the clinical centres for additional visits. In some specific cases, and agreed by national ethics bodies, transport facilities, payments or vouchers will be given to participants or their families in compensation for the time spent in clinic particularly during substudies.

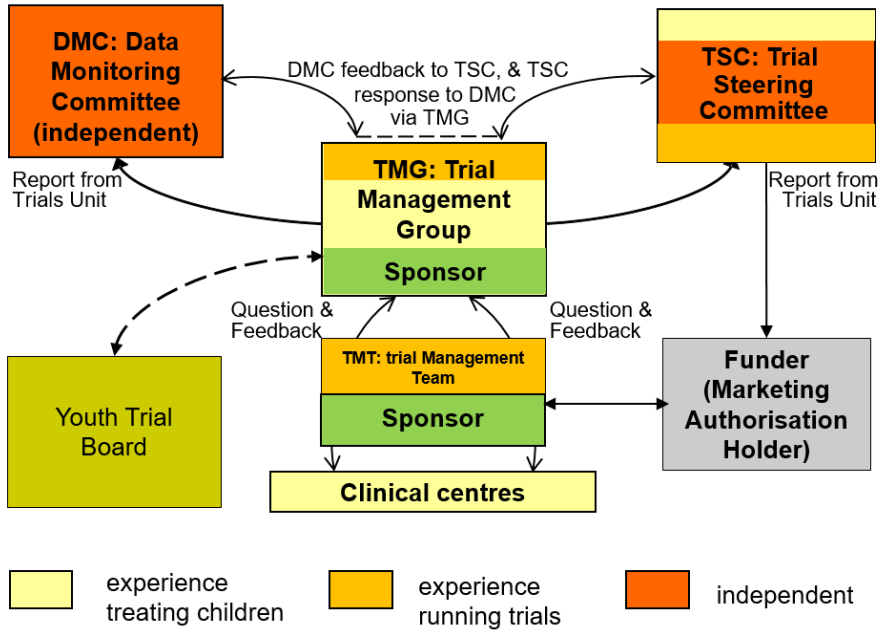
In some countries and as required by national legislation the health service cost of all protocol visits will be covered by the sponsor or sponsor's representative.

Financial reports for the trial will be produced by Fondazione Penta Onlus finance team at least annually and reviewed by the independent TSC chair and the Chief Investigator of the trial.

14 OVERSIGHT, TRIAL COMMITTEES AND PATIENT & PUBLIC INVOLVEMENT

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them expressed in **Figure 4:**.

Figure 4: Trial Organogram



Trial Steering Committee includes community representatives..

14.1 TRIAL MANAGEMENT TEAM (TMT)

A Trial Management Team will be formed at MRC CTU to conduct the day-to-day management of the trial. This will include the Chief Investigator, trial statistician, trial physician, clinical project manager, trial manager and data manager. The group will meet at least once per month, although may meet more often if required. The Penta D3 project manager and Penta regulatory affairs and quality assurance manager will be closely working with the TMT, providing Sponsor oversight of the trial.

The PHPT Trial Management Team will co-ordinate the day-to-day management of the trial at clinical sites in the PHPT network in Thailand. The PHPT CTU team will include the project lead, trial physician, trial manager, clinical research assistants (CRA), safety manager, research nurses, lab technicians and data management teams. The CTU will meet at least once per month.

14.2 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator; Sponsor Representatives, Principal Investigators of the sites in South Africa and Uganda, and Principal

Investigators in the leading sites in Thailand and Europe, other lead investigators (clinical and non-clinical) and members of MRC CTU at UCL and PHPT. The TMG will be responsible for the management of the trial. It will meet approximately once a year in-person and will hold a regular teleconference at approximately monthly intervals during the recruitment phase at which sites will summarise progress and challenges and bring up for discussion any difficulties, as well as discuss and decide matters of general importance for the trial. The decisions regarding the overall running of the trial will be made in this forum with the exception of matters of fundamental importance to the viability of the trial or that require major changes to the protocol. These will be referred to the Trial Steering Committee (TSC). The full details can be found in the TMG Charter.

14.3 TRIAL STEERING COMMITTEE (TSC)

The Trial Steering Committee (TSC) has selected membership from the TMG plus independent members, including the Chair and PPI contributor. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chair. The ultimate decision for the continuation of the trial lies with the TSC. Further details of TSC functioning are presented in the TSC Charter.
The TSC will include a majority of independent members and will consider representation from participating countries/regions (Europe, South Africa, Thailand, Uganda) as well as community representation. The trial team members on the TSC will include representation from participating countries/regions.

14.4 DATA MONITORING COMMITTEE (DMC)

An independent Data Monitoring Committee (DMC) will be formed. The DMC will be the only group who sees comparative confidential, accumulating data by trial arm for the trial. Reports to the DMC will be produced by the MRC CTU at UCL statisticians. Note, data on the Intensive PK study participants will be provided to ViiV Healthcare in confidence for the purpose of regulatory submissions.

The first meeting of the DMC will be arranged before trial recruitment begins and at this meeting the schedule for reviewing viral loads will be discussed and agreed. Viral loads at weeks 4 and 12 will be tested and reviewed within 6 weeks of the first 20 participants in the DTG/3TC arm attending their 12 week trial visit. At the first review, six of 20 participants with a confirmed VL≥50 would give evidence that VL suppression rates were less than 90% (14/20 suppressed = 70% (95%CI 46%, 88%)) and would give cause for concern. A second review will take place after the first 20 participants in the DTG/3TC arm have attended their 24 week trial visit, at which point their 4, 12 and 24 week viral loads will be reviewed, in addition to 4 and 12 week viral loads in participants recruited after the initial 20 (likely to be around ~40 additional participants). Based on these reviews, assuming the trial continued, the frequency of subsequent meetings will be determined by the DMC. The DMC will consider data using the statistical analysis plan and will advise the TSC (see **Section 9.4**). The DMC will be asked to inform the Chair of the TSC, if in their view, the results provide either:

(a) unequivocal evidence that one of the two treatment groups (DTG/3TC or control) is performing poorly for all participants or for a particular category of participants, and there was a reasonable expectation that this new evidence would materially influence patient management; or

(b) good evidence that the control arm is superior to DTG/3TC arm in terms of the primary outcome and that non-inferiority of the DTG/3TC arm is unlikely to be demonstrated with continued enrolment and/or follow-up.

The criteria for the strength of evidence are left to the judgement of the IDMC. However, as an example, if in an interim analysis the 99% confidence interval of the difference between the treatment groups in the proportion of participants with virological rebound (the primary outcome) excluded 0, this may be considered as providing good evidence of a difference in risk between the two groups. If, the 99.9% confidence interval also excluded 0, this may be regarded as providing unequivocal evidence of a difference between the two groups.

14.5 PATIENT AND PUBLIC INVOLVEMENT ADVISORY GROUPS

In this trial Youth Trial Boards (YTBs) will work alongside the TMT and TMG (**Section 15**). A community representative will be invited to the TSC to represent the community interests and their views.

14.6 ROLE OF STUDY SPONSOR

Fondazione Penta Onlus is the Sponsor of the D3 trial and has overall accountability for the trial. The Sponsor delegates responsibility to oversee the implementation of the study to the MRC CTU at UCL and ensure that arrangements are put into place for adequate management, monitoring, analysis and reporting of the trial. Fondazione Penta Onlus delegate responsibility to PHPT CTU for the co-ordination of the trial implementation at clinical sites in the PHPT network in Thailand.

15 PATIENT & PUBLIC INVOLVEMENT

The participating sites will either use their existing patient liaison group, such as their Community Advisory Board (CAB) and/or Youth Trial Board (YTB). The YTB is a model of engagement and participation of adolescent patient representatives in paediatric clinical trials and research studies, developed as part of the ODYSSEY trial.[34] The model provides a supportive structured environment for young people living with HIV to meaningfully engage in discussions about clinical trials. It enables the young people to guide research teams on how to engage and communicate with trial participants, and how to promote trial findings to their community. The existing YTBs in South Africa, Uganda and the UK will be involved in this trial. At the sites where there are no YTBs, existing patient liaison groups, such as Community Advisory Boards (CABs), will be engaged.

A representative of CABs or YTBs will liaise with the TMT on the concerns and questions from the community and will hear from the TMT about the latest developments in the trial. The TMT will provide the CAB/YTB feedback to the TMG and the TSC. A community representative member of the TSC will represent the CAB and YTB views at the TSC meetings.

15.1 IDENTIFYING PPI CONTRIBUTORS

Each YTB consists of 8-10 young people living with HIV aged 14 to 19 years at the point of joining the group. YTBs include both male and female members from different backgrounds representing young people living with HIV in their country. Their membership is cyclical (2-3 years) and all new members receive training to ensure understanding of HIV, clinical trials and research and their role as patient advocates.

Each YTB meets face-to-face a few times a year. The groups are facilitated by individuals skilled in working with young people and in research to ensure effective communication between the sites and TMT. It is expected that representatives of the YTBs will attend face-to-face TMG meetings. The YTB activities related to the D3 trial are supported by the trial funding.

15.2 PROTOCOL DESIGN AND STUDY SET-UP

The YTBs in South Africa, Uganda and the UK were engaged during the design of the study. They agreed to take part in D3 as youth advisory groups and provide input in different aspects of the trial, starting from reviewing the lay summary and providing assistance with patient information materials. The YTB are working on additional patient information sheets for children and adolescents, to aid their understanding of the trial.

15.3 PPI IN THE ONGOING RUNNING OF STUDY

The YTBs will take part in the site training and set-up of the trial. Through their formal and informal meetings with the participants and the families they will be providing feedback to the TMG and TSC on patients' perspectives of the trial. Together with the TMT, they will be actively involved in the designing of the tools of the trial information dissemination to the trial participants, their peers and the community.

15.4 INTERPRETING AND PLANNING DISSEMINATION OF STUDY RESULTS

A variety of tools will be developed by the teams in the MRC CTU at UCL, Penta and the sites to communicate the results to different audiences. These will include the trial participant meetings, press releases for local, national and international media, journal articles for Open Access publication in high impact journals, news articles for MRC CTU at UCL and Penta websites and the websites of the participating sites, PowerPoint slide sets for presentations at the scientific conferences and the briefing papers and infographics summarising the results for policymakers.

YTBs/CABs will be actively involved in discussion of the trial results and designing the tools for the results dissemination to participants, public and other relevant stakeholders. They will work alongside the TMT, TMG and the site teams in developing key messages about the results and audience-friendly ways to communicate those messages to different audiences.

15.5 REPORTING AND EVALUATING IMPACT OF PPI

YTBs will be acknowledged in the main publications. YTBs will be supported by the TMT to explore the evaluation of impact of their PIS and other tools they helped to design on understanding and perception of the provided information to the trial participants.
Each site will either use their existing patient liaison group, such as their Community Advisory Board (CAB) and/or Youth Trial Board (YTB) or form a YTB who will be responsible for liaising with the patient representatives on the TSC, will feedback concerns and questions from the community and also hear about the latest developments in the trial and the wider scientific community. All the sites currently have active patient participation groups.

16 PUBLICATION AND DISSEMINATION OF RESULTS

The D3 TSC is the custodian of the data and specimens generated from this trial; trial data are not the property of individual participating investigators or health care facilities where the data were generated.

It is anticipated that a number of opportunities will arise for publication during the course of and following completion of the D3 trial. Publications include papers (including abstracts) for presentation at national and international meetings, as well as the preparation of manuscripts for peer-reviewed publication. In order to avoid disputes regarding authorship, it is important to establish a consensus approach that will provide a framework for all publications derived in full or in part from this clinical trial. The following approach is derived from the *Lancet* and from the publication policies used in other clinical trials coordinated by the MRC CTU at UCL:

- All publications are to be approved by the TMG and TSC before submission for publication. Any publication arising before the primary analysis will also be approved by the DMC in order to ensure that the primary objective of the trial (the randomised comparison) is not compromised. The TMG and TSC will resolve problems of authorship and maintain the quality of publications.

- In line with MRC policy that the results of publicly-funded research should be freely available, manuscripts arising from the trial will, wherever possible, be submitted to peer-reviewed journals which enable Open Access via UK PubMed Central (PMC) within six months of the official date of final publication. All conference presentations will be made available as soon as possible after the event via the D3 website. All publications will acknowledge the trial's funding sources.

- For all publications, the TMG will nominate or approve an individual's request to lead on manuscript writing. The lead investigator on the publication will usually be the primary or senior author and will be responsible for identifying fellow authors and for determining with the writing group the order of authorship that will appear on the manuscript. The TSC will resolve any problems of authorship and maintain the quality of publications.

- The TMG will maintain a list of investigators to be presented in an appendix at the end of the paper. This list will include investigators who contributed to the investigation being reported but who are not members of the writing committee. In principle, substudy reports should include all investigators for the main study, although in some instances where a smaller number of investigators have made any form of contribution, it may be appropriate to abbreviate the listing. All headline authors in any publication arising from the main study or sub-studies must have a made a substantive academic or project management contribution to the work that is being presented. "Substantive" must be defined by a written declaration of exactly what the contribution of any individual is believed to have been. In addition to fulfilling the criteria based on contribution, additional features that will be considered in selecting an authorship group will include the recruitment of patients who contributed data to any set of analyses contained in the manuscript and/or the conduct of analyses (laboratory and statistical), leadership and coordination of the project in the absence of a clear academic contribution.

- The data derived from this clinical trial are considered the property of the D3 TSC. The presentation or publication of any data collected by the participating investigators on patients entered into this trial is under the direct control of the TMG and TSC (and the DMC before the end of the trial). This is true whether the publication or presentation is concerned directly with

the results of the trial or is associated with the trial in some other way. However, although individual participating investigators will not have any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any of the data other than under the auspices of and with the approval of the TMG and TSC (and the DMC before the end of the trial), they will be encouraged to develop sub-studies or propose analyses subject to the approval by the TMG and TSC (and the DMC before the end of the trial). Any requests for access to raw data will be welcomed as long as they are scientifically valid and do not conflict with the integrity of the trial or ongoing analyses by the trial team

Outcome data by randomised group will not be revealed to the participating investigators until the data collection phase and primary full analysis of the trial has been completed. This policy safeguards against possible bias affecting the data collection. The DMC will be monitoring the outcome results and may recommend that the trial be stopped for safety reasons or if a definitive answer is reached earlier than the scheduled end of the trial.

17 DATA AND/OR SAMPLE SHARING

Data will be shared according to the MRC CTU at UCL's controlled access approach, [96] based on the following principles:

- No data should be released that would compromise an ongoing trial or study.
- There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
- Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers.
- The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
- Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

Data will be available for sharing after publication of the primary trial results. Researchers wishing to access data should contact the Trial Management Group in the first instance.

18 PROTOCOL AMENDMENTS

Changes to protocol version 1.0 creating version 2.0

Front page

- Update to date and version

General Information

- Removal of option for relevant CTU to perform randomisation
- Update to SAE and notable event reporting process
- Updates to contact information and qualifications

Summary of Trial

- Update to date and version
- Update to interventions to be compared, hypotheses and randomisation
- Clarification of method to be used in secondary safety outcome measures
- Removal of trial manager names

Trial Schema

- Update to stratification factors for randomisation and randomised treatment regimen in control arm

Trial Assessment Schedule

- Removal of requirement for HBcAb and HBsAb testing and update to related footnote
- Update to remove restriction of sparse PK and pharmacogenomics sample storage to DTG/3TC arm
- Update to timing of intensive PK visit to make it more flexible
- Added footnote to clarify visit windows
- Update to footnotes to clarify timepoints for NGS testing; sparse PK and pharmacogenomics samples will only be collected from participants at sites in South Africa, Thailand and Uganda; added further information on sparse PK sample collection; update to timing of intensive PK visit
- Correction to range of blood volume required for virology, safety and sparse PK blood samples
- Update to range of blood volume required for Intensive PK and PD substudy in the first DTG/3TC participants
- Update to footnotes to amend number of blood samples and range of blood volume required for Intensive PK and PD substudy

Lay Summary

- Update due to change of randomised treatment regimen in control arm to DTG + 2 NRTIs
- Other minor updates for consistency

Abbreviations

- New abbreviations added
- Removal of abbreviations not used

Section 1.1.1

- Updated information on current HIV treatment guidelines
- Change of randomised treatment regimen in control arm to DTG + 2 NRTIs

Section 1.1.2

- Updated information on availability of DTG formulation

Section 1.1.3

- Updated data from other relevant clinical trials

Section 1.1.4

- Updated information on licensing of DTG

- Updated information on ODYSSEY trial results

Section 1.1.5

- Minor clarification as study referenced is no longer recent

Section 1.1.6

- Updated data on DTG and pregnancy from TSEPAMO study

Section 1.1.7

- Removal of reference to SOC

Section 1.2

- Updated comparison to DTG-based triple-drug ART

Section 1.2.1

- Updated comparison to DTG + 2 NRTIs

Section 1.2.2

- Updated comparison to DTG + 2 NRTIs

Section 1.2.3

- Updated comparison to DTG + 2 NRTIs

Section 1.3

- Updated in line with change to eligibility criteria
- Change of randomised treatment regimen in control arm to DTG + 2 NRTIs
- Use of DTG at enrolment (≥1 month; <1 month or no use) added as stratification factor

Section 1.4

- Statement that choice of participating countries may be revisited has been removed as this is no longer the case

Section 2.1

- Removal of abbreviation for site specific approval

Section 2.2

- Removal of reference to archiving of CRFs

Section 2.3

- Correction that site's pharmacist/*designee* will be consulted prior to site activation
- Clarification that a list of activated sites may be obtained from the MRC CTU at UCL

Section 2.4

- Updated to use appropriate abbreviation

Section 3.1

- Removal of criteria to be on same triple drug ART regimen for at least 3 months
- Rephrased definition of virological suppression in footnotes for clarity
- Removal of requirement for screening viral load sample to be undiluted
- Corrected phrasing in footnote for highly effective contraception methods to be used

Section 3.2

- Removal of criteria regarding changes in ART in the last 6 months
- Removal of abbreviation for prevention of mother to child transmission
- Removal of requirement for HBcAb and HBsAb testing and related footnote
- Removal of criteria related to hepatitis C virus therapy
- Reduction in required creatinine clearance level from <50 mL/min/1.73m to <30 mL/min/1.73m
- Clarification in footnotes that resistance testing is not required at trial entry; clarification that bedside Schwartz equation should be used

Section 3.5

- Rephrasing regarding provision of patient information sheet for clarity
- Removal of abbreviation for Consent Form
- Removal of requirement for HBcAb and HBsAb testing

Section 4.1

- Samples for pharmacogenomics testing will only be collected from participants in South Africa, Thailand and Uganda.
- Updated phrasing regarding details that might be recorded if there is doubt about a child's place of residence

Section 4.2

- Updated wording regarding process for randomising a participant
- Removal of option for CTU to perform randomisation

Section 4.2.1

- Updated in line with eligibility criteria

Section 5.1

- Updated randomised treatment regimen in control arm in line with current HIV treatment guidelines

Section 5.3

- Updated randomised treatment regimen in control arm to DTG + 2 NRTIs
- Updated information on formulations being provided by ViiV Healthcare

Section 5.5.1

- Updated permitted ART changes in control arm

Section 5.5.2

- Updated sub-section number referenced following addition of sub-section

Section 5.6

- Additional section on management of participants with confirmed viral load ≥50 c/mL

Section 5.8

- Clarification regarding management of grade 2 adverse events/toxicity

Section 5.8.1.A

- Clarification regarding testing for illicit drugs and alcohol
- Added that testing for local infections should be considered
- Removed information on atazanavir

Section 5.8.1.B

- Removed reference to all third agents other than dolutegravir

Section 5.8.1.C

- Removed reference to all third agents other than dolutegravir

Section 5.8.1.D

- Recommendation for creatinine clearance level requiring 3TC dose adjustment updated in line with eligibility criteria

Section 5.9

- Updated to clarify that ART modifications are required for all children on DTG

Section 5.9.1

- Amended title
- Added sentence to clarify that all NRTIs except TAF can be co-administered with rifampicin-containing anti-TB treatment

Section 5.9.2

- Removal of section on management of children with tuberculosis receiving third agents other than dolutegravir

Section 5.10

- Updated in line with change to related eligibility criteria

Section 5.12

- Updated in line with change of randomised treatment regimen in control arm

Section 5.14.2

- Update to clarify reference to comorbidities is at time of enrolment and that children should not be enrolled in the trial if the required treatment has significant drug interactions with DTG or 3TC

Section 6

- Removed reference to visit windows to avoid confusion

Section 6.1

- Clarified that viral load test at end of trial visit is not optional
- Clarified that HbA1c test at end of trial visit is as per local practice
- Sample for pharmacogenomics testing is only to be taken from participants in South Africa, Thailand and Uganda
- Removed restriction to participants in DTG/3TC arm for sparse PK
- Sparse PK samples are only to be taken from participants in South Africa, Thailand and Uganda
- Amended volume of sparse PK samples
- Change to number of blood samples and range of blood sample volume taken at an intensive PK visit
- Change to window for intensive PK visit depending on prior exposure to DTG

Section 6.4.2

- Clarified how changes in sleep and mood will be assessed and appropriate cut-off ages for sleep and mood questionnaires
- Moved information on suicidal ideation assessment to its own section

Section 6.4.3

- New section for information on assessment of suicidal ideation

Section 6.5.1

- Updated in line with change of randomised treatment regimen in control arm
- Clarification of how and which data will be collected

Section 6.6

- Removed reference to third agents other than dolutegravir
- Updated based on more recent information from TSEPAMO study and recommendations for women conceiving on dolutegravir

Section 6.6.1

- Updated based on more recent information from TSEPAMO study
- Removed reference to all third agents other than dolutegravir

Section 6.7

- Updated in line with change of randomised treatment regimen in control arm
- Clarification that data will be collected in an eCRF

Section 6.8

- Clarification that original site will not need to provide copies of CRFs to new site

Section 6.9

- Clarification that data will be collected in an eCRF

Section 7.1.1

- Update to which ARVs fall under the definition of IMP in line with change of randomised treatment regimen in control arm
- Reiterated that reactions to IMP will be reported appropriately

Section 7.2.1

- Update to reporting process
- Clarification that data will be collected in eCRFs

Section 7.2.2

- Update to reporting process

- Clarification that data will be collected in eCRFs

Section 7.2.3

- Update to reporting process
- Clarification that data will be collected in eCRFs

Section 7.2.4

- Update to reporting process
- Clarification that data will be collected in eCRFs

Section 7.3

- Update to reporting process
- Clarification that data will be collected in eCRFs; worksheet may be used

Section 7.3.1.A

- Update to reporting process
- Clarification that data will be collected in eCRFs

Section 7.3.1.D

- Updated for clarity due to change in the ARVs that fall under the definition of IMP in line with change of randomised treatment regimen in control arm

Section 7.3.1.E

- Updated for clarity due to change in the ARVs that fall under the definition of IMP in line with change of randomised treatment regimen in control arm

Section 7.3.2

- Update to reporting process
- Clarification that data will be collected in eCRFs; worksheet may be used
- Removal of fax number for back up reporting process to MRC CTU at UCL
- The participant's month and year of birth will be collected as part of the safety reporting processes

Section 7.4

- Updated information regarding CTU responsibilities

Section 7.5

- Section deleted as delegation of responsibility to PIs is covered in section 7.4.

Section 8.4.2

- Clarification that data will be collected in eCRFs

Section 9.1

- Updated in line with change of randomised treatment regimen in control arm
- Stratification by use of DTG at enrolment (≥1 month; <1 month or no use)

Section 9.2.5

- Updated in line with change of randomised treatment regimen in control arm

Section 9.3

- Updated in line with change of randomised treatment regimen in control arm

Section 9.5

- Updated in line with change of randomised treatment regimen in control arm

Section 9.5.1

- Subgroup analyses by randomisation stratification factors now includes use of DTG at enrolment (≥1 month; <1 month or no use)

Section 10.1

- Added additional exclusion criteria for the Intensive PK substudy in line with TB-PK substudy: Illnesses that could influence drug pharmacokinetics, i.e. severe diarrhoea, vomiting, renal disease or liver disease
- Change to window for intensive PK visit depending on prior exposure to DTG
- Removal of PK sample collection at 23 hour timepoint and updated total number of plasma samples taken over 24 hours

- Clarified different total blood draw volume depending on weight
- Clarified fasting duration for participants weighing ≥10 kg and participants weighing 6-<10kg
- Clarified that procedure details will be outlined in the Intensive PK Manual of Operations (MOP)

Section 10.2

- All participants on DTG-based ART at sites in South Africa, Thailand and Uganda will have samples taken for pharmacogenomics testing and sparse PK sampling
- Specification that 5 x 1ml blood samples will be collected for the sparse PK sampling
- Update to analytical methods to be used for pharmacogenomics testing

Section 10.3

- Correction on PK and safety data required for younger children
- Updated in line with change of randomised treatment regimen in control arm
- Severe malnutrition added as an Exclusion Criteria
- Updated blood volume per sample for DTG and rifampicin PK sampling
- Clarified total blood draw volume per PK curve
- Added information explaining fasting requirements
- Clarified that further details will be outlined in the Intensive PK MOP

Section 10.5

- Updated in line with change of randomised treatment regimen in control arm
- Removal of abbreviation for cost-effectiveness thresholds
- Clarification that data will be collected in eCRFs

Section 11.1.3

- Removed reference to CRF storage
- Removed year that the EU Clinical Trial Regulation was expected to come into application
- Updated in line with change of randomised treatment regimen in control arm

Section 11.2.1

- Clarified that the participant's month and year of birth may be collected as an identifier

Section 11.3

- Removal of abbreviation for Clinical Trial Authorisation
- Removed reference to countries outside of EU for clarity

Section 11.3.1

- Removal of abbreviation for Consent Form

Section 14.2

- Removed reference to YTB

Minor corrections throughout for spelling, punctuation and grammar.
References to "SOC arm" changed to "control arm" throughout for clarity.
Updated reference to ViiV Healthcare throughout for consistency.

19 LIST OF APPENDICES

1. Appendix I. Safe Limits of Blood Sample Volume in Children
2. Appendix II. WHO staging of HIV infection
3. Appendix III. Product Information – Unregistered Products
4. Appendix IV. DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
5. Appendix V. Liver Safety – Study Treatment Restart or Re-challenge Guidelines
6. Appendix VI. Management of Participants with Suspected TB
7. Appendix VII. Recommendations for Co-Administration of Different Types of Highly Effective Contraception with Antiretrovirals
8. Appendix VIII. Modified FDA Snapshot Algorithm

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Appendices

D3 (Penta 21)

A randomised non-inferiority trial with nested PK to assess DTG/3TC fixed dose formulations for the maintenance of virological suppression in children with HIV infection aged 2-<15

Sponsor:

Collaborating academic groups:

Funder:

Version: 2.0
Date: 04-Oct-2021

MRC CTU AT UCL ID: D3
ISRCTN #: ISRCTN17157458
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APPENDIX I. MAXIMUM ALLOWABLE TOTAL BLOOD-DRAW VOLUMES FOR CHILDREN

The blood volumes taken from children for clinical and research purposes should not exceed maximum allowable limits for children.

Allowable blood draw limits for children:[1,2]

- For healthy children:
  - 3% total blood volume (TBV) in a 24-hour period
  - 10% total blood volume in a 30 day period
- For sick/unwell children:
  - 2.5% total blood volume in a 24 hour period
  - 5% total blood volume in a 30 day period

Estimated total blood volume for term infants (Wt >2kg) and children is 80 ml/kg.

Table AI-1: Maximum allowable total blood draw volumes

Wt, kg	TBV, ml	Max allowable volume in 24 hours, ml		Total volume in 30-days, ml	
		Unwell (2.5% TBV)	**Healthy (3% TBV)**	Unwell (2.5% TBV)	**Healthy (3% TBV)**
6	480	12	**14**	24	**48**
7	560	14	**17**	28	**56**
8	640	16	**19**	32	**64**
9	720	18	**22**	36	**72**
10	800	20	**24**	40	**80**
11-15	880-1200	22-30	**27-36**	44-60	**88-120**
16-20	1280-1600	32-40	**38-48**	64-80	**128-160**
21-25	1680-2000	42-50	**50-60**	64-100	**168-200**
26-30	2080-2400	52-60	**62-72**	104-120	**208-240**
31-35	2480-2800	62-70	**74-84**	124-140	**248-280**
36-40	2880-3200	72-80	**86-96**	144-160	**288-320**
41-45	3280-3600	82-90	**98-108**	164-180	**328-360**
46-50	3680-4000	92-100	**110-120**	184-200	**368-400**

*Adapted from Jack 2001[2]

APPENDIX II. WHO STAGING OF HIV INFECTION

DIAGNOSTIC CRITERIA FOR WHO STAGE 1, 2, 3 AND 4 CONDITIONS IN INFANTS AND CHILDREN UNDER 15 YEARS[3]

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Clinical Stage 1		
Asymptomatic	No HIV related symptoms reported and no clinical signs on examination.	Not applicable.
Persistent generalized lymphadenopathy	Persistent swollen or enlarged lymph nodes >1 cm at two or more non-contiguous sites (excluding inguinal) without known cause.	Clinical diagnosis
Clinical Stage 2		
Unexplained persistent hepatosplenomegaly	Enlarged liver and spleen without obvious cause.	Clinical diagnosis
Papular pruritic eruptions	Papular pruritic vesicular lesions. Also common in uninfected children: scabies and insect bites should be excluded.	Clinical diagnosis
Extensive wart virus infection	Characteristic warty skin lesions; small fleshy grainy bumps, often rough, flat on sole of feet (plantar warts); facial, more than 5% of body area or disfiguring.	Clinical diagnosis
Extensive molluscum contagiosum infection	Characteristic skin lesions: small flesh-coloured, pearly or pink, dome-shaped or umbilicated growths, may be inflamed or red; facial, more than 5% of body area or disfiguring. Giant molloscum may indicate more advanced immunodeficiency	Clinical diagnosis
Fungal nail infections	Fungal paronychia (painful, red and swollen nail bed) or onycholysis (painless separation of the nail from the nail bed.) Proximal white subungual onchomycosis is uncommon without immunodeficiency	Clinical diagnosis
Recurrent oral ulcerations	Current event plus at least one previous episode in past six months. Aphthous ulceration, typically with a halo of inflammation & yellow-grey pseudomembrane.	Clinical diagnosis
Unexplained persistent parotid enlargement	Asymptomatic bilateral swelling that may spontaneously resolve and recur, in absence of other known cause, usually painless	Clinical diagnosis
Lineal gingival erythema	Erythematous band that follows the contour of the free gingival line; may be associated with spontaneous bleeding	Clinical diagnosis

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Herpes zoster	Painful rash with fluid-filled blisters, dermatomal distribution, can be haemorrhagic on erythematous background, and can become large and confluent. Does not cross the midline	Clinical diagnosis
Recurrent upper respiratory tract infection	Current event with at least one episode in past 6 months. Symptom complex; fever with unilateral face pain and nasal discharge (sinusitis) or painful swollen eardrum (otitis media), sore throat with productive cough (bronchitis), sore throat (pharyngitis) and barking croup-like cough (LTB). Persistent or recurrent ear discharge.	Clinical diagnosis
Clinical Stage 3		
Unexplained moderate malnutrition	Weight loss: low weight-for-age, up to −2 standard deviations from the mean (*weight-for-age for children 2-<5 years and BMI-for-age for children 5-<19years), not explained by poor or inadequate feeding and or other infections, and not adequately responding to standard management.	Documented loss of body weight of −2 standard deviations from the mean (*weight-for-age for children 2-<5 years and BMI-for-age for children 5-<19years), failure to gain weight on standard management and no other cause identified during investigation.
Unexplained persistent diarrhoea	Unexplained persistent (14 days or more) diarrhoea (loose or watery stool, three or more times daily), not responding to standard treatment.	Confirmed by stools observed and documented as unformed. Culture and microscopy reveal no pathogens.
Unexplained persistent fever (>37.5C intermittent or constant for longer than one month)	Reports of fever or night sweats for longer than one month, either intermittent or constant, with reported lack of response to antibiotics or antimalarial agents. No other obvious foci of disease reported or found on examination. Malaria must be excluded in malarious areas.	Confirmed by documented fever of >37.50C with negative blood culture, negative malaria slide and normal or unchanged chest X-ray, and no other obvious foci of disease.
Oral candidiasis (after first 6-8 weeks of life)	Persistent or recurring creamy white to yellow soft small plaques which can be scraped off (pseudomembranous), or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Confirmed by microscopy or culture.
Oral hairy leukoplakia	Fine small linear patches on lateral borders of tongue, generally bilaterally, which do not scrape off.	Clinical diagnosis
Lymph node tuberculosis	Non acute, painless "cold" enlargement of peripheral lymph nodes, localized to one region. May have draining sinuses. Response to standard anti- tuberculosis treatment in one month.	Confirmed by histology or fine needle aspirate for Ziehl-Nielsen stain or culture.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Pulmonary tuberculosis	Nonspecific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. History of contact with adults with smear-positive pulmonary tuberculosis. No response to standard broad-spectrum antibiotic treatment.	Confirmed by one or more sputum positive smear for acid-fast bacilli and/or radiographic abnormalities consistent with active tuberculosis and/or culture-positive for Mycobacterium.
Severe recurrent bacterial pneumonia	Cough with fast breathing, chest indrawing, nasal flaring, wheezing, and grunting. Crackles or consolidation on auscultation. Responds to course of antibiotics. Current episode plus one or more in previous 6 months.	Confirmed by isolation of bacteria from appropriate clinical specimens (induced sputum, BAL, lung aspirate).
Acute necrotizing ulcerative gingivitis or stomatitis, or acute necrotizing ulcerative periodontitis	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour, and rapid loss of bone and/or soft tissue.	Clinical diagnosis
Symptomatic lymphocytic interstitial pneumonitis	No presumptive clinical diagnosis.	Diagnosed by chest X-ray: bilateral reticulonodular interstitial pulmonary infiltrates present for more than two months with no response to antibiotic treatment and no other pathogen found. Oxygen saturation persistently <90%. May present with cor pulmonale and may increased exercise-induced fatigue. Characteristic histology.
Chronic HIV-associated lung disease (including bronchiectasis)	History of cough productive of copious amounts of purulent sputum (bronchiectasis only), with or without clubbing, halitosis, and crepitations and/or wheezes on auscultation	Confirmed by chest X-ray: may show honeycomb appearance (small cysts) and/or persistent areas of opacification and/or widespread lung destruction, with fibrosis and loss of volume.
Unexplained anaemia (<8g/dl), or neutropaenia (<0.5 x 109 per litre) and/or chronic thrombocytopaenia (<50 x 109 per litre)	No presumptive clinical diagnosis.	Diagnosed on laboratory testing, not explained by other non-HIV conditions, not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in WHO Integrated Management of Childhood Illness (IMCI) guidelines.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Clinical Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy	Persistent weight loss stunting wasting or malnutrition not explained by poor or inadequate feeding, other infections and not adequately responding in two weeks to standard therapy. Visible severe wasting of muscles, with or without oedema of both feet, and/or *weight-for-age for children 2-<5 years and BMI-for-age for children 5-<19 years of more than –3 standard deviations from the mean.	Documented weight-for-age *for children 2-<5 years and BMI-for-age for children 5-<19years of more than –3 standard deviations from the mean with or without oedema.
Pneumocystis pneumonia	Dry cough, progressive difficulty in breathing, cyanosis, tachypnoea and fever; chest indrawing or stridor. (Severe or very severe pneumonia as in WHO IMCI guidelines). Usually rapid onset especially in infants under six months of age. Response to high-dose co-trimoxazole with or without prednisolone. Chest X-ray shows typical bilateral perihilar diffuse infiltrates	Confirmed by: cytology or immunofluorescent microscopy of induced sputum or BAL or histology of lung tissue.
Recurrent severe bacterial infection, e.g. empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia	Fever accompanied by specific symptoms or signs that localize infection. Responds to antibiotics. Current episode plus one or more in previous 6 months	Confirmed by culture of appropriate clinical specimen.
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)	Severe and progressive painful orolabial, genital, or anorectal lesions caused by HSV infection present for more than one month.	Confirmed by culture and/or histology
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs).	Difficulty in swallowing or pain on swallowing (food and fluids). In young children, suspect particularly if oral Candida observed and food refusal occurs and/or difficulties or crying when feeding.	Confirmed by macroscopic appearance at endoscopy, microscopy of specimen from tissue or macroscopic appearance at bronchoscopy or histology.
Extrapulmonary or disseminated tuberculosis	Systemic illness usually with prolonged fever, night sweats, and weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis or orchiti, pericardial or abdominal	Confirmed by positive microscopy showing acid-fast bacilli or culture of Mycobacterium TB from blood or other relevant specimen except sputum or BAL. Biopsy and histology.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Kaposi sarcoma	Typical appearance in skin or oropharynx of persistent, initially flat, patches with a pink or blood-bruise colour, skin lesions that usually develop into nodules.	Not required but may be confirmed by: - typical red-purple lesions seen on bronchoscopy or endoscopy; - dense masses in lymph nodes, viscera or lungs by palpation or radiology; and - histology.
CMV retinitis or CMV infection affecting another organ, with onset at age over 1 month.	Retinitis only. CMV retinitis may be diagnosed by experienced clinicians: typical eye lesions on serial fundoscopic examination; discrete patches of retinal whitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal vasculitis, haemorrhage and necrosis.	Definitive diagnosis required for other sites. Histology. Cerebrospinal fluid polymerase chain reaction
CNS toxoplasmosis with onset at age over 1 month.	Fever, headache, focal neurological signs, convulsions. Usually responds within 10 days to specific therapy.	Not required but confirmed by computed tomography (CT) scan (or other neuroimaging) showing single or multiple lesions with mass effect or enhancing with contrast.
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion and behavioural changes that respond to cryptococcal therapy.	Confirmed by CSF microscopy (India ink or Gram stain), serum or CSF CRAG test or culture.
HIV encephalopathy	At least one of the following, progressing over at least two months in the absence of another illness: - failure to attain, or loss of, developmental milestones, loss of intellectual ability; OR - progressive impaired brain growth demonstrated by stagnation of head circumference; OR - acquired symmetric motor deficit accompanied by two or more of the following: paresis, pathological reflexes, ataxia, gait disturbances.	Confirmed by neuroimaging (brain CT scan or MRI) demonstrating atrophy and basal ganglia calcification and excluding other causes.
Disseminated mycosis (coccidiomycosis, histoplasmosis, penicilliosis)	No presumptive clinical diagnosis.	Diagnosed by: Histology: usually granuloma formation. Isolation: antigen detection from affected tissue; culture or microscopy from clinical specimen or blood culture.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Disseminated mycobacteriosis, other than TB	No presumptive clinical diagnosis.	Nonspecific clinical symptoms including progressive weight loss, fever, anaemia, night sweats, fatigue or diarrhoea; plus culture of atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding lung.
Chronic cryptosporidiosis	No presumptive clinical diagnosis.	Confirmed by cysts identified on modified Ziehl-Nielsen microscopic examination of unformed stool
Chronic Isospora	No presumptive clinical diagnosis.	Confirmed in children with chronic diarrhoea by microscopic examination.
Cerebral or B-cell non-Hodgkin lymphoma	No presumptive clinical diagnosis.	Diagnosed by CNS neuroimaging: at least one lesion with mass effect on brain scan; histology of relevant specimen
Progressive multi focal leukoencephalopathy	No presumptive clinical diagnosis.	Diagnosed by progressive nervous system disorder (cognitive dysfunction, gait or speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuroimaging or positive polyomavirus Jacob Creutzfeldt PCR on cerebrospinal fluid
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis.	Renal biopsy
Symptomatic HIV-associated cardiomyopathy	No presumptive clinical diagnosis.	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography

*Definitions for stage 3 and 4 malnutrition are modified and BMI-for-age z-scores for children 5-19 years will be used as weight-for-age z-scores reference data don't go beyond 10 years of age

WHO Child Growth Standards (z-score charts).
Weight-for-age, Girls 2-5
https://www.who.int/childgrowth/standards/cht_wfa_girls_z_2_5.pdf?ua=1
Weight-for-age, Boys 0-5
https://www.who.int/childgrowth/standards/cht_wfa_boys_z_2_5.pdf?ua=1
BMI-for-age, Girls 5-19
https://www.who.int/growthref/bmifa_girls_z_5_19_labels.pdf?ua=1
BMI-for-age, Boys 5-19
https://www.who.int/growthref/bmifa_boys_z_5_19_labels.pdf?ua=1

DIAGNOSTIC CRITERIA FOR WHO STAGE 1, 2, 3 AND 4 CONDITIONS FOR YOUNG PEOPLE 15 YEARS AND OLDER

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Clinical Stage 1		
Asymptomatic.	No HIV-related symptoms reported and no signs on examination.	Not applicable.
Persistent generalized lymphadenopathy.	Painless enlarged lymph nodes >1 cm in two or more non-contiguous sites (excluding inguinal) in the absence of known cause and persisting for three months or more.	Histology.
Clinical Stage 2		
Unexplained moderate weight loss (<10% of body weight).	Reported unexplained involuntary weight loss in pregnancy failure to gain weight.	Documented weight loss <10% of body weight.
Recurrent upper respiratory tract infections (current event plus one or more in last six-month period).	Symptom complex, such as unilateral face pain with nasal discharge (sinusitis), painful inflamed eardrum (otitis media) or tonsillopharyngitis without features of viral infection (such as coryza or cough).	Laboratory studies where available, such as culture of suitable body fluid.
Herpes zoster.	Painful vesicular rash in dermatomal distribution of a nerve supply, does not cross the midline.	Clinical diagnosis.
Angular cheilitis.	Splits or cracks at the angle of the mouth not due to iron or vitamin deficiency, usually respond to antifungal treatment.	Clinical diagnosis.
Recurrent oral ulceration (two or more episodes in last six months).	Aphthous ulceration, typically painful with a halo of inflammation and a yellow grey pseudomembrane.	Clinical diagnosis.
Papular pruritic eruption.	Papular pruritic lesions, often with marked postinflammatory pigmentation.	Clinical diagnosis.
Seborrhoeic dermatitis.	Itchy scaly skin condition, particularly affecting hairy areas (scalp, axillae, upper trunk and groin).	Clinical diagnosis.
Fungal nail infection.	Paronychia (painful red and swollen nail bed) or onycholysis (separation of the nail from the nail bed) of the fingernails (white discoloration – especially involving proximal part of	Fungal culture of the nail or nail plate material.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
	nail plate – with thickening and separation of the nail from the nail bed).	
Clinical Stage 3		
Unexplained severe weight loss (more than 10% of body weight).	Reported unexplained involuntary weight loss (>10% of body weight) and visible thinning of face, waist and extremities with obvious wasting or body mass index <18.5 kg/m2; in pregnancy, the weight loss may be masked.	Documented loss of more than 10% of body weight.
Unexplained chronic diarrhoea for longer than one month.	Chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month.	Three or more stools observed and documented as unformed, and two or more stool tests reveal no pathogens.
Unexplained persistent fever (intermittent or constant and lasting for longer than one month).	Fever or night sweats for more than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarial agents, without other obvious foci of disease reported or found on examination; malaria must be excluded in malarious areas.	Documented fever >37.5°C with negative blood culture, negative Ziehl-Nielsen stain, negative malaria slide, normal or unchanged chest X-ray and no other obvious focus of infection.
Persistant oral candidiasis.	Persistent or recurring creamy white curd-like plaques that can be scraped off (pseudomembranous) or red patches on tongue, palate or lining of mouth, usually painful or tender (erythematous form).	Clinical diagnosis.
Oral hairy leukoplakia.	Fine white small linear or corrugated lesions on lateral borders of the tongue that do not scrape off.	Clinical diagnosis.
Pulmonary tuberculosis (current).	Chronic symptoms: (lasting at least 2–3 weeks) cough, haemoptysis, shortness of breath, chest pain, weight loss, fever, night sweats; PLUS EITHER positive sputum smear; OR negative sputum smear; AND compatible chest radiograph (including but not restricted to upper lobe infiltrates, caritation, pulmonary fibrosist shrinkage. No evidence of extrapulmonary disease.	Isolation of M. tuberculosis on sputum culture or histology of lung biopsy (with compatible symptoms).
Acute necrotizing ulcerative gingivitis or	Severe pain, ulcerated gingival papillae, loosening of teeth, spontaneous bleeding, bad odour	Clinical diagnosis.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
necrotizing ulcerative periodontitis.	and rapid loss of bone and/or soft tissue.	
Severe bacterial infection (such as pneumonia, meningitis, empyema, pyomyositis, bone or joint infection, bacteraemia and severe pelvic inflammatory disease).	Fever accompanied by specific symptoms or signs that localize infection and response to appropriate antibiotic.	Isolation of bacteria from appropriate clinical specimens (usually sterile sites).
Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 109 per litre) or chronic (more than one month) thrombocytopaenia (<50 × 109 per litre).	Not presumptive clinical diagnosis.	Diagnosed on laboratory testing and not explained by other non-HIV conditions; not responding to standard therapy with haematinics, antimalarial agents or anthelmintic agents as outlined in relevant national treatment guidelines, WHO Integrated Management of Childhood Illness guidelines or other relevant guidelines.
Clinical Stage 4		
HIV wasting syndrome	Unexplained involuntary weight loss (>10% baseline body weight), with obvious wasting or body mass index <18.5; PLUS EITHER unexplained chronic diarrhoea (loose or watery stools three or more times daily) reported for longer than one month; OR reports of fever or night sweats for more than one month without other cause and lack of response to antibiotics or antimalarial agents; malaria must be excluded in malarious areas.	Documented weight loss (>10% of body weight); PLUS EITHER two or more unformed stools negative for pathogens; OR documented temperature of >37.5°C with no other cause of disease, negative blood culture, negative malaria slide and normal or unchanged chest X-ray.
Pneumocystis pneumonia	Dyspnoea on exertion or nonproductive cough of recent onset (within the past three months), tachypnoea and fever; AND Chest X-ray evidence of diffuse bilateral interstitial infiltrates; AND	Cytology or immunofluorescent microscopy of induced sputum or bronchoalveolar lavage or histology of lung tissue.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
	No evidence of bacterial pneumonia; bilateral crepitations on auscultation with or without reduced air entry.	
Recurrent bacterial pneumonia (this episode plus one or more episodes in last six months)	Current episode plus one or more previous episodes in the past six months; acute onset (<2 weeks) of severe symptoms (such as fever, cough, dyspnoea, and chest pain) PLUS new consolidation on clinical examination or chest X-ray; response to antibiotics.	Positive culture or antigen test of a compatible organism.
Chronic herpes simplex virus infection (orolabial, genital or anorectal) of more than one month or visceral infection of any duration.	Painful, progressive anogenital or orolabial ulceration; lesions caused by recurrence of herpes simplex virus infection and reported for more than one month. History of previous episodes. Visceral herpes simplex virus requires definitive diagnosis.	Positive culture or DNA (by polymerase chain reaction) of herpes simplex virus or compatible cytology or histology.
Oesophageal candidiasis	Recent onset of retrosternal pain or difficulty on swallowing (food and fluids) together with oral candidasis.	Macroscopic appearance at endoscopy or bronchoscopy, or by microscopy or histology.
Extrapulmonary tuberculosis	Systemic illness (such as fever, night sweats, weakness and weight loss). Other evidence for extrapulmonary or disseminated tuberculosis varies by site: Pleural, pericardia, peritoneal involvement, meningitis, mediastinal or abdominal lymphadenopathy or ostetis. Discrete peripheral lymph node Mycobacterium tuberculosis infection (especially cervical) is considered a less severe form of extrapulmonary tuberculosis.	M. tuberculosis isolation or compatible histology from appropriate site or radiological evidence of miliary tuberculosis; (diffuse uniformly distributed small miliary shadows or micronodules on chest X-ray).
Kaposi sarcoma	Typical gross appearance in skin or oropharynx of persistent, initially flat, patches with a pink or violaceous colour, skin lesions that usually develop into plaques or nodules.	Macroscopic appearance at endoscopy or bronchoscopy, or by histology.
Cytomegalovirus disease (other than liver, spleen or lymph node)	Retinitis only: may be diagnosed by experienced clinicians. Typical eye lesions on fundoscopic examination: discrete patches of retinal hitening with distinct borders, spreading centrifugally, often following blood vessels, associated with retinal	Compatible histology or cytomegalovirus demonstrated in cerebrospinal fluid by culture or DNA (by polymerase chain reaction).

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
	vasculitis, haemorrhage and necrosis.	
Central nervous system toxoplasmosis	Recent onset of a focal nervous system abnormality consistent with intracranial disease or reduced level of consciousness AND response within 10 days to specific therapy.	Positive serum toxoplasma antibody AND (if available) single or multiple intracranial mass lesion on neuroimaging (computed tomography or magnetic resonance imaging).
HIV encephalopathy	Disabling cognitive and/or motor dysfunction interfering with activities of daily living, progressing over weeks or months in the absence of a concurrent illness or condition other than HIV infection that might explain the findings.	Diagnosis of exclusion: and (if available) neuroimaging (computed tomography or magnetic resonance imaging).
Extrapulmonary cryptococcosis (including meningitis)	Meningitis: usually subacute, fever with increasing severe headache, meningism, confusion, behavioural changes that respond to cryptococcal therapy.	Isolation of Cryptococcus neoformans from extrapulmonary site or positive cryptococcal antigen test on cerebrospinal fluid or blood.
Disseminated nontuberculous mycobacteria infection	No presumptive clinical diagnosis.	Diagnosed by finding atypical mycobacterial species from stool, blood, body fluid or other body tissue, excluding the lungs.
Progressive multifocal leukoencephalopathy	No presumptive clinical diagnosis.	Progressive nervous system disorder (cognitive dysfunction, gait/speech disorder, visual loss, limb weakness and cranial nerve palsies) together with hypodense white matter lesions on neuro-imaging or positive polyomavirus JC polymerase chain reaction on cerebrospinal fluid.
Chronic cryptosporidiosis (with diarrhoea lasting more than one month)	No presumptive clinical diagnosis.	Cysts identified on modified Ziehl-Nielsen stain microscopic examination of unformed stool.
Chronic isosporiasis	No presumptive clinical diagnosis.	Identification of Isospora.
Disseminated mycosis (coccidiomycosis or histoplasmosis)	No presumptive clinical diagnosis.	Histology, antigen detection or culture from clinical specimen or blood culture.
Recurrent non-typhoid Salmonella bacteraemia	No presumptive clinical diagnosis.	Blood culture.
Lymphoma (cerebral or B-cell non-Hodgkin)	No presumptive clinical diagnosis.	Histology of relevant specimen or, for central nervous system

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
		tumours, neuroimaging techniques.
Invasive cervical carcinoma	No presumptive clinical diagnosis.	Histology or cytology.
Atypical disseminated leishmaniasis	No presumptive clinical diagnosis.	Diagnosed by histology (amastigotes visualized) or culture from any appropriate clinical specimen.
Symptomatic HIV-associated nephropathy	No presumptive clinical diagnosis.	Renal biopsy.
Symptomatic HIV-associated cardiomyopathy	No presumptive clinical diagnosis.	Cardiomegaly and evidence of poor left ventricular function confirmed by echocardiography.

APPENDIX III. PRODUCT INFORMATION – UNREGISTERED PRODUCTS

The following unregistered products will be supplied for the trial by ViiV Healthcare Ltd:

DTG 5 mg paediatric dispersible tablets are white, round, film-coated, and debossed with 'SV H7S' on one side and '5' on the opposite side. Each tablet contains 5.26 mg dolutegravir sodium, which is equivalent to 5 mg of dolutegravir free acid. The tablets are designed to be dispersed in small amount of water prior to oral administration. The tablets are packaged in HDPE bottles with child-resistant closures that include an induction seal and a desiccant. Store and dispense in the original package, protect from moisture, and keep bottles tightly closed. Do not remove desiccant. The tablets should be stored up to 30°C (86°F).

Dolutegravir/Lamivudine Dispersible Tablets, 5mg/30mg are white, film-coated, oval, biconvex tablets for oral administration. The tablets are debossed with 'SV53' on one side and plain on the other side. The tablets contain 5.26mg dolutegravir sodium (equivalent to 5mg dolutegravir) and 30mg lamivudine. The tablets are designed to be dispersed in a small amount of water prior to administration. The tablets are packed into HDPE bottles with desiccant and child-resistant closures that include an induction seal. The bottles may contain a desiccant. Protect from moisture, and keep bottles tightly closed. The tablets should be stored up to 30°C (86°F).

Dolutegravir/Lamivudine Tablets, 50mg/300mg are white, biconvex, oval, film-coated tablets for oral administration. The tablets are debossed with 'SV137' on one side and plain on the other side. The tablets contain 52.6mg dolutegravir sodium which is equivalent to 50mg dolutegravir free acid and 300mg lamivudine. The tablets are packaged into HDPE bottles with child-resistant closures that include an induction seal. The bottles may contain a desiccant. Protect from moisture, and keep bottles tightly closed. The tablets should be stored up to 30°C (86°F).

APPENDIX IV. TOXICITY GRADINGS AND MANAGEMENT

Adapted Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Paediatric Adverse Events (Corrected Version 2.1 - July 2017) [4]

Modifications to reporting:

- Neutrophil grading is based on WHO guidelines[5] recognising the lower normal levels in African populations.

	Grade 1	Grade 2	Grade 3	Grade 4
Absolute Neutrophil Count	750-<1000mm^3 0.75 x10^9 - <1x 10^9/L	500-749/mm^3 0.5 x10^9 – 0.749 x 10^9/L	250-499/mm^3 0.25 x 10^9 – 0.499 x 10^9/L	<250mm^3 <0.250 x 10^9/L

- For creatinine grading DAIDS criteria based on upper limit of normal values rather than comparison with the baseline will be used
- For creatinine clearance DAIDS ranges of estimated creatinine clearance rather than comparison with the baseline will be used

General Instructions:

If the need arises to grade a clinical adverse event (AE) that is not identified in the DAIDS AE grading table, use the category "Estimating Severity Grade" located at the top of the table.

If the severity of an AE could fall under either one of two grades (e.g. the severity of an AE could be either Grade 2 or Grade 3) select the higher of the two grades for the AE.

Definitions:

Basic self-care functions	Adults: Activities such as bathing, dressing, toileting, transfer or movement, continence, and feeding. Young children: Activities that are age and culturally appropriate, such as feeding one's self with culturally appropriate eating implements.
Chemical pregnancy	A pregnancy in which a positive pregnancy test is followed by a negative pregnancy test without evidence of a clinical pregnancy loss.
Disability	A substantial disruption of a person's ability to conduct normal life functions.
Intervention	Medical, surgical, or other procedures recommended or provided by a healthcare professional for the treatment of an adverse event.
Hospitalisation	Does not include the following hospital admissions: under 24 hours, unrelated to an adverse event (e.g., for labour and delivery, cosmetic surgery, social or administrative for temporary placement [for lack of a place to sleep]), protocol-specified, and for diagnosis or therapy of a condition that existed before the receipt of a study agent and which has not increased in severity or frequency.
LLN	Lower limit of normal
Medical intervention	Use of pharmacologic or biologic agent(s) for treatment of an AE
NA	Not applicable
Operative intervention	Surgical OR other invasive mechanical procedures.
ULN	Upper limit of normal
Usual social & functional activities	Activities which adults and children perform on a routine basis and those which are part of regular activities of daily living, for example: Adults: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby. Young children: Activities that are age and culturally appropriate, such as social interactions, play activities, or learning tasks.

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
CLINICAL CONDITIONS: ESTIMATING SEVERITY GRADE FOR PARAMETERS NOT IDENTIFIED IN THE GRADING TABLE				
Clinical adverse event NOT identified elsewhere in this DAIDS AE grading table	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 Medical or operative intervention indicated to prevent permanent impairment, persistent disability, or death
MAJOR CLINICAL CONDITIONS				
CARDIOVASCULAR				
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
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 + 5 mmHg 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)

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)
DERMATOLOGICAL				
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
ENDOCRINE and METABOLIC				
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
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

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

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

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
PSYCHIATRIC and SLEEP PROBLEMS				
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				
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)

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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 Weight-for-height 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 Weight-for-length 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)
URINARY				
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

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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
Creatinine Clearance [14] or eGFR, Low **Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m^2 OR 10 to < 30% decrease from participant's baseline	< 60 to 30 ml/min or ml/min/1.73 m^2 OR 30 to < 50% decrease from participant's baseline	< 30 ml/min or ml/min/1.73 m^2 OR ≥ 50% decrease from participant's baseline or dialysis needed
Glucose (mg/dL; *mmol/L*) ***Fasting, High***	110 to 125 *6.11 to < 6.95*	> 125 to 250 *6.95 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Nonfasting, High	116 to 160 *6.44 to < 8.89*	> 160 to 250 *8.89 to < 13.89*	> 250 to 500 *13.89 to < 27.75*	≥ 500 *≥ 27.75*
Glucose, Low (mg/dL; *mmol/L*) *≥ 1 month of age*	55 to 64 *3.05 to <3.55*	40 to < 55 *2.22 to < 3.05*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
< 1 month of age	50 to 54 *2.78 to < 3.00*	40 to < 50 *2.22 to < 2.78*	30 to < 40 *1.67 to < 2.22*	< 30 *< 1.67*
Lactate, High	ULN to < 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life-threatening consequences	Increased lactate with pH < 7.3 with life- threatening consequences
Lipase, High	1.1 to < 1.5 x ULN	1.5 to < 3.0 x ULN	3.0 to < 5.0 x ULN	≥ 5.0 x ULN
Lipid Disorders (mg/dL; *mmol/L*) ***Cholesterol, Fasting, High*** *≥ 18 years of age*	200 to < 240 *5.18 to < 6.19*	240 to < 300 *6.19 to < 7.77*	≥ 300 *≥ 7.77*	NA
< 18 years of age	170 to < 200 *4.40 to < 5.15*	200 to < 300 *5.15 to < 7.77*	≥ 300 *≥ 7.77*	NA
LDL, Fasting, High *≥ 18 years of age*	130 to < 160 *3.37 to < 4.12*	160 to < 190 *4.12 to < 4.90*	≥190 *≥ 4.90*	NA
> 2 to < 18 years of age	110 to < 130 *2.85 to < 3.34*	130 to < 190 *3.34 to < 4.90*	≥ 190 *≥ 4.90*	NA
Triglycerides, Fasting, High	150 to 300 *1.71 to 3.42*	>300 to 500 *>3.42 to 5.7*	>500 to < 1,000 *>5.7 to 11.4*	> 1,000 *> 11.4*
Magnesium[15], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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*
HAEMATOLOGY				
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/mm3; x109cells/L) > 5 years of age (not HIV infected)	600 to < 650 0.600 to < 0.650	500 to < 600 0.500 to < 0.600	350 to < 500 0.350 to < 0.500	< 350 < 0.350
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

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

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

ULN = upper limit of normal; LLN = lower limit of normal

[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.

[2] As per Bazett's formula.

[3] For pruritus associated with injections or infusions, see the Site Reactions to Injections and Infusions section.

[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.

[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.

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

[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.

[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.

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

[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.

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

[16] Male and female sex are defined as sex at birth. For transgender participants ≥13 years of age who have been on hormone therapy for more than 6 consecutive months, grade hemoglobin based on the gender with which they identify (i.e., a transgender female should be graded using the female sex at birth hemoglobin laboratory values).

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

APPENDIX V. LIVER SAFETY – STUDY TREATMENT RESTART OR RE-CHALLENGE GUIDELINES AND CHECKLIST

If a causal relationship between the liver event and DTG or other suspected antiretroviral drugs cannot be ruled out, then the suspected antiretroviral drug(s) must be permanently discontinued and the participant not re-challenged.

DRUG RESTART FOLLOWING TRANSIENT RESOLVING LIVER EVENTS NOT RELATED TO STUDY DRUG

Restart can be considered when liver chemistries improve to within 1.5x baseline and ALT<3xULN where:

- Liver chemistries have a clear underlying cause other than drug-induced liver injury (e.g. biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity, and the drug should not be associated with HLA markers of liver injury.
- If restart of TRIUMEQ or any other ABC-containing product is being considered then the participant must be HLA-B*5701 negative (even in countries where HLA-B*5701 screening is not considered standard of care).
- The participant is receiving compelling benefit and benefit of drug restart exceeds risk
- Approval from the MRC CTU at UCL and the site PI for the drug restart has been obtained.
- The participant has been provided with a clear description of the possible benefits and risks of drug restart, including the possibility of recurrent, more severe liver injury or death.
- The participant has also provided signed informed consent specifically for the restart. Documentation of informed consent must be recorded in the study file.
- Following drug restart, the participant will return to the clinic once a week for liver chemistry tests for one month or for as long as clinically indicated and then laboratory monitoring may resume as per protocol. If protocol defined stopping criteria for liver chemistry elevations (see **Protocol Section 5.8.1.A Liver Toxicity**) are met, study drug must be stopped.

LIVER SAFETY – CHECKLIST FOR DRUG RESTART APPROVAL OR REFUSAL

"Drug restart" after discontinuation of Study Drug due to Liver Stopping Criteria (as defined in **Protocol Section 5.8.1.A Liver Toxicity**), can only be approved by the MRC CTU at UCL Trial Management Team and Site Principal Investigator for **transient, defined non-drug-induced liver injury with NO evidence of:**

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

Investigators MUST:

1. Hold study drug while laboratory investigations and evaluations are completed to assess diagnosis, and not restart until "Drug restart" has been approved by the Chief Investigator, Trial Physician and Site Principal Investigator.
2. Complete the table below and submit to the MRC CTU at UCL Trial Management Team. The Liver Event case report form should already have been submitted to the MRC CTU at UCL Trial Management Team, along with liver imaging and/or liver biopsy case report forms and/or SAE case report form where applicable. Where restart of TRIUMEQ or any other ABC-containing product is being considered, provide documentation verifying HLA-B*5701 status.

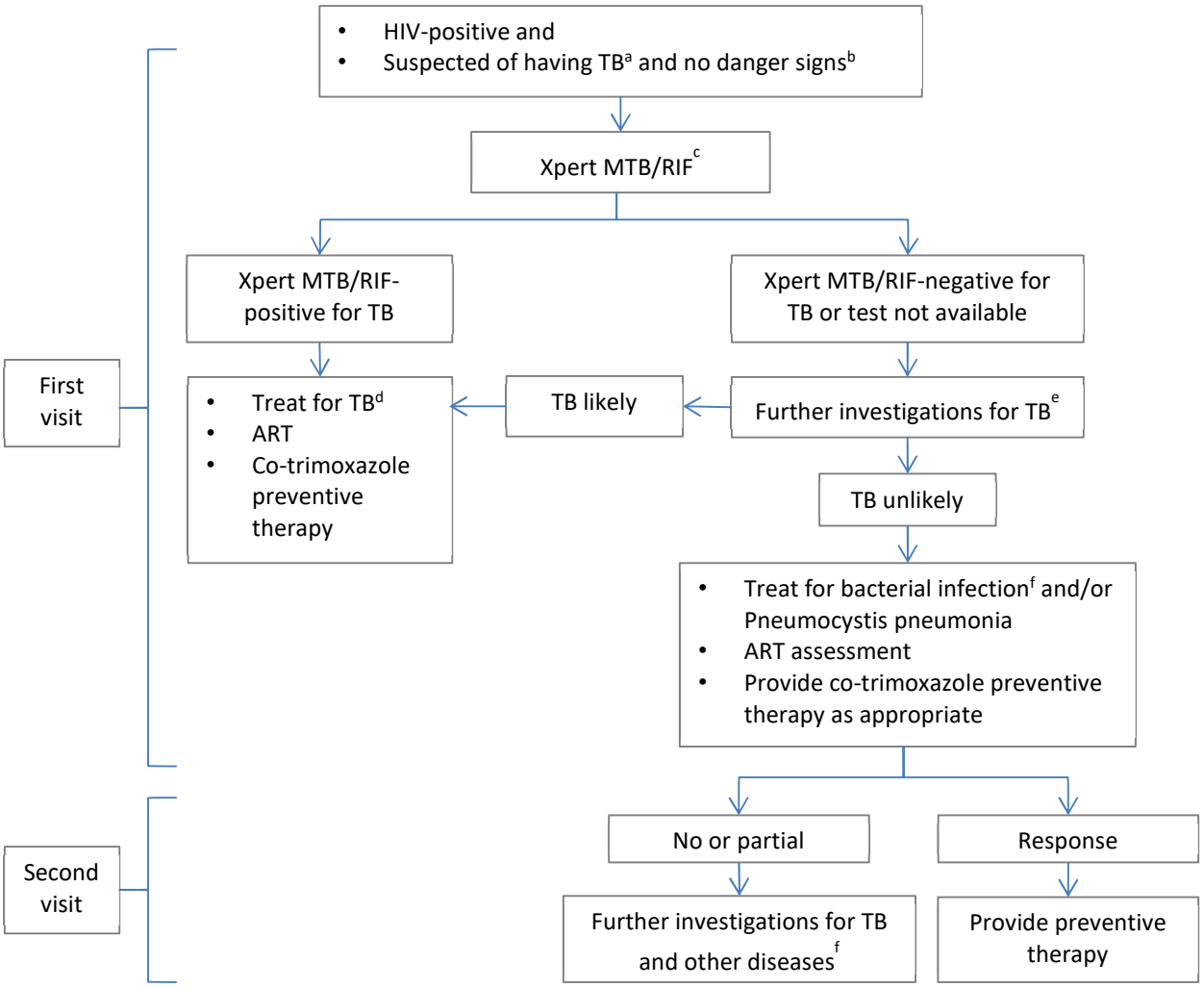
Participant Number:	**Yes**	**No**
Have liver chemistries improve to within 1.5x baseline and ALT<3xULN?		
Was participant's HIV infection stable or improving on Study Drug?		
Were any of the **following high risk factors** included in the initial liver injury event? **(Do not restart if 'Yes' for any one of the following high risk factors)**:		
• Fever, rash, eosinophilia, or hypersensitivity		
• Drug-induced liver injury		
• Alcoholic hepatitis (aspartate aminotransferase>ALT, typically <10xULN)		
• Study Drug (other than ABC) has an HLA genetic marker associated with liver injury		
For restart of TRIUMEQ, or any other abacavir-containing Study Drug, the participant MUST be HLA-B*5701 negative[1] Specify HLA-B*5701 status[2]:		

[1] In countries/regions where HLA-B*5701 pre-therapy screening is not considered standard of care, participants stopping abacavir- containing study drug due to Liver Stopping Criteria MUST be tested and found to be negative for the HLA-B*5701 allele before abacavir-containing Study Drug can be re-started.

[2] If study drug does not containing ABC then record HLA-B*5701 status as "not applicable"

APPENDIX VI. MANAGEMENT OF PARTICIPANTS WITH SUSPECTED TB

Algorithm for managing participants with suspected TB (adapted from WHO 2016 guidelines[6])



[a] Suspicion of TB is defined by the presence of any one of the following symptoms
– For adults and adolescents living with HIV: current cough, fever, weight loss or night sweats
– For children with HIV: poor weight gain, fever, current cough or history of contact with a TB case

[b] Danger signs include any one of the following: respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided

[c] For participants suspected of having extrapulmonary TB, extrapulmonary specimens should be obtained for Xpert MTB/RIF (cerebrospinal fluid, lymph nodes and other tissues: Xpert MTB/RIF has low sensitivity for pleural fluid and data are limited for stool, urine or blood)

[d] If Xpert MTB/RIF shows rifampicin resistance, treatment for multidrug-reistant TB should be initiated. A second Xpert MTB/RIF test should be performed on a fresh specimen. Collect and send a sample for culture and additional drug sensitivity testing

[e] Further investigations for TB include chest X-ray, clinical assessment and a repeat Xpert MTB/RIF using a fresh specimen. Send a sample for TB culture where feasible. If Xpert MTB/RIF is not available, conduct acid-fast bacillus (AFB) microscopy. If extrapulmonary TB is suspected, extrapulmonary specimens should be obtained and sent for culture and abdominal ultrasound may be performed. These investigations may require additional visits.

[f] Antibiotics with broad-spectrum antibacterial activity (except fluoroquinolones) should be used

As rifampicin interacts with many antiretroviral drugs, a change of regimen may be needed for children who develop TB in the trial. Management of children on DTG-based ART who are treated for TB is outlined in the protocol (**Protocol Section 5.9 TB Management Strategies**).

Guidance on the choice of ART for children with TB who are no longer on DTG-based ART can be found in the WHO 2021 guidelines[7] or national guidelines and may differ between countries. As efavirenz does not interact in a clinically significant manner with rifampicin, children receiving efavirenz-based ART can continue the same regimen. Children receiving lopinavir/ritonavir (LPV/r)-based ART can continue on their regimen if they receive super-boosted ritonavir (increasing ritonavir to achieve a LPV/r ratio of 1:1),[8,9] . Children on raltegravir-based ART should have their raltegravir dose doubled.[10,11] Please note, that raltegravir formulations are not interchangeable (granules and chewable tablets have ~1.3 times better bioavailability than film-coated tablets). Nevirapine, atazanavir or darunavir cannot be co-administered with rifampicin and children on these drugs should be switched to alternative antiretrovirals.

APPENDIX VII. HIGHLY-EFFECTIVE CONTRACEPTION

All female participants who are sexually active and randomised to receive DTG must use highly effective contraception.[12]

TYPE OF CONTRACEPTION	Boosted protease inhibitors (PIs)			NNRTIs				CCR5	NRTIs	Integrase		
	Atazanavir/r	Darunavir/r	Lopinavir/r	Efavirenz	Nevirapine	Etravirine	Rilpivirine	Maraviroc	All	Raltegravir	Dolutegravir	Elvitegravir/c
Combined												
Combined PILL	**Not recommended** as ↓oestrogen *but if no other acceptable option consider* ***pill (e.g. Cilest) with at least 35mcg ethinylestradiol***	**Not recommended** as ↓oestrogen *but if no other acceptable option consider* ***double dose pill and monitor symptoms***		**NOT ADVISED**	**Not recommended as** ↓ in oestrogen and progestogen exposure, unlikely to be clinically significant *but if no other acceptable option consider* ***and monitor symptoms***	**SAFE** to use with standard pill (e.g. Maexeni) ethinyestrodiol 30mcg desogestrel 150mcg	**SAFE** with all listed contraception	**SAFE** with all listed contraception	**SAFE** with all listed contraception	**SAFE** with all listed contraception	**SAFE** with all listed contraception	↓oestrogen ***use pill (e.g. Cilest) with at least 35mcg ethinylestradiol***
Progesterone only												
Progesterone only PILL (containing 75 micrograms desogestrel)	**Not recommended** as ↑ progesterone, unlikely to be significant but can consider *but if no other acceptable option consider* ***and monitor symptoms***			**NOT ADVISED**	**Not recommended as** ↓ progesterone, unlikely to be significant *but if no other acceptable option consider* ***and monitor symptoms***	**SAFE** to use, ↓ progesterone, unlikely to be significant						↑progesterone unlikely to be significant but ***monitor symptoms***
IMPLANT	**Not recommended** as ↑ progesterone, unlikely to be significant *but if no other acceptable option consider* ***and monitor symptoms***			**Not recommended** as ↓progesterone levels *but if no other acceptable option consider* ***replacing in 12 months***								
DEPO-PROVERA	**SAFE** with all ART											
MIRENA IUS	**SAFE** with all ART											
Non-hormonal												
Copper IUD	**SAFE** with all ART											
KEY	Safe to administer (note dose adjustments)			Refer to complex contraception clinic for advice, monitoring and follow up and use with caution								Not advised

Adapted, with permission, from: Hamzah L and Samuel I, June 2018

APPENDIX VIII. MODIFIED FDA SNAPSHOT ALGORITHM

Categorisation of Virological Outcomes at 48/96 weeks (within window 42-54/90-102 weeks)

A modified version of the FDA snapshot algorithm will be used to describe virological failure at weeks 48 and 96 as described in the table below (Table AVIII-1).

Table AVIII-1. Modified FDA snapshot algorithm

	DTG/3TC	SOC
	N (%)	N (%)
HIV RNA≥50 c/mL[1]		
Treatment difference (95% CI)		
HIV RNA<50 c/mL[2]		
No virological data in week 48/96 window		
Discontinued study regimen due to AE or death and last on treatment HIV-1 RNA <50 c/mL[3]		
Discontinued study regimen for other reasons and last on treatment HIV-1 RNA <50 c/mL[4]		
On study regimen[5] but missing HIV RNA data in window		

[1]Includes (i) participants on study drug (DTG/3TC) or SOC (including with prior permitted changes while HIV-RNA<50 c/mL) who had confirmed HIV-RNA≥50 c/mL in 48/96 week window; (ii) participants who changed any component of initial regimen because of lack of efficacy prior to/during week 48/96 window; (iii) participants who discontinued/changed any component of initial regimen for reasons other than lack of efficacy prior to/during week 48/96 with the last on treatment (prior to/on the date of change) HIV-1 RNA ≥50 c/mL

[2] Includes (i) participants on study drug (DTG/3TC) or SOC (including with prior permitted changes while HIV-RNA<50 c/mL) and HIV-RNA<50 c/mL at week 48/96

[3]Includes participants who discontinued any component of initial regimen for toxicity/death before or during week 48/96 where last on treatment HIV-RNA<50 c/mL

[4]Includes participants who discontinued or changed any component of initial regimen for reasons other than an AE/death or lack of efficacy, e.g., withdrew consent, lost to follow-up, pregnancy (or desire to become pregnant), transferred care to a non-study site or had non-permitted change of any component of initial regimen before or during week 48/96 where last on treatment HIV-RNA<50 c/mL

[5]DTG/3TC or SOC (including with prior permitted changes while HIV-RNA<50 c/mL)

Permitted changes to ART are specified in the protocol (**Protocol Section 5.5.1 Permitted ART Changes**). All other changes to ART are non-permitted (including stopping ART).

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