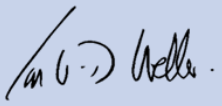
ODYSSEY (PENTA 20):
A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Version: 6.0
Date: 8th November 2019

ISRCTN #: ISRCTN91737921
EUDRACT #: 2014-002632-14
NCT #: NCT02259127

Authorised by:

Name: Professor Ian Weller
Role: Chair ODYSSEY Trial Steering Committee
Signature:



Date: 8th November 2019

Name: Professor Carlo Giaquinto
Role: Chair, PENTA Foundation
Signature:

Date: 11th November 2019

GENERAL INFORMATION

The trial will be co-ordinated and monitored by the UK Medical Research Council (MRC) Clinical Trials Unit at University College London (UCL), (hereafter referred to as MRC CTU) in collaboration with INSERM-ANRS SC10-US019, France (INSERM-ANRS) and the Program for HIV Prevention and Treatment, Thailand (PHPT). Liaison between these Clinical Trials Units (CTUs) and clinical centres in each country will be similar to that organised for other trials conducted by the Paediatric European Network for the treatment of AIDS (PENTA), with a combination of direct liaison with a CTU (see Section 2.3) and liaison via a local co-ordinating centre. Clinical centres in South Africa, Uganda and Zimbabwe will be coordinated by MRC CTU; clinical centres in US, Uganda and South Africa joining the trial from the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT, US) will also be coordinated through MRC CTU. The trial will be supervised by the ODYSSEY Trial Management Group (TMG) who will report to the ODYSSEY Trial Steering Committee (TSC) (see Appendix XVII for the committee structure within PENTA). The TSC may decide to terminate the trial for any reason including the recommendation of the Independent Data Monitoring Committee (IDMC).

This document was constructed using the MRC CTU Protocol Template Version 7.0. The CTU endorses the Standard Protocol Items: Recommendations For Interventional Trials (SPIRIT) initiative. It describes the

ODYSSEY (PENTA 20): trial, coordinated by the MRC CTU, INSERM-ANRS and PHPT, 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 children or young people with HIV infection. Every care was taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering participants for the first time are advised to contact one of the co-ordinating CTUs to confirm they have the most up-to-date version. Clinical problems relating to this trial should be addressed with the relevant CTU.

COMPLIANCE

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki 2013, the principles of Good Clinical Practice (GCP) as laid down by the ICH topic E6 (R2), Commission Clinical Trials Directive 2005/28/EC* with the implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, General Data Protection Regulation and the UK Data Protection Act 2018 (DPA number: Z6364106), and the UK Policy Framework for Health and Social Care Research.

*Until the Clinical Trials Regulation EU No 536/2014 becomes applicable, the trial will be conducted in accordance with the Clinical Trials Directive as implemented in the UK statutory instrument. When the directive is repealed on the day of entry into application of the Clinical Trial Regulation the trial will work towards implementation of the Regulation (536/2014) following any transition period.

SPONSOR

Paediatric European Network for Treatment of AIDS (PENTA) Foundation is the trial Sponsor and has delegated responsibility for the overall management of the

ODYSSEY (PENTA 20): trial to the MRC CTU at UCL, INSERM-ANRS and PHPT. Queries relating to Penta sponsorship of this trial should be addressed to Carlo Giaquinto, Chair of Penta Foundation, Torre di Ricerca Pediatrica, Corso Stati Uniti 4, Padova, 35127, Italy.

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FUNDING

This study is funded by ViiV Healthcare. MRC CTU at UCL and INSERM SC10 are supported by the MRC (UK) and INSERM-ANRS (France) respectively. INSERM-ANRS supports the trial in France. PENTA Foundation and EuroCoord provide support to sites in Europe.

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.

TRIAL REGISTRATION

This trial has been registered with EudraCT, ISRCTN and Clinicaltrials.gov.

RANDOMISATIONS

For those sites randomising directly, training will be provided for DIRECT RANDOMISATION ONLINE as part of the site initiation and database training. Individual passwords will be provided.

Alternatively, sites can fax or send by password protected email the Randomisation CRF to the relevant CTU:

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SAE REPORTING

Within 24 hours of becoming aware of an SAE, please fax or email a completed Event form to the relevant CTU. Please ensure that an acknowledgment of receipt by the CTU is received.

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Please direct all queries to the relevant CTU (see contacts below) in the first instance; clinical queries will be passed to the Medical Experts via the MRC CTU Trial Manager.

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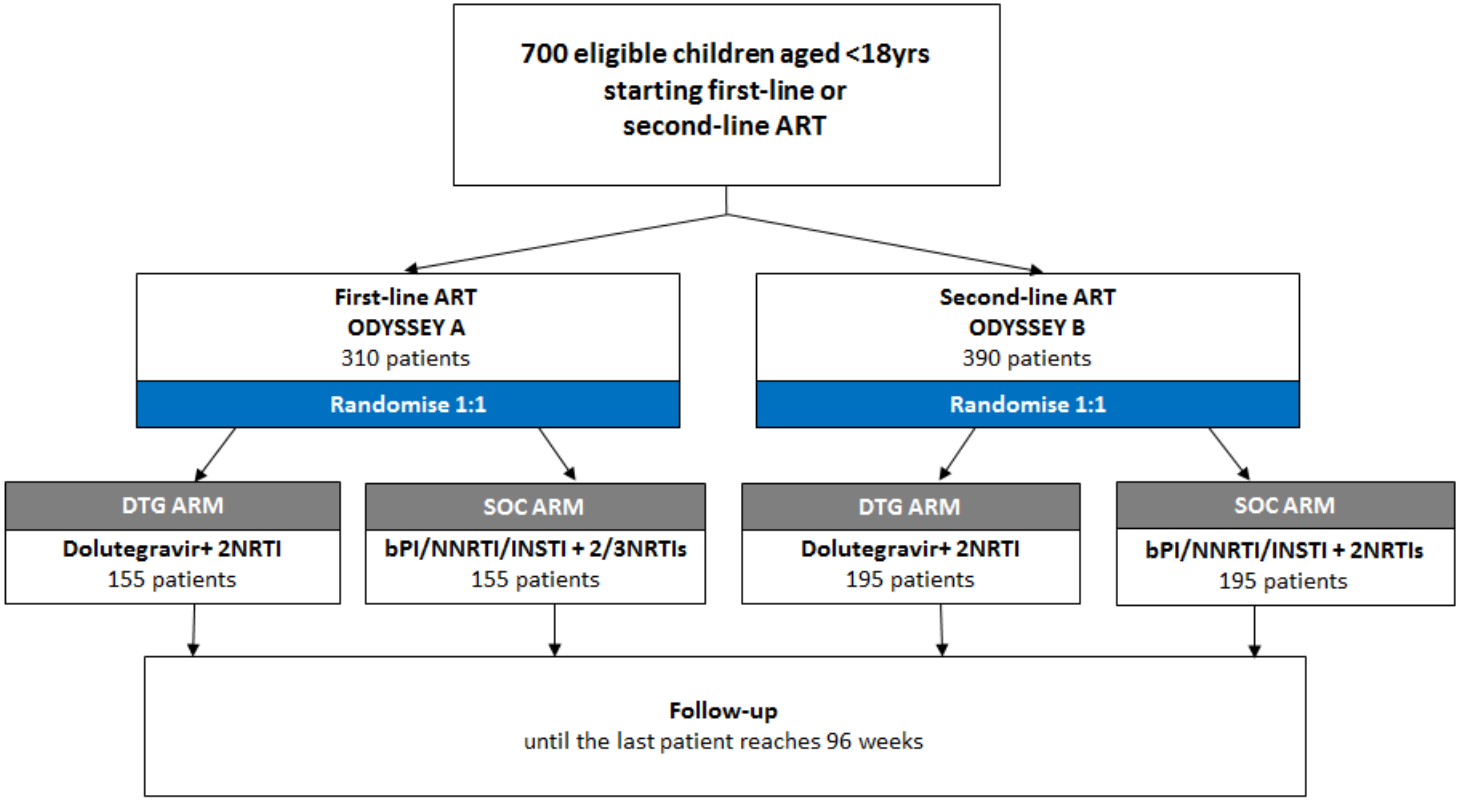
SUMMARY OF TRIAL

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
ACRONYM	ODYSSEY (Once daily dolutegravir based ART in young people vs. standard therapy)
Long Title of Trial	A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART (PENTA 20)
Version	5.0
Date	1st March 2019
ISRCTN #	ISRCTN91737921
EudraCT #	2014-002632-14
NCT #	NCT02259127
Study Design	An open-label, multi-centre, randomised (1:1), non-inferiority, Phase II/III, 96-week, 2-arm clinical trial to compare the efficacy and toxicity of DTG plus 2 NRTI vs. standard of care (SOC) in HIV-infected children aged less than 18 years who are starting first-line ART (ODYSSEY A) or switching to second-line ART (ODYSSEY B).
Type of Participants to be Studied	HIV-1 infected children younger than 18 years planning to start first-line or second-line antiretroviral therapy
Setting	International
Interventions to be Compared	DTG + 2 NRTI (DTG arm) vs. SOC (SOC arm) in first-line and second-line antiretroviral regimens
Study Hypothesis	DTG + 2 NRTIs is non-inferior to SOC (NNRTI or bPI or INSTI + 2 or 3 NRTIs) in terms of efficacy and superior in terms of toxicity profile
Primary Outcome Measure(s) for the Randomised Phase	Difference in proportion with failure (clinical or virological) by 96 weeks, estimated using time to the first occurrence of any of the following components: • Insufficient virological response defined as <1 $\log_{10}$ drop at week 24 and switch to second/third line ART for treatment failure • Viral load (VL)≥400 c/ml at or after 36 weeks confirmed by next visit • Death due to any cause • Any new or recurrent AIDS defining event (WHO 4) or severe WHO 3 event, adjudicated by the Endpoint Review Committee
Secondary Outcome Measure(s) for the Randomised Phase	Secondary efficacy outcomes: • Difference in proportion with clinical or virological failure (as defined above) by 48 weeks • Time to any new or recurrent AIDS defining event (WHO 4) or severe WHO 3 event, confirmed by the Endpoint Review Committee • Proportion of children with VL <50 c/ml at 48 and 96 weeks • Proportion of children with VL <400 c/ml at 48 and 96 weeks • Rate of clinical events over 96 weeks: WHO 4, severe WHO 3 events and death • Change in CD4 count, CD4 percentage and CD4 / CD8 ratio from baseline to weeks 48 and 96 • Proportion developing new resistance mutations Secondary safety outcomes:

	• Change in total cholesterol, triglycerides and lipid fractions (LDL, HDL) from baseline to weeks 48 and 96. Change in total cholesterol from baseline to week 96 will be used to formally assess superiority of DTG arm vs SOC arm • Incidence of serious adverse events • Incidence of new clinical and laboratory grade 3 and 4 adverse events • Incidence of adverse events (of any grade) leading to treatment modification Other secondary outcomes: • Quality of life • Adherence and acceptability
Randomisation	Children starting first- and second-line ART will be randomised separately (both in 1:1 ratio) : ODYSSEY A (first-line ART): • DTG + 2 NRTIs • SOC (defined as NNRTI or bPI or INSTI + 2 or 3 NRTIs) ODYSSEY B (second-line ART): • DTG + 2 NRTI • SOC (defined as NNRTI or bPI or INSTI+ 2 NRTIs)
Number of Participants to be Studied	700 HIV-1 infected children, including 310 children starting first-line (ODYSSEY A) and 390 starting second-line ART (ODYSSEY B). At least 60 additional children weighing 3-<14kg will be enrolled in separate strata.
Duration	Participants will be enrolled in the main trial over 96-120 weeks; with up to 78 weeks (July 2018 to end of 2019) to recruit participants weighing 3-<14kg. Participants recruited in the main trial (≥14kg) will be followed until the last recruited participant reaches week 96; participants recruited weighing 3-<14kg will each be followed for a minimum of 96 weeks.
Ancillary Studies/Substudies	The following sub-studies will be performed in selected sites (see Section 10 for participating countries): TB-PK substudy will evaluate the pharmacokinetics of dolutegravir co-administered with rifampicin in HIV/TB co-infected children. Weight band PK substudies WB-PK1 and WB-PK2 will be undertaken in children 3 to < 40 kg with the aims of simplifying doses and formulations of DTG using WHO weight bands. Immunology/virology substudy will explore mechanisms of CD4 reconstitution, immune activation, HIV reservoir and replication in DTG and SOC arms. Qualitative substudy will investigate how best to support children and young people to maintain optimal adherence to second-line treatment. The Youth Trial Board will develop a model of meaningful engagement and participation of adolescent patient representatives in paediatric clinical trials. Folate substudy will look at possible differences in folate and vitamin B12 levels between the DTG and SOC arms
Sponsor	PENTA Foundation
Funder	Funded by ViiV Healthcare and the PENTA Foundation. MRC CTU at UCL and INSERM SC10 are supported by the MRC (UK) and INSERM-

	ANRS (France) respectively; INSERM-ANRS supports the trial in France; Eurocoord provide support for the sites in Europe
Partners	MRC CTU at UCL, INSERM-ANRS, PHPT, IMPAACT, Eurocoord, PENTA
Chief Investigator	Pablo Rojo and Diana M Gibb

TRIAL SCHEMA



Note:
At least 60 additional children weighing 3-<14kg will be enrolled and followed up for 96 weeks

TRIAL ASSESSMENT SCHEDULE FOR RANDOMISED PHASE OF THE TRIAL

WEEK	Screening	Randomisation 0[a]	(2)	4	12	24	36	48	60	72	84	96	Further follow-up	Study visit at end of randomised phase*
Patient information sheet and consent for screening	X													
Informed consent for trial enrolment		X												
History and clinical assessment [b]	X	X	(X)[t]	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Tanner scale [c]		X				X		X		X		X	Every 24 weeks	X
Lipodystrophy assessment [p]		X						X				X	Every 48 weeks	X
Drug supply to next visit		X	(X)	X	X	X	X	X	X	X	X	X	Every 12 weeks	
HIV-1 RNA viral load [d]	X[d]	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	As per local practice	X[d]
T cell lymphocyte subsets [e]	X	X		X	X	X	(X)	X	(X)	X	(X)	X	As per local practice	X
Biochemistry [f]	X	(X)	(X)[t]	X	(X)	X	(X)	X	(X)	X	(X)	X	As per local practice	X
Haematology [g]	X	X	(X)[t]	X	(X)	X	(X)	X	(X)	X	(X)	X	As per local practice	X
Lipids/glucose [h]		X[o]				(X)		X				X	Every 48 weeks	X
Bone profile [i]		(X)						(X)				(X)	(Every 48 weeks)	(X)
Urine dipstick [j]		X						X				X	Every 48 weeks	X
Quality of Life questionnaire [c]		X			X	X		X				X	Every 48 weeks	X
Pregnancy test [k]	X	X[k]	X	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Plasma storage [l, q]	X	X	(X)	X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Red blood cell folate (RBC)/RBC storage and B12/serum storage [u]												X	(At next clinic visit if the 96 week sample is not collected)	
PBMC (Cell) storage [m]		X[m]			X[m]			X[m]				X[m]		
Adherence questionnaire [q, r]	X[n]			X	X	X	X	X	X	X	X	X	Every 12 weeks	X
Acceptability, sleep & mood questionnaire [q, r, v]		X[s]		X	X	X		X		X		X	Every 24 weeks	X

Notes:

( ) Optional, not mandatory.

* For participants recruited weighing ≥14kg this will be after the last participant reaches 96 weeks follow-up; for participants recruited weighing <14kg this will be their 96 week visit which should be at or after 96 weeks. Participants receiving DTG 5mg in sites in sub-Saharan Africa (South Africa, Uganda and Zimbabwe) and DTG 50mg or Triumeq in Thailand (at PHPT sites and HIV-NAT) at their study visit at the end of the randomised phase will be asked to consent to extended follow-up in order to collect safety data so that DTG can continue to be provided to these participants. Other participants will also be asked to consent to extended follow-up. Please see Appendix XX for more details.

Darker shaded boxes indicate visits where overnight fasting is required for blood lipids/glucose.

Up to 12 mls of blood may be collected at each visit for routine assays and tests plus an additional 8-18 mls blood may be collected for storage (plasma and when requested, PBMCs). Total amounts drawn will depend upon the size of the child and their health, please refer to Appendix XI for the maximum allowable blood-draw volumes for children.

a. Randomisation visit should take place within 4 weeks after the screening visit, ideally within 2 weeks
b. Clinical assessment: including height, weight (and adjustment of drug doses accordingly) and mid upper arm circumference (MUAC), change in HIV disease stage, clinical events and presence of adverse events
c. In children aged 8 or over
d. Real-time viral loads will be measured on all children in ODYSSEY B at the screening visit, unless a viral load result of ≥500 c/ml dated within four weeks of the screening visit is available. If such a result is not available it is **mandatory** that this test is done in ODYSSEY B participants. **Please always ensure that there is enough blood taken for this assay as it is a priority test at screening for ODYSSEY B**. For children recruited in ODYSSEY A, this is not mandatory. Thereafter in both ODYSSEY A and B, viral loads should be measured locally at sites according to the routine frequency, where viral loads are not measured in real time, they will be run retrospectively in batches on stored plasma
e. CD4 and CD8 percentage and absolute, total lymphocyte count. In addition, immunophenotyping (IPT) on the same blood draw will be done at the sites participating in the immunology/virology substudy, and where IPT tests are available. At the other sites IPT will be done on the cell storage samples.
f. Biochemistry: mandatory: creatinine, bilirubin, ALT; optional (if results are available or routinely done): AST
g. Haematology: Hb, MCV, WBC, lymphocytes, neutrophils, platelets
h. Lipids/Glucose: triglycerides, cholesterol (total, HDL, LDL), glucose (overnight fasting required at randomisation and weeks 24 and 48, and then every 48 weeks, and at the study visit at the end of the randomised phase)
i. Bone profile (optional): calcium, phosphate, alkaline phosphatase
j. Urine dipstick: for protein and glucose, performed at randomisation and then every 48 weeks and at end of study visit
k. Pregnancy test: urine sample; the test should be performed for all females of childbearing potential at screening, randomisation and all trial follow-up visits and at other time-points if required.

l. Plasma storage: for retrospective HIV-1 RNA viral load, resistance testing where not routinely available locally, sparse PK sampling, folate substudy and immunology/virology substudy. See Appendix XII, Appendix XIII, Manual of Operations (MOP) and Lab MOP for more details. Samples may be assayed locally, or moved to another country.
m. Peripheral blood mononuclear cells (PBMCs) will be stored at selected sites only, for use in the immunology/virology substudy. Please see Appendix XII, MOP and Lab MOP for more details.
n. Baseline adherence questionnaire for patients screened for ODYSSEY B and currently taking their first-line treatment
o. The glucose test at the randomisation visit may be omitted if there is a medical justification (e.g. anaemia) to limit the total volume of blood drawn.
p. At selected sites bioelectrical impedance analysis (BIA) measurements will be done.
q. In case of attendance at an unscheduled visit at the point of treatment failure, plasma storage and adherence and acceptability questionnaires should be done. (The acceptability questionnaire should also be done if treatment failure occurs at a scheduled visit where it is not normally done, e.g. week 36).
r. Adherence and acceptability questionnaires should also be completed if ART regimen is changed.
s. The mood and sleep section of the acceptability questionnaire should be completed at the enrolment visit.
t. Clinical assessment, haematology and biochemistry tests at week 2 are required for all children 3-<14kg and optional for children ≥14kg.
u. RBC storage for RBC folate levels and serum / serum storage for B12 levels for Folate/B12 substudy at selected sites only (see section 10.5). The bloods will be taken from the same blood draw as used for plasma isolation and storage.
v. The sleep and mood section of the acceptability questionnaire should only be completed for participants aged 6 years and over.

CONTENTS

ABBREVIATIONS

Abbreviation	Expansion
ABC	Abacavir
AE	Adverse Event
ANRS	National Agency for Research (France)
AR	Adverse Reaction
ART	Antiretroviral Therapy
ARV	Antiretrovirals
ATV	Atazanavir
AUC	Area Under Curve
BIA	Bioelectrial impedance analysis
BID	Twice Daily
bPI	Boosted Protease Inhibitor
c/ml	Copies per ml
CDC	Centres for Disease Control
COBI or c	Cobicistat
CI	Confidence Interval
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trials Authorisation (Europe)
CTU	Clinical Trials Unit (MRC, INSERM-ANRS, PHPT - as appropriate for the country)
d4T	Stavudine
ddI	Didanosine
DRV/r	Darunavir/ritonavir
DSMS	Drug Supply Management System
DSUR	Development Safety Update Report
DT	Dispersible tablet
DTG	Dolutegravir
EFV	Efavirenz
EMA	European Medicines Agency
ERC	Endpoint Review Committee
EU	European Union
EUDRACT	European Union Drug Regulatory Agency Clinical Trial
EVG	Elvitegravir

Abbreviation	Expansion
EVI	Eviplera
FCT	Film-coated tablet
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HDL	High-Density Lipoproteins
HIV	Human Immunodeficiency Virus
HIV NAT	HIV Netherlands Australia Thailand Research Collaboration
HSR	Hypersensitive Reaction
IB	Investigator's Brochure
ICH GCP	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medical Product
IMPAACT	International Maternal Paediatric Adolescents AIDS Clinical Trials
INSTI	Integrase Strand Transfer Inhibitor
INSERM-ANRS	Institut National de la Santé et de la Recherche Médicale
INSERM-ANRS SC10-US019	Institut National de la Santé et de la Recherche Médicale Service Commun 10 – Unité de Services 019
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trial Number
LDL	Low-Density Lipoproteins
LPV/r	Lopinavir/ritonavir
MOP	Manual of Operations
MRC CTU	Medical Research Council Clinical Trials Unit at UCL (UK)
MUAC	Mid Upper Arm Circumference
NHS	National Health Service (UK)
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
QD	Once daily
QoL	Quality of Life Questionnaire
PENTA	Paediatric European Network for Treatment of AIDS
PHPT	Program for HIV Prevention and Treatment (Thailand)

Abbreviation	Expansion
PI	Protease Inhibitor
PIS	Patient information Sheet
PK	Pharmacokinetics
pMTCT	Prevention of Mother to Child Transmission
QA	Quality Assurance
QC	Quality Control
R&D	Research & Development
RAL	Raltegravir
RBC	Red blood cell
RPV	Rilpivirine
RTV or r	Ritonavir
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SOC	Standard Of Care (defined as the antiretroviral regimen routinely prescribed at a particular site for an ART-naïve or for an ART-experienced patient)
SPF	Summary of Product Characteristics
SSA	Sub-Saharan Africa
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAF	Tenofovir alafenamide
TAM	Thymidine Analogue resistance Mutation
TB	Tuberculosis
TDF	Tenofovir
TDM	Therapeutic Drug Monitoring
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
ULN	Upper Limit of Normality
VL	Viral Load
YTB	Youth Trial Board
ZDV	Zidovudine
3TC	Lamivudine

1 BACKGROUND

With the development of new antiretroviral drugs (ARVs), including new drug classes, which offer simplified, more potent options for first- and second-line therapy with fewer adverse effects in adults, there is a need to evaluate their place in paediatric HIV treatment.

Unique issues for HIV-infected children include: potential for perinatal transmission of viruses resistant to antiretroviral therapy (ART) regimens taken by mothers during pregnancy and breastfeeding; special consideration of adverse events as children take drugs during growth and development and will be on them for much longer than adults; and the need for age appropriate once daily formulations, preferably fixed dose scored dispersible combinations which may require different ratios of drugs from those used in adults.

Globally, more than 80% of HIV-infected children live in Sub Saharan Africa (SSA). Although there has been substantial improvement in ART coverage over the last few years, only half of children in need of treatment have access to ART [1, 2]. Rapid disease progression and high early mortality require that ART is started early in life and many children still die before they are diagnosed. Children <3 years in low/middle income countries are taking either non-nucleoside reverse transcriptase inhibitors (NNRTI)-based ART (e.g. most African countries, India, Eastern Europe) or ritonavir boosted protease inhibitor (bPI) lopinavir/ritonavir (LPV/r)-based ART (South Africa; some centres of excellence in SSA). Children >3 years in SSA, including South Africa, start NNRTI-based ART. In both well-resourced and resource-limited settings, there is a need for alternative first- and second-line regimens which can be given in the face of possible transmitted resistance (from prevention of mother to child transmission pMTCT) or resistance arising from first-line ART, whether PI or NNRTI based. New regimens need to be potent, durable, non-toxic and available in acceptable once daily formulations with correct drug ratios. Ideally regimens should be robust with a high barrier to resistance, have minimal cross-resistance and minimal interactions with anti-tuberculosis drugs.

Dolutegravir (DTG) is a second-generation integrase inhibitor (INSTI) with the advantage of once daily dosing, a good short-term safety profile, low pharmacokinetic variability, few drug-to-drug interactions, rapid and robust virological response with an optimised background treatment, a distinct resistance profile from raltegravir, a high genetic barrier to resistance and high potency at a low milligram dose. Combination regimens with DTG will therefore be attractive for children starting first-line ART and for those switching to second-line for reasons of toxicity or failure.

1.1 DTG ADULT TRIALS

There are encouraging efficacy and safety data from Phase II and III studies of DTG in adults [3-6] with reassuring safety data reported at 96 week endpoints [3, 4]. SPRING-2, SINGLE and FLAMINGO Phase III studies were conducted on treatment-naïve adults. SPRING-2 showed that DTG once daily (QD) is non-inferior to twice daily (BID) raltegravir in combination with ABC+3TC or TDF+FTC at 96 weeks, and superior in patients with VL >100,000 c/ml [4]. SINGLE compared DTG in combination with ABC+3TC to efavirenz (EFV) in combination with TDF+FTC. Results showed that the DTG combination is superior in efficacy and safety at 48 weeks and are consistent for patients with VL </>100,000 c/ml and CD4 count </>200 cells/mm^3 [6]. A subsequent analysis of bone marker changes at 48 weeks demonstrated that DTG+ABC+3TC was associated with significantly smaller changes compared to Atripla (EFV/TDF/FTC) indicating more active bone turnover in patients on Atripla, which may correlate with the known TDF-associated effect on bone mineral density over time [7, 8].
FLAMINGO, an open-label, non-inferiority trial compared DTG with darunavir (DRV) boosted with ritonavir (/r) plus investigator-selected TDF+FTC or ABC+3TC in previously untreated adults. The trial showed that DTG was superior to DRV/r at 48 and 96 weeks [9]. The difference was most pronounced

in participants with baseline viral load ≥100,000 c/ml. There was no treatment-emergent resistance to study drugs [9]. Patients randomised to DTG had better lipid profiles with significantly less grade 2 or above low-density lipoprotein cholesterol results (2% versus 7%, p<0.001).

A recently published systematic reviews and meta-analyses of ART regimens in adults compared virological efficacy (HIV-1 RNA <50 c/ml) at 48 and 96 weeks and CD4 change at 48 weeks of DTG-based ART and other recommended third agents for the first-line treatment . Results showed that DTG has a higher probability of virological suppression and better CD4 cell responses than most guideline recommended third agents (standard-dose EFV, atazanavir (ATV)/r, DRV/r and LPV/r) [10, 11] .
The studies in treatment-experienced adult patients also showed encouraging results. SAILING, a Phase III trial in treatment-experienced, INSTI-naïve patients, with at least two-class drug resistance, compared QD DTG- versus raltegravir-based ART combined with no more than 2 other agents, one of which was fully active: by 48 weeks, 71% vs. 64% patients reached undetectable viral load [12]. VIKING-3, a Phase II study of safety and efficacy of BID DTG in highly treatment-experienced patients with previous resistance to INSTI and 2 other classes (70% patients had mutations to PIs), showed that 69% reached undetectable viral load at 24 weeks and 56% at 48 weeks of treatment. Only 3% of patients discontinued treatment due to adverse events [13].

A single tablet of DTG + 3TC + ABC has been developed, providing an attractive option of a one-pill once daily regimen for older children >12 years. A PK study in healthy volunteers demonstrated that FDC DTG 50mg/ABC 600mg/3TC 300mg is bioequivalent to DTG alone in combination with ABC/3TC [14].

In order to inform the ODYSSEY design, an exploratory analysis of subjects receiving DTG plus 1-2 NRTIs in SAILING was conducted. None of the 32 subjects in the DTG arm, who received an NRTI-based background regimen, experienced protocol defined virological failure by week 48, including no cases of virological failure in 13 subjects receiving less than 2 fully active NRTIs by phenotype (12 received one fully active NRTI and 1 received two inactive NRTIs)[15]. Based on this exploratory analysis, DTG + 2 NRTIs appears to have good activity through 48 weeks in treatment-experienced patients when at least one of the NRTIs was fully active by phenotype. However, because of the small sample size, an increased risk of virological failure in subjects receiving DTG with less than 2 fully active NRTIs cannot be ruled out based on these data alone.

1.2 DTG IN CHILDREN

A paediatric dose-finding Phase I/II study IMPAACT P1093 is ongoing. The results are available for children 6 to 18 years of age. The study enrolled treatment-experienced children failing their regimen who were started on DTG with an optimized background regimen containing at least one fully active antiretroviral drug [16, 17] . In 23 children aged 12-18 years who received DTG 50 mg PK results were comparable to adults [17]. 48-week data showed that DTG was well tolerated with two patients experiencing grade 3 laboratory adverse events, which were evaluated as not related to DTG; 74% children (95% CI 52% to 90%) achieved viral load of <400 c/ml. There were no drug-related clinical adverse events, no grade 3 or 4 clinical events, and no serious adverse events. 48-week results of the PK, safety and virological efficacy study in 23 children 6 to 12 years of age were recently reported and showed adequate AUC_{24} and C_{24} with the dose of ~1 mg/kg [18]. Three subjects experienced grade 3 laboratory events all of which were unrelated to DTG. There were no grade 4 AEs, SAEs or study discontinuations secondary to AEs. The study in children less than 6 years of age down to 4 weeks of age is ongoing.

1.3 FIRST- AND SECOND-LINE ART OPTIONS FOR CHILDREN: THE PLACE OF DTG

DTG-based treatment with two NRTIs offers a potent regimen, with advantages of low toxicity, and the potential for once daily dosing. The rapid virological response observed following initiation of ART with DTG-based ART will be highly relevant for children with very high viral loads, which is commonly observed in younger children. DTG has high potency at a low milligram dose, and therefore it could be particularly attractive for young children in both well-resourced and resource-limited settings, who have limited options and may be more likely to be infected with resistant viruses through mother-to-child transmission (MTCT). A DTG-based first-line regimen is likely to be better tolerated and logistically advantageous for ART programmes currently using liquid LPV/r, as well as needing to be dosed once rather than twice daily.

The choice of NRTI backbone depends on the child's age, history of previous NRTI exposure (for ART experienced children) and drug availability in a country. The combination of abacavir (ABC) + lamivudine (3TC) is already frequently used as a preferred first-line nucleoside reverse transcriptase inhibitors (NRTI) 'backbone' and tenofovir disoproxil fumarate (TDF) + emtricitabine (FTC) or TDF + 3TC are increasingly being used in older children (TDF recently received regulatory approval by both Food and Drug Administration (FDA) and European Medicines Agency (EMA) for children >2 years of age). Furthermore, there are reasons to use ABC or TDF as part of a first-line regimen as resistance to both these drugs follows the same 'resistance pathway' and does not affect potency to zidovudine (ZDV) for second-line (and in fact may result in hyper-susceptibility to ZDV), whereas using ZDV in first-line typically results in accumulation of thymidine analogue resistance mutations (TAMs) which may limit second-line NRTI options. The WHO 2016 guidelines recommend ABC as part of preferred first-line ART in children 3 to <10 years and ABC or ZDV in children <3 years; if ZDV is used in first-line, then ABC + 3TC are recommended in second-line [19]. PK data from PENTA trials [20, 21] and most recently, 96-week viral load and clinical efficacy data as well as safety data from the paediatric ARROW trial, have shown that once daily dosing with ABC + 3TC is non-inferior to twice daily in terms of viral load suppression, safety and clinical efficacy [22] . Thus, with ABC + 3TC, DTG has the potential to be part of a potent, safe and simple fixed dose combination (FDC) for both first- and second-line ART in children.

DTG can be used as part of a second-line regimen in children failing first-line PI-based therapy; despite the presence of viral rebound for long periods, the NRTI backbone remains relatively protected in the presence of a boosted PI (bPI). No TAMs developed in children failing LPV/r-based first line ART in a large paediatric study (CHER) [23] and only 3/22 (14%) developed ≤2 TAMs and none developed >2 TAMs in the PENPACT1 trial [24] when switch was delayed until children had viral load (VL) >30,000 c/ml. Children failing NNRTI-based regimens developed TAMs more frequently. The PENPACT1 study showed that 3/20 (15%) children who were randomised to switch their first-line ART at VL of 1000 c/ml developed one TAM, whereas children randomised to switch at VL of 30,000 c/ml developed TAMs at higher rates: 9/22 (41%) developed ≥1 TAM, 5/22 (23%) ≥2 TAMs and 4/22 (18%) had 3 TAMs [24]. In small studies in Uganda nearly 10% of children developed a first TAM by 6 months of early virological failure on NNRTI-based regimen [25, 26] and 9% developed 2 TAMs by 12 months of virological failure [26]. ABC is expected to retain its potency in the presence of no more than two TAMs. Therefore, for children in resource-limited countries in whom ZDV has been used first-line and VL and resistance testing are not available, it might still be expected that ABC potency might not be unduly compromised when used with DTG (which itself has a high barrier to resistance) and that this regimen might have similar potency and greater acceptability compared with a bPI-based second-line regimen. Patients who are failing ABC + 3TC or stavudine (d4T) + 3TC containing first-line ART are at risk of accumulating the K65R mutation and thus susceptibility to ABC or TDF containing second-line ART may be reduced. Variable rates of acquiring the K65R mutation are reported in paediatric trials. In the PENPACT1 trial 1/14 children on ABC + 3TC developed the K65R mutation [24, 27]. A multi-centre study in sub-Saharan Africa found that K65R occurred in 3/20 (15%) and 13/47 (28%) adults

failing on d4T-or TDF-containing ART respectively, after 12 months of virological failure [27]. However, the majority of patients switching empirically to ZDV, ABC or TDF-containing ART would be expected to have at least 2 active drugs with a DTG-based regimen, and therefore to have an effective ART regimen. Supporting this, adult studies from Africa showed high rates of virological re-suppression with empirically prescribed and re-cycled second-line ART even when switching ART very late [27-30]. Of note, DTG can be used in liver and renal impairment without dose modification [14, 31].

1.4 DTG WITH ANTI-TUBERCULOSIS (TB) THERAPY

A PK study of co-administration of DTG with rifampicin in healthy adult volunteers showed that BID DTG overcomes the induction effect of rifampicin [32] and therefore can be used in HIV/TB co-infection. A recently reported study in HIV-infected adults with TB treated confirmed that increasing DTG dose to 50mg BID co-administered with rifampicin results in a similar DTG exposure to DTG 50mg QD without rifampicin [33]. The study showed DTG was effective and well-tolerated in HIV/TB co-infected adults receiving rifampicin-based TB treatment. It will be important to study the DTG PK in children on ART who require anti-TB treatment with rifampicin, as in many settings TB is common in HIV-infected children, even when on ART.

1.5 DTG AND PREGNANCY

Reproductive toxicology animal studies, including embryofetal development studies in rats and rabbits, showed no evidence of adverse developmental outcomes [34]

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 DTG-based regimens prior to pregnancy. The study reported 4 cases of NTD out of 426 infants in women who conceived on DTG (risk 0.9%), this compares to 14 out of 11,173 infants born to women receiving non-DTG-based regimens (risk 0.13%)[35]. In a further report including all data through to March 2019 there were 5 cases of NTD in 1683 deliveries where their mother was taking DTG at conception (0.3% of deliveries) (36), suggesting the increased risk is ~3-fold, lower than the 10-fold risk initially estimated.

There were no reported NTDs in infants of 1729 women in the TSEPAMO study who started DTG during pregnancy, including 280 women who initiated ART during the first trimester of pregnancy [37].

This study and other surveilance studies are ongoing and other reproductive studies on DTG safety have been initiated. More data on safety of DTG for women of childbearing age and their infants are expected in the next year.

Following the alert, it was communicated to the ODYSSEY sites that all female participants who are sexually active must use highly effective contraception (section 6.8; [38])).

1.6 DTG FORMULATIONS AND MARKETING AUTHORISATION

DTG is available as film-coated 10mg, 25mg and 50mg tablets and dispersible 5mg tablets and all formulations are provided by ViiV for the ODYSSEY trial. The dispersible tablets are approximately 1.6 times more bioavailable than the film-coated tablets and are currently being studied in DTG paediatric trials (ODYSSEY and IMPAACT P1093[38, 39]).

FDA and EMA have approved DTG 50mg QD for adolescents ≥40kg and DTG 35mg QD for children weighing 30 to <40kg, and EMA has approved DTG 25mg QD for children 20-<25kg and DTG 20mg QD for children ≥6 years weighing 15-<20kg. FDC (DTG+3TC+ABC) is approved in paediatric patients weighing ≥40kg by EMA and FDA. The dose finding and safety assessment study IMPAACT P1093 in younger children is ongoing.

1.7 RATIONALE AND OBJECTIVES

DTG is a new drug which offers the potential to be highly effective, safe and simple when used as part of first- or second-line ART regimens. Following adult Phase II/III trials, DTG needs evaluation to determine its place as first-line and second-line therapy in adolescent and paediatric HIV treatment.

Standard ART for children is a NNRTI or bPI, plus 2 NRTI and where possible fixed drug combinations (FDC) are preferred to support adherence. Concerns have been raised about the potency of NVP-based ART in infants [40], and EFV is not readily available for children <3 years. Neither EFV nor NVP are available in a 3-drug once-daily FDC for children <12 years of age. The most frequently used FDC in adolescents is EFV+TDF+FTC (or 3TC). With currently used doses, EFV may cause significant neuropsychological side effects [42]. The commonly available bPI for young children is LPV/r, an unpleasant tasting liquid requiring a cold chain. LPV/r tablets for children are relatively large and need to be swallowed whole or they lose bioavailability. Two other PIs, ATV and DRV, are available for older children in high-income countries but need to be boosted with ritonavir tablets. Adult US and European guidelines now recommend integrase inhibitors as part of first-line regimens. In contrast, INSTI are used infrequently in children: raltegravir-based ART is used in some clinics, generally for second-line, following treatment failure on LPV/r-based regimens and elvitegravir-based FDC has been recently introduced for adolescents in high-income countries, mostly for simplification. Finally, TDF, a preferred NRTI in adults and adolescents [19], has long-term renal and bone toxicity, and therefore concerns remain for its use in growing children.

DTG with two NRTIs will potentially offer a potent and safe regimen for both ART-naïve and ART-experienced children and is available as a FDC with ABC and 3TC for children >12 years.
No randomised trial has been undertaken comparing this new regimen with standard of care in children, who potentially have more to gain in terms of minimising long term HIV and ART complications, improving long-term adherence to medication and gaining better quality of life than adults.

ODYSSEY will be a pragmatic strategy trial evaluating the efficacy and safety of once daily DTG-based ART compared with standard of care in children and adolescents starting first- or second-line ART in resource-limited and well-resourced settings.

2 SELECTION OF SITES/CLINICIANS

The trial sponsor has overall responsibility for site and investigator selection.

2.1 SITE/INVESTIGATOR INCLUSION CRITERIA

Clinical sites invited to enrol children and young people in ODYSSEY will usually have previously collaborated in trials with the MRC CTU, INSERM-ANRS, PHPT or IMPAACT. In the case of a new site wishing to participate, the site will need to demonstrate sufficient resources to conduct clinical trial research with children and young people.

The principal investigator will sign an Investigator's Agreement for that institution on behalf of all staff at that site who will be working on the ODYSSEY trial. The principal investigator will sign to confirm that:

- The institution has an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- All staff assisting with the trial are adequately informed about the protocol, the investigational products and their trial-related duties.
- The trial will be conducted in accordance with the current protocol and changes will only be made when necessary to protect the safety, rights or welfare of participants.
- The trial will be conducted in compliance with the principles of ICH GCP and applicable regulatory requirements.
- The institution will permit monitoring and auditing by the relevant CTU and inspection by the appropriate regulatory authorities. Direct access will be made available to all trial-related sites, data/documents and reports.
- The institution will maintain an Investigator Site File (ISF), which will contain essential documents for the conduct of the trial.
- All trial data will be submitted in a timely manner and as described in the protocol.
- All Serious Adverse Events (SAEs) will be reported to the relevant CTU within 24 hours of the investigator becoming aware of the event. The initial SAE report shall be promptly followed by detailed follow up reports.
- All employees, students or agents engaged in the research shall maintain the confidentiality of information.
- No data on trial participants will be disclosed without the approval of the Trial Steering Committee (TSC).
- All trial-related documents will be retained for at least 15 years after the completion of the trial.

In addition to the points above and in compliance with the principles of ICH GCP, all institutions participating in the trial will complete a delegation log and forward this to the CTU. Each person working on the ODYSSEY trial must complete a section of this log and indicate their responsibilities as agreed with the principal investigator. The CTU must be immediately notified of any changes to trial personnel and/or their responsibilities. An up-to-date copy of this log must be stored in the ISF at the institution and also in the Trial Master File (TMF) at the CTU.

2.2 APPROVAL AND ACTIVATION

MRC CTU, INSERM-ANRS or PHPT staff will visit new sites prior to the trial commencing at that site in order to carry out a site and lab risk assessment and set-up visit. This visit should be attended by the

principal investigator at that site (the clinician), the clinic nurse(s), and representatives from the laboratory and pharmacy and any other staff who will be involved in the ODYSSEY trial. At the trial set-up visit the trial management staff should ensure that the following minimum criteria are met before the site enrols participants into the trial:

- The clinician should be experienced in the management of children/young people with HIV or work in close contact with a specialist HIV unit/site.
- Staff involved in the trial must have training in Good Clinical Practice (GCP).
- Pharmacy staff are able to keep detailed records of the trial medications prescribed.
- There exists good communication between all of the above departments.
- Laboratories have quality certification procedures, are enrolled with an EQA program and have the capacity to run the trial scheduled assays/store trial samples.

Training will be provided for all sites participating in ODYSSEY. Where sites have participated in previous PENTA trials, site initiation training may be conducted via web conferencing or similar. Training in the use of ABC will be included in the site initiation.

2.3 SITE MANAGEMENT

Sites in the United Kingdom are managed by the MRC CTU. Sites in Germany, South Africa, Thailand (HIV-NAT), Uganda, US and Zimbabwe are managed by the MRC CTU together with national co-ordinators and local monitors. This includes those sites in Uganda that are supported by IMPAACT. Sites in France are managed by INSERM-ANRS; sites in Argentina, Portugal and Spain are managed by INSERM-ANRS together with national co-ordinators and local monitors. PHPT sites in Thailand are managed directly by PHPT.

3 SELECTION OF PATIENTS

Participants will be selected by medical investigators at the participating sites, who should be aware of eligibility criteria in advance of screening participants for the trial.
Eligible participants (or carers, as appropriate) must:

- Be able to understand and comply with protocol requirements, instructions, and restrictions
- Be likely to complete the study as planned
- Be considered appropriate candidates for participation in an investigative clinical trial with oral medication

The eligibility criteria are the standards used to ensure that only medically appropriate participants are considered for this study. Participants 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 children and adolescents with HIV, it is important that no exceptions be made to these criteria for admission to the study.

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

3.1 PATIENT INCLUSION CRITERIA

3.1.1 ALL PATIENTS:

- Children ≥28 days and <18 years weighing ≥3kg with confirmed HIV-1 infection*
- Parents/carers and children, where applicable, give informed written consent
- Girls who have reached menses must have a negative pregnancy test at screening and randomisation and be willing to adhere to effective methods of contraception if sexually active
- Children with co-infections who need to start ART according to local/national guidelines
- Parents/carers and children, where applicable, willing to adhere to a minimum of 96 weeks' follow-up

*Children weighing 3 to <14kg must be eligible and willing to participate in the Weight band (WB)-PK1 substudy unless direct enrolment for the child's weight band has opened following the WB-PK1 substudy (see Section 5.3.1 and Appendix XIII) and/or dosing information has become available from the IMPAACT P1093 DTG dose-finding study.

3.1.2 ADDITIONAL CRITERIA FOR ODYSSEY A:

- Planning to start first-line ART

3.1.3 ADDITIONAL CRITERIA FOR ODYSSEY B:

- Planning to start second-line ART defined as either: (i) switch of at least 2 ART drugs due to treatment failure; or (ii) switch of only the third agent due to treatment failure where drug sensitivity tests show no mutations conferring NRTI resistance (see Section 5.2.2)
- Treated with only one previous ART regimen. Single drug substitutions for toxicity, simplification, changes in national guidelines or drug availability are allowed
- At least one NRTI with predicted preserved activity available for a background regimen

- In settings where resistance tests are routinely available, at least one active NRTI from TDF/TAF, ABC or ZDV should have preserved activity based on cumulative results of resistance tests (see Section 5.2.2)
- In settings where resistance tests are not routinely available, children who are due to switch according to national guidelines should have at least one new NRTI predicted to be available from TDF/TAF, ABC or ZDV (see Section 5.2.2)
- Viral load ≥500 c/ml at screening visit or within 4 weeks prior to screening

See Section 3.3 for additional considerations for inclusion in the study depending on NRTI backbone.

3.2 PATIENT EXCLUSION CRITERIA

- History or presence of known allergy or contraindications to DTG
- History or presence of known allergy or contraindications to proposed available NRTI backbone or proposed available SOC third agent.
- Alanine aminotransferase (ALT) ≥5 times the upper limit of normal (ULN), OR ALT ≥3xULN and bilirubin ≥2xULN
- 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), known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
- Anticipated need for Hepatitis C virus (HCV) therapy during the study
- Pregnancy or breastfeeding
- Evidence of lack of susceptibility to integrase inhibitors or more than a 2-week exposure to antiretrovirals of this class

3.3 CONSIDERATIONS FOR USE OF DIFFERENT NRTI

3.3.1 ABC-CONTAINING PRODUCTS

*HLA-B*5701 testing*

In countries where HLA-B*5701 screening is considered standard of care and HLA-B*5701 status is unknown (even if the subject has previously tolerated ABC), investigators must test for HLA-B*5701 and the results of the test must be received prior to starting ABC. Children who are HLA-B*5701 positive must not be given ABC.

In countries where HLA-B*5701 screening is not considered standard of care, investigators must obtain a complete history of previous exposure to ABC-containing products. In cases requiring discontinuation of abacavir, they should evaluate for the possibility of a clinically suspected hypersensitivity reaction (HSR). If the possibility of a HSR cannot be ruled out then treatment with any ABC-containing product should not be started, due to the risk for a potential life-threatening and sometimes fatal re-challenge reaction. Where participants have previously tolerated treatment with ABC, restarting ABC treatment as part of this study must be done in a setting where medical assistance is readily available.

The use of ABC-containing products in participants should be in accordance with the corresponding local product information.

3TC-, FTC- and TDF/TAF-containing products

HBV-co-infected patients

Patients known to have chronic HBV infection (HBsAg positive OR anti-HBc positive with HBV DNA present) should be treated with TDF ideally in combination with either 3TC or FTC. Monotherapy with either 3TC or FTC for treatment of HBV is not recommended, and 3TC should not be used in combination with FTC. In young patients for whom TDF is not available, consideration should be given to use of 3TC- or FTC-sparing regimens to avoid development of 3TC or FTC resistance in HBV.

Some participants with chronic HBV disease may experience clinical or laboratory evidence of recurrent hepatitis upon discontinuation of 3TC, FTC or TDF/TAF. If 3TC, FTC or TDF/TAF is discontinued in participants co-infected with HBV, periodic monitoring of liver chemistry tests should be considered.

Renal impairment

The use of TDF is not recommended in children with renal impairment. TDF should be discontinued in children who develop renal impairment on TDF therapy.

In patients with moderate-severe renal impairment and creatinine clearance <50 ml/min, the dose of 3TC or FTC should be adjusted in accordance with the local product information.

ZDV-containing products

Patients with either of the following haematology results at screening should not receive ZDV-containing products:

- Haemoglobin (Hb) concentration <7.5 g/dL or 4.65 mmol/L
- Absolute neutrophil count <500/mm^3 or 0.5 x 10^9/L

Alternative causes for anaemia and/or neutropenia, such as concurrent bacterial, mycobacterial or fungal infection, malaria, helminthiasis, malignancy and/or malnutrition should be investigated. ZDV should be substituted with an alternative NRTI if alternative causes for anaemia and/or neutropenia cannot be identified.

3.4 NUMBER OF PATIENTS

A minimum of 700 children will be enrolled into the main trial over 96-120 weeks. This will include ≥310 children starting first-line (ODYSSEY A) and ≥390 children starting second-line ART (ODYSSEY B). Children will be recruited from clinical centres in Africa, Europe, Asia, North and South America.

All children randomised into ODYSSEY weighing ≥14kg will contribute to the target numbers of 310 in ODYSSEY A and 390 in ODYSSEY B.

In addition, over a period of up to 78 weeks (July 2018 to end of 2019) we will recruit a minimum of 20 children in each of the 3 lower weight bands (3-6kg, 6-10kg, 10-14kg; total ≥60 children).

3.5 CO-ENROLMENT GUIDELINES

Co-enrolment in previous or future trials is considered in Section 4.2.

3.6 SCREENING PROCEDURES & PRE-RANDOMISATION INVESTIGATIONS

3.6.1 SCREENING VISIT

At screening, parents/carers of HIV-infected children and adolescents will be given an information sheet about the ODYSSEY trial and asked to give written consent before any trial-specific procedures are performed or any blood is taken for the trial (see Appendices I - II).
Signed consent forms must be kept by the investigator in the ISF, a copy in the child's clinical records and a copy given to the participant or family.

At this visit the patient will be allocated a Trial Number and an anonymous code taken from a sequential list included in the ISF.

Screening procedures will include a clinical assessment, T cell lymphocyte subsets (including total lymphocytes, CD4, CD8), haematology, biochemistry (see Trial Assessment Schedule, page x) and plasma/cell storage. Stored samples will be discarded if the patient is not randomised into the study; HIV-1 RNA viral load is required for ODYSSEY B at screening or within 4 weeks prior to screening. Girls who have started menses will be given information about the risks of pregnancy in the trial and advised on how to avoid pregnancy. A pregnancy test will be performed at screening in girls who have started menses. Any female participant found to be pregnant will not be eligible for the trial.

For children being screened for ODYSSEY B, i.e. children requiring a switch to second-line ART, the parent/carer, or any young person who administers their own medication, should complete an adherence questionnaire (See Appendix IV).

As soon as the results are received and eligibility has been confirmed, the Screening Form with confirmation of eligibility and receipt of informed consent, clinical history and assessment, haematology, biochemistry, previous immunology and virology should be entered on the trial database or sent to the appropriate CTU. Eligibility for the study will be confirmed and the randomisation visit should be scheduled within 4 weeks after the screening visit.

4 REGISTRATION & RANDOMISATION

Randomisation should take place within 4 weeks after the screening visit, ideally within 2 weeks.

The participant's eligibility for enrolment will be confirmed, including the results of screening laboratory tests. Participants or carers must confirm that they have read the relevant patient information sheets (see Appendix I). Continued agreement to enter in the trial must be confirmed from parents/carers after explanation of the aims, methods, benefits and potential hazards (see Appendix II). Older children should give assent to trial participation if they know their HIV status. Signed consent forms must be kept by the investigator and documented in the CRF, a copy stored in the clinical records and a copy given to the participant or family. It must be made completely and unambiguously clear that the participant (or parent/carer 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 compromising the care of the child.

The randomisation process will be securely embedded within the database, a web-based system controlled through an authorised user name and password. Selected sites will be able to randomise patients directly. An option to fax the Randomisation Form to the appropriate CTU, who will perform the randomisation, will also be available. Patients will be randomised to DTG or SOC arms in a 1:1 ratio (see Section 4.1 below).

Enrolment assessments will be performed as summarised in the Trial Assessment Schedule. Blood should be taken for plasma storage. Cells will be stored in selected sites with this capacity. A repeat pregnancy test should be performed in girls who have started menses. Any female participant found to be pregnant will not be eligible for the trial. The questions relating to sleep and mood on the Acceptability, Sleep and Mood Questionnaire should be completed at the enrolment visit.

The clinician should complete the Enrolment Form and send to the appropriate CTU once all the laboratory results are available, or enter the CRF data directly onto the secure web-based trial database.

A clinic visit should be scheduled for 4 weeks after the week 0 visit (week 4 visit). At the sites where children are routinely seen at 2 weeks after the start of new ART, this can be included as an additional visit and procedures undertaken as per the Trial Assessment Schedule.

4.1 RANDOMISATION PRACTICALITIES

The participant (child) and carer should be physically present together with a study clinician at the time of randomisation.

To randomise a participant, the information contained on a completed Randomisation Form will be entered into the online trial database accessible from the CTU (or the clinical site if appropriate) to automatically check for eligibility. Only those with completed and verified screening forms on the database will be able to be randomised. The details of the participant's treatment allocation and trial number will be notified to clinical staff.

If a centre's internet connection to the database is unavailable at the time of randomisation, the participant's details can be provided to staff at the relevant CTU by fax or by telephone. At the CTU, staff will verify eligibility and perform the randomisation using the online system. The details of the

participant's treatment allocation and trial number will be notified to the trial team at the site by fax or phone, with follow-up confirmation.

The clinician should complete a prescription with the participant's details and ART regimen as allocated. The pharmacist or pharmacy technician should ensure that the participant and/or carers know how to take/administer the different drugs before they leave the clinic.

RANDOMISATIONS THROUGH A CTU

To randomise fax or send by password protected email the Randomisation CRF to the relevant CTU:

- **MRC CTU**, UK, Monday to Friday 9:00 AM to 17:00
  Tel: +44 (0) 20 7670 4786
  Fax: +44 (0) 20 7670 4814
  Email: mrcctu.trial-odyssey@ucl.ac.uk

- **Inserm-ANRS**, France, Monday to Friday 9:00 AM to 17:00
  Tel: + 33 1 45 59 50 83 / 52 55
  Fax: + 33 1 46 58 72 93
  Email: penta.sc10@inserm.fr

- **PHPT**, Thailand, Monday to Friday 9:00 AM to 18:00
  Tel: +66 (0) 53 814 633 ext 710
  Fax: +66 53 814 269
  Email: kanchana.than-in-at@phpt.org

For those sites randomising directly, training will be provided as part of the site initiation and database training. Individual passwords will be provided.

ENROLMENT OF MULTIPLE PARTICIPANTS FROM THE SAME FAMILY/HOUSEHOLD INTO THE TRIAL

If more than one child from a family/household is to be enrolled at the same time and in the same stratum (ODYSSEY A or ODYSSEY B) they will be allocated to the same arm to facilitate their care (please refer to Manual of Operations).

4.2 CO-ENROLMENT GUIDELINES

Co-enrolment in compatible studies is allowed by the protocol but must first be approved by the CTU with previous discussion within the TMG. Centres should also adhere to local guidelines concerning co-enrolment in other trials.

5 TREATMENT OF PATIENTS

5.1 GENERAL INFORMATION

Participants will be enrolled in two different strata depending on their previous ART experience:

- ODYSSEY A: children starting first-line ART
- ODYSSEY B: children starting second-line ART.

Within each stratum, children will be randomised 1:1 to either DTG-based ART (DTG arm) or standard of care (bPI-, or NNRTI- or INSTI-based ART; SOC arm).

DTG (including Triumeq, as appropriate) will be provided by ViiV for the duration of the randomised phase of the ODYSSEY trial. Triumeq will only be supplied in countries where it is licensed. At sites where generic DTG-containing FDCs are available through the national programme it may be preferred for participants in the DTG arm to be on a once-daily, one-pill regimen, rather than taking DTG supplied by ViiV as a separate tablet, in order to aid adherence, but this must not lead to a change to the NRTI backbone. If the DTG-containing FDC is to be dispensed from a general clinic/Department of Health pharmacy rather than the clinical trial pharmacy it must be ensured that all necessary local requirements are met and approvals are in place for the pharmacy to do so. All cases where this may apply should be discussed with MRC CTU at UCL prior to switching the participant.

For sites outside Europe, the following NRTIs will also be provided by ViiV where required for the duration of the ODYSSEY trial: ABC, 3TC, Kivexa and Combivir. After the end of the randomised phase of the trial, DTG will be provided by ViiV for those children randomised to the DTG arm at the discretion of their clinician until it is available and recommended for children in their country of residence. For sites in sub-Saharan Africa the Mylan formulation of ABC/3TC 120/60mg will be provided for the duration of the randomised phase, if required.

All carers of children starting ABC will receive warning cards and additional information about this drug. In the countries where HLA-B*5701 testing is routinely performed, the test results should be received prior to starting ABC. Children who are HLA-B*5701 positive should not be given ABC.

The NRTI choice in children who are starting second-line ART will depend on the history of previously used NRTIs and the resistance profile, if performed. The decision will be made by the treating clinician

The following should be considered:

1. In countries, where resistance tests are routinely performed, at least one active NRTI from TDF/TAF, ABC or ZDV should be chosen based on all resistance test results in the child (historic and recent). The interpretation of the mutations should be based on the up-to-date version of the Stanford HIV Drug Resistance Database (http://hivdb.stanford.edu/). If the child has been on ZDV or D4T first-line, and ABC or TDF/TAF are in the planned SOC for second-line, then no more than two TAMs or one TAM + M184V are allowed. If the chosen regimen contains ABC or TDF/TAF, no presence (historic or recent) of K65R mutation is allowed.

2. In countries where resistance tests are not routinely performed, clinicians should follow national/WHO Guidelines. At least one new NRTI with presumed preserved activity (from ABC, TDF or ZDV) should be chosen.

The planned SOC regimen to be used if randomised to SOC should be recorded on the screening and randomisation CRFs. Treatment should start on the day of randomisation or the following morning.

Treatment will be open-label and will be dispensed at randomisation for 4 weeks and then at maximum 12 weekly intervals. Where drug has been supplied for the trial, it will be stored separately from routine clinic drug supplies in a designated section at the study site.

5.1.1 NRTI BACKBONE CHANGE DURING FOLLOW UP

The proposed NRTI backbone for all participants should be chosen following the considerations in sections 3.1 to 3.3 and 5.2 to 5.3. Participants must be prescribed the NRTI backbone that was chosen prior to randomisation irrespective of the randomised allocation as randomisation is stratified by NRTI backbone.

Additionally participants should remain on the same backbone throughout the duration of the trial unless substituting for toxicity, intolerance or switching for treatment failure. Change of NRTI backbone for simplification while in the trial should be avoided, if possible. In cases where the clinician thinks that this should be done in the patient's best interest, this should be discussed with the relevant CTU and/or TMG.

Upon completion of the randomised phase of the trial clinicians are free to change NRTI backbone as per international/national treatment guidelines.

5.2 SOC ARM

All participants in the SOC arm will receive ART including either an NNRTI (e.g. NVP, EFV or RPV), a bPI (e.g. LPV/r, ATV/r, ATV/c, DRV/r, DRV/c) or an INSTI other than DTG (e.g. RAL, EVG/c), plus 2 (or 3 (ODYSSEY A only)) NRTIs following international (WHO, PENTA, US), national or local recommendations for first- or second-line therapy. See Tables 1 and 2 below for commonly used first- and second-line options for standard of care. The exact choice of antiretrovirals will be made by the treating clinician, but should take into account what is being used in national programmes, as this will ensure that participants can stay on the same regimens long-term. Inclusion of different regimens in the trial increases generalisability, and will form a pre-planned subgroup analysis population.

Participants randomised to SOC must be prescribed the class of non-NRTI drug that was chosen prior to randomisation as randomisation is stratified by bPI vs. non-bPI. The doses of antiretrovirals should be in accordance to those recommended in the product information or according to international (WHO, PENTA, US)/national guidelines as appropriate for the country. Doses should be recalculated at every visit (until the adult dose is reached).

See Section 3.3 for additional considerations that investigators should take into account before selecting and initiating the NRTI backbone.

5.2.1 SOC ODYSSEY A

SOC first-line ART varies across the sites and countries in ODYSSEY. See Table 1 for commonly used first-line ART options. D4T or ddI may still be an option for young children in whom ZDV and ABC are contraindicated and if these NRTIs are included in the national guidelines.

Table 1. ART in ODYSSEY A (First-line treatment)

Population		Examples of first-line ART regimens for SOC		
		NNRTI + 2or3 NRTI	bPI + 2NRTI	INSTI +2NRTI
Children <3 years	WHO 2016§ preferred first-line		**LPV/r + ABC(or ZDV) + 3TC**	
	Other first line options	NVP + ABC(or ZDV) + 3TC		RAL+ ABC(or ZDV) + 3TC
		NVP + ZDV + ABC + 3TC*		
Children 3 to <10 years	WHO 2016§ preferred first-line	**EFV + ABC + 3TC**		
	Other first line options	NVP + ABC + 3TC	LPV/r + ABC+ 3TC	RAL + ABC +3TC
		EFV(or NVP) + ZDV +3TC	ATV/r + ABC + 3TC	RAL + ZDV +3TC
		EFV(or NVP) + TDF + 3TC(or FTC)	LPV/r (or ATV/r) + ZDV + 3TC	
Adolescents	WHO 2016§ preferred first-line	**EFV + TDF + 3TC(or FTC)**		
	Other first-line options	EFV + ABC + 3TC(or FTC)	ATV/r (ATV/c or DRV/r or DRV/c) + TDF(TAF or ABC) + 3TC(or FTC)	EVG/c+TDF (or TAF)+FTC
		EFV(or NVP) + ZDV + 3TC	ATV/r(ATV/c or DRV/r or DRV/c) + ZDV + 3TC	RAL + ABC +3TC
		NVP + TDF(TAF or ABC) + 3TC(or FTC)	LPV/r + TDF(TAF or ABC) + 3TC(or FTC)	RAL + ZDV +3TC
		RPV + TDF(TAFor ABC) + 3TC(or FTC)	LPV/r + ZDV +3TC	

§ World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. June 2016. Available: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1

*For infants and children aged less than 3 years, at the sites where this regimen is routinely used

5.2.2 SOC ODYSSEY B

For all children failing their first-line regimen, adherence issues should be addressed prior to switching to second-line as per standard practice in the clinic. Children and adolescents are eligible for enrolment once their clinician decides to switch them to second-line. Once daily regimens should be considered where possible to sustain adherence.

The choice of second-line ART will be based on international (WHO, PENTA, US) or national guidelines. See Table 2 for possible second-line ART options.

Table 2. ART in ODYSSEY B (Second-line treatment)

Population	Examples of sequencing of ART regimens following treatment failure on first-line for SOC		
	Failed first-line ⇨	WHO 2016§ preferred second-line	Other second-line options
Children <3 years	NVP + 2NRTI	LPV/r + 2NRTI*	RAL + 2NRTI*
	LPV/r + 2NRTI	RAL + 2NRTI*	NVP + 2NRTI*
Children 3 to <10 years	EFV(or NVP) + 2NRTI	LPV/r + 2NRTI*	DRV/r(or ATV/r) + 2NRTI*
	LPV/r + 2NRTI	EFV + 2NRTI*	RAL + 2NRTI* or DRV/r(or ATV/r) + 2NRTI*
Adolescents	EFV(or NVP) + 2NRTI	ATV/r (or LPV/r) + 2NRTI*	DRV/r (or DRV/c) + 2NRTI* or EVG/c +TAF + FTC
	LPV/r + 2NRTI	-	RAL + 2NRTI* or DRV/r(or DRV/c) + 2NRTI* or ATV/r(or ATV/c)+2NRTI* or EFV (orNVP or RPV) + 2NRTI* or EVG/c +TDF(or TAF) + FTC

§ World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach – 2nd ed. June 2016. Available: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1

*NRTI for second-line - at least one NRTI with preserved activity (measured by resistance tests or presumed from the history of previous ART) from ABC, TDF/TAF or ZDV. Didanosine or d4T may be used in second-line where no other drugs are available.

In countries, where resistance tests are routinely performed, the cumulative results of all resistance tests should be taken into account. Resistance tests give the most reliable results when collected while the patient is still taking the failing regimen or within 4 weeks of stopping the drugs. If the tests are taken without drug pressure, they may give false negative results (show no resistance mutations) and should not be relied on when choosing the second-line ART.

In general, children with treatment failure on an NNRTI-based regimen are switched to a bPI-based regimen. Children experiencing treatment failure on bPI-based ART may be switched to a more potent bPI (for example change of LPV/r to DRV/r in children >3 years) or to an NNRTI-based or INSTI-based regimen if adherence can be assured.

5.3 DTG ARM

Children randomised to the DTG-containing regimen (DTG-arm) will receive DTG plus 2 NRTIs, with at least one NRTI having preserved activity. The choice of NRTI will be at the clinician's discretion and depend on guidelines and drug availability (See Section 5.2 above on choice of NRTI backbone for the first and second-line ART in the participating sites).

For children starting second-line ART, the same considerations should be given to addressing adherence, as outlined in the previous section (Section 5.2.2).

Options for drug regimens for ODYSSEY A:

- DTG + ABC + 3TC
- DTG + ZDV + 3TC
- DTG + TDF + 3TC (or FTC)
- DTG + TAF +3TC (or FTC)

Options for drug regimens for ODYSSEY B:

- DTG + 2 NRTI

At least one of the NRTIs from ZDV, ABC, TDF (or TAF) should have preserved activity (measured by resistance tests or presumed from the history of previous ART). D4T or ddi may be used where the listed NRTIs are contraindicated or not available.

5.3.1 DTG

Dosing will be once daily according to weight bands (Table 3). The dose should be adjusted accordingly for a child who moves weight band. Children 3 - <14kg are enrolled via the Lower Weight Band PK (WB-PK) substudy (Appendix XIII) until the doses are confirmed acceptable and safe.

On the basis of WB-PK1 part I [43] and WB-PK1 part II [44] results (see Appendix XIII), reviewed by the IDMC, TMT, TMG and TSC, the TSC made a recommendation that all children ≥20kg should be changed to DTG 50mg FCT. Patients 14-<20kg who participated in PK substudies on 25mg DT should continue on the same dose. Participants on 30mg DT who remain in the same weight band should complete 24-weeks follow-up before moving to DTG 50mg FCT.

Following the review of the results of the ongoing PK substudies, other DTG doses and formulations may be studied with accompanying PK as appropriate.

Based on ODYSSEY WB-PK2 results [45] (see Appendix XIII), reviewed by IDMC, TMT<TMG and TSC, the TSC recommended that children in the weight bands 25 - <40kg previously receiving DTG 25mg (<30kg) or 35mg (30 - <40kg) should be changed to DTG 50mg QD (film-coated tablet).

Table 3: Dolutegravir dosing in ODYSSEY

WHO Wt bands, kg	**Once daily DTG dose and formulations in ODYSSEY**	
	5mg, Dispersible tablet	50mg, Film-coated tablet
3-<6 ψ	1 (5mg) / 2 (10mg)*	
6-<10	3 (15mg)*	
10-<14	4 (20mg)*	
14-<20	5 (25mg)§	
20-<25	-	1 (50mg)¥
25-<35	-	1 (50mg)
≥35	-	1 (50mg)

ψ Infants <6 months of age should receive DTG 5mg QD while infants ≥6 months of age should receive DTG 10mg QD, both as dispersible tablets.

* Children 3-<14kg will be recruited at WB-PK sites and must be willing to go into the PK substudy if randomised to DTG (Lower WB-PK1 substudy); first children 6-<14kg will be recruited aged ≥6 months (Appendix XIII). The dose may be modified based on data from the ongoing P1093 study and the data from this study.
§ Children 14-<20kg previously receiving either DTG 20mg QD as two 10mg film-coated tablets or DTG 25mg QD as one film-coated tablet will be changed to DTG 25mg QD given as five 5mg dispersible tablets.
¥ Children 20-<25kg previously receiving DTG 25mg QD as one 25mg film-coated tablet were initially changed to either DTG 30mg QD (six 5mg dispersible tablets) or DTG 50mg QD (one 50mg film-coated tablet) depending on site. From protocol v5.0, all children 20-<25kg should receive DTG 50mg QD as one film-coated tablet. Those who prefer to remain on DTG 30mg DT will be able to do so until they move weight band.

Children weighing 3 to <14kg

Children 3-<14kg will be recruited at PK sites and must be willing to go into the initial PK substudy if randomised to DTG (Appendix XIII).

Children weighing 3-<6kg randomised to the DTG arm will receive DTG 5mg or 10mg depending on age (<6 months and ≥6 months of age, respectively) as dispersible tablets QD. Children 6-<10kg and 10-<14kg receive 15mg and 20mg QD as dispersible tablets respectively (Table 3). The dose rationale for dosing in these weight bands is provided in Appendix XIII. These doses (with the exception of the 5mg DT dose for children <6 months of age and between 3-<6kg) are better aligned to the planned paediatric Triumeq dispersible tablet (DTG/ABC/3TC 5/60/30) which is under development as one of the future mid-priority paediatric formulations recommended by WHO-led Paediatric Antiretroviral Drug Optimization (PADO) group [46].

Based on available PK and safety data from ODYSSEY and/or P1093 (36), doses in ODYSSEY in the 3 lowest weight bands will be reviewed and may be modified (with further PK and safety data if required) leading to a decision on the appropriate DTG dose for children in these weight bands. (Appendix XIII).

Children weighing 14 to <20kg

Children in the 14 - <20kg weight band previously receiving either DTG 20mg QD (two 10mg film-coated tablets) or DTG 25mg QD (one 25mg film-coated tablet) will be changed to DTG 25mg QD (five 5mg dispersible tablets; see rationale in Appendix XIII).

Children weighing 20 to <25kg

Children weighing 20 to <25kg previously receiving DTG 25mg QD as one 25mg film-coated tablet were initially changed to either DTG 30mg QD (six 5mg dispersible tablets) or DTG 50mg QD (one 50mg film-coated tablet) depending on site (Appendix XIII). Following the review of PK and safety data from WB-PK1 part II, all children 20-<25kg will now receive DTG 50mg QD as one film-coated tablet. Those who prefer to remain on DTG 30mg DT will be able to do so until they move weight band.

Children weighing 25 to <40kg

Following the review of PK and safety data from WB-PK2 (Appendix XIII), all children 25-<40kg will now receive DTG 50mg QD as one film-coated tablet or as part of a fixed dose combination.

Children weighing ≥40 kg

Children in this weight band receive DTG 50mg film-coated tablet QD.

In countries where a paediatric licensed DTG dose for a particular weight band differs from the doses to be used in ODYSSEY, the DTG dosing to be used at the site should be discussed with the lead CTU.

5.3.2 FIXED DOSE COMBINATION OF DTG, ABC AND 3TC

For all children above 12 years (≥40 kg), whether ART-naïve or ART-experienced (with chosen NRTI backbone ABC + 3TC), a three drug fixed dose combination (FDC) tablet containing DTG 50 mg + ABC 600 mg + 3TC 300 mg (Triumeq) can be provided.

Following the analysis of WB-PK2 results for children weighing 25-<40kg which were reviewed by ODYSSEY and ViiV experts and the IDMC, and considered acceptable, children ≥25kg on DTG and ABC+3TC in the main trial are able to move to FDC (DTG 50mg + ABC 600 mg + 3TC 300mg) QD provided they are able to swallow the large tablet.

5.4 DISPENSING

For all trial drugs, the designated trial pharmacist or nurse will confirm receipt of supplies prior to the commencement of the trial. Inventories will be conducted regularly, and logs returned to the appropriate CTU.

All drugs dispensed to participants will be recorded on a dispensing log or logged online. At each site, a named person (trial pharmacist or research nurse) must maintain complete records of all medication dispensed and returned.

Throughout the treatment period, carers will be provided with a supply of drugs sufficient to last until the next clinic visit and will be requested to return all empty container packs and to bring any container packs 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 trial drug must be returned to the site if a participant withdraws from treatment.

5.5 ART MODIFICATIONS, INTERRUPTIONS & DISCONTINUATIONS

5.5.1 GENERAL CONSIDERATIONS ON CHANGES OF ARVS DURING THE TRIAL

For both arms, should the study clinician believe ART should be interrupted, discontinued, or that a change in treatment is necessary, then the relevant CTU should be notified.

Switching of the current ART regimen in the randomised phase should only occur if there is immunological, virological or clinical treatment failure (according to local clinical practice), at which point a new regimen should be chosen. Resistance tests or Therapeutic Drug Monitoring (TDM) may be used to inform change of regimen, according to local clinical practice. In exceptional circumstances where standard-of-care third-line is not available at site, and with prior agreement from the relevant CTU and the Trial Management Group, study drug may be used as third-line for children in the SOC arm who have failed second-line treatment. If simplification of the ART regimen in the randomised phase is deemed necessary for clinical reasons during follow-up, this may be allowed, but must first be discussed with the appropriate CTU. In the extended follow-up phase simplification is allowed and could be done as per routine practice.

If a female participant on DTG-based regimen is identified as pregnant within the first 8 weeks after their last menstrual period, the site clinician should discuss the risks and benefits of their current regimen. If there are other good options to replace DTG, then switching to a non-DTG ART regimen is recommended.

Toxicity will be managed according to standard clinical practice. Blood tests additional to those described in the trial schedule may be requested for clinical management of the participant. Wherever possible and appropriate, side effects will initially be managed by symptomatic measures and administration of appropriate (non-contraindicated) medication. Interruption or substitution of drugs should be avoided except in the event of grade 3 or 4 toxicity that is considered at least possibly related to one or more of the ARVs. Wherever possible, an alternative ARV should be substituted from the same class in order to maintain the participant's randomised treatment strategy.

Management of adverse events/toxicity should generally follow the criteria below, but clinicians should use their clinical judgment as to the best management for an individual participant. If in doubt, contact the relevant CTU to obtain advice.

NOTE: In the event of a discontinuation of an ABC-containing product for any reason (aside from possible hypersensitivity), re-initiation of this drug should be undertaken with caution. The investigator must obtain a complete history of the events surrounding the discontinuation of the ABC-containing product and evaluate for the possibility of a clinically suspected hypersensitivity reaction (HSR) to ABC. Regardless of a subject's HLA-B*5701 status, if a hypersensitivity reaction cannot be excluded, then ABC must not be restarted.

Grade 1 and 2

- Continue ARVs
- Manage using symptomatic measures and other concomitant medication, if appropriate

Raised serum aminotransferase ≥3xULN *and* total serum bilirubin level ≥2xULN (or coagulopathy (INR >1.5) without hyperbilirubinemia) may indicate idiosyncratic drug induced liver injury [47] and recommendations for Grade 3 or 4 toxicity events as outlined below should be followed.

Grade 3 or 4:

- Request laboratory results and repeat confirmatory laboratory results within 72 hours if relevant
- Continue study drugs pending receipt of the confirmatory laboratory tests/repeat observations, unless there is an immediate need to substitute ART
- Continue to work-up to exclude other causes
- Following confirmation of toxicity, and lack of other cause data:
    - if the child is not too sick, substitute ART immediately
    - otherwise, stop all drugs and restart with substituted drugs when the child has improved
    - stagger stop NNRTI wherever possible to avoid functional monotherapy and risk of resistance (as per PENTA/national guidelines)

5.5.2 ADVERSE REACTIONS & DISCONTINUATIONS OF DTG

5.5.2.A Liver toxicity

Stopping criteria based on liver function test thresholds have been designed to assure participant safety during administration of the medication and the follow-up period. It may be necessary to substitute DTG should any of the following criteria be met:

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

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

Participants who develop ALT ≥5xULN should be followed weekly until resolution or stabilization (ALT <5xULN on 2 consecutive evaluations).

When liver chemistry stopping criteria are met, investigator must:

- Notify the relevant CTU of the event by e-mail within 24 hours of its occurrence and report the event on the Event form (see 7.1.5.A). Additional information will then be requested from the sites.
- Discontinue DTG and substitute for an appropriate alternative (the child will continue follow up in the study). If an alternative cause of the raised liver enzymes is more likely (e.g. Hepatitis A, anti-TB treatment) then the investigator must contact the MRC CTU.

If DTG is discontinued for liver toxicity, participants should not restart DTG due to the risk of a recurrent reaction. If an alternative cause of the raised liver enzymes is more likely, restarting of DTG may be permitted but the investigator must have discussed and agreed this with the MRC CTU.

5.5.2.B Allergic reaction or rash

Participants may continue DTG for grade 1 or 2 allergic reactions or rash at the discretion of the investigator. Consideration should be made as to whether another ARV or another drug maybe 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 DTG should permanently discontinue DTG and substitute with an appropriate alternative; the participant will remain in the study. Investigators should contact the CTU to discuss cases if there is any uncertainty about the course of action. Participants should be treated as clinically appropriate and follow-up of the AE should be reported on CRFs as appropriate.

Participants receiving an ABC-containing product should be evaluated for the possibility of a clinically suspected HSR and managed appropriately as outlined in the local product information, regardless of a subject's HLA-B*5701 status.

5.5.2.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 infrequently reported with the use of several antiretroviral drugs, including efavirenz, darunavir, atazanavir and integrase inhibitors. Suicidal ideation has also been associated with efavirenz and integrase inhibitors, primarily in patients with pre-existing depression or psychiatric conditions.
Therefore, participants in both arms in ODYSSEY should be monitored appropriately for suicidal ideation and behaviour or any other unusual changes in behaviour. It is recommended that the subjects who experience signs of suicidal ideation or behaviour have prompt clinical evaluation and the investigator considers mental health consultation or referral and discontinuation of the corresponding drugs. See section 7.1.5 C for reporting of these events.

5.6 ACCOUNTABILITY & UNUSED DRUGS/DEVICES

Procedures for drug shipping, labelling, resupply, accountability and destruction will be detailed in the ODYSSEY Pharmacy MOP. Drug accountability will be regularly monitored and the remaining stocks checked against the amounts dispensed.

5.7 ADHERENCE & ACCEPTABILITY

Adherence to ART will be assessed by pill counts and short adherence questions at study visits (see Appendix IV). The importance of adherence should be reinforced at each visit. Non-adherence should prompt the study clinician to identify and address the cause(s) (e.g. side effects, social challenges).
An acceptability, sleep and mood questionnaire at enrolment and at weeks 4, 12, 24, 48, 72, 96 and then 24 weekly until the end of study, will elicit participant opinions about the different regimens, particularly with regard to pill burden; complexity and stigma (see Appendices V-VI). At enrolment, only the questions about sleep and mood should be answered.

5.8 OVERDOSE OF TRIAL MEDICATION

All participants/carers should be counselled about the importance of taking/administering the medications as prescribed. It is particularly important that participants and carers understand the quantity of medicines they should be given. Participants must be told to contact the clinic immediately if they take too much medication. If the overdose fits the criteria of an SAE (see Section 7.1) it should be reported appropriately.

5.9 PROTOCOL TREATMENT DISCONTINUATION

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

(i) Unacceptable toxicity (clinical or laboratory) or adverse event
(ii) Disease progression necessitating change of regimen
(iii) Virological failure
(iv) Withdrawal of consent for treatment by the participant or carer

As the child's participation in the trial is entirely voluntary, they or their carer 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 and/or carer are not required to give a reason for discontinuing their trial treatment, reasonable effort should be made to establish this reason while fully respecting the participant's rights.

Participants should remain in the trial for the purpose of follow-up and data analysis (unless the participant or carer withdraws their consent from all stages of the trial). If a patient is withdrawn from follow-up, refer to **Section 6.9**.

Data will be kept and included for participants who stop follow-up early, up to the point of exit.

5.10 NON-TRIAL TREATMENT AND SIGNIFICANT DRUG INTERACTIONS

Families and participants should be advised to notify their clinician of any current or proposed concomitant medication, whether prescribed or over-the-counter. All necessary concomitant medications will be recorded in the study CRFs.

Dofetilide, a class III antiarrhythmic agent, not licensed in children <18 years, is the only drug that is contraindicated for co-administration with DTG.

A few drugs have important drug interactions with DTG and require dose adjustment of DTG or their intake should be separated in time. Table 4 shows some of the interacting drugs that may be relevant for the patients in ODYSSEY. For full information see dolutegravir SPC.

Table 4. Significant drug interactions with DTG and recommended actions

Anticonvulsants	
Oxcarbazepine Phenytoin Phenobarbital	Weight-appropriate dose of DTG should be doubled (given twice daily).
Sodium valproate	Careful clinical and adherence monitoring are advised and a repeat VL can be considered.
Herbal products	
St. John's wort	Weight-appropriate dose of DTG should be doubled (given twice daily).
Antacids and supplements	
Magnesium/ aluminium-containing antacid Calcium supplements Iron supplements Multivitamin	Calcium supplements, iron supplements or multivitamins should be taken well separated in time from the administration of DTG (minimum 2 hours after or 6 hours before DTG). Alternatively DTG can be taken with food.
Antimycobacterials	
Rifampicin	Weight-appropriate dose of DTG should be doubled (given twice daily).

Please refer to DTG SmPC (https://www.medicines.org.uk/emc/product/5248/smpc) and the University of Liverpool HIV Drug Interactions site (https://www.hiv-druginteractions.org/drug_queries/new) for the full list of the possible drug interactions.

6 ASSESSMENTS & FOLLOW-UP

Trial visit schedules will be prepared for each participant at randomisation, and participants should be followed on the same schedule even if their trial medication is discontinued. The target dates for trial visits are determined by the date of randomisation and are not affected by subsequent events. The schedule sent or generated after randomisation defines visit dates (with windows) necessary for data collection, but the participant may be seen more frequently for clinical care as needed.

Participants should attend on the scheduled day whenever possible, unless agreed in advance with the clinic. Clinics may choose to re-schedule visits to allow for public holidays or other unavoidable circumstances that affect the scheduled visit date. During the treatment period, if participants are unable to attend on the day, every effort should be made to complete the visit as soon as possible and within 14 days of the scheduled date. If a scheduled visit is missed without notice then the research team 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 (during the treatment period), an additional visit will be performed as soon as possible, including the appropriate assessments that were specified in the trial schedule for the visit week that was missed.

6.1 TRIAL ASSESSMENT SCHEDULE

6.1.1 RANDOMISED PHASE

All participants will be seen at screening, enrolment (randomisation, week 0) and then at weeks 2 (for children 3-<14kg), 4, 12, 24, 36, 48, 60, 72, 84 and at week 96 (see Trial Assessment Schedule). All participants should then be followed-up in clinic every 12 weeks until the last participant enrolled up to the end of recruitment for the main trial (see 3.4) reaches week 96 or for a minimum of 96 weeks, whichever is greater. Clinical assessment at week 2 is required for children 3-<14kg and optional for children ≥14kg at sites with the standard practice to review participants at 2 weeks after starting new antiretrovirals.

A full clinical assessment and the following will be undertaken as specified in the Trial Assessment Schedule:

- Medical history since last visit including intercurrent illnesses, all AEs, signs and symptoms of HIV disease with WHO stage on every visit
- Weight, height and mid-upper arm circumference (MUAC) on every visit
- Viral load as per local practice (in ODYSSEY B viral load must be measured at screening unless the viral load has been done within 4 weeks prior to screening)
- Haematology at screening, weeks 0, 2 (for children 3-<14kg), 4, 24, 48, 72, 96 and at the study visit at the end of the randomised phase, and at other time points as per local practice.
- T cell lymphocyte subsets at screening, weeks 0, 4, 12, 24, 48, 72, 96 and at the study visit at the end of the randomised phase, and at other time points as per local practice.
- Plasma storage at screening, week 0, 4, 12 and then 12 weekly and at the study visit at the end of the randomised phase.
- RBC folate/RBC storage and B12/serum storage at week 96 or later
- Cell storage (at the selected sites) at week 0, 12, 48, and 96
- Biochemistry at screening, 2 (for children 3-<14kg), week 4, 24, 48, 72 and 96 and at the study visit at the end of the randomised phase, and if indicated or if required by local practice. Participants should be fasting at week 0, 48 and 96, every 48 weeks and at the study visit at the end of the randomised phase in order to obtain fasting lipids and glucose values
- Bone profile (optional) at randomisation, week 48, 96 and then 48 weekly, and at the study visit at the end of the randomised phase at the sites where these tests are done routinely

- Urine dipstick at randomisation, week 48, 96 and then 48 weekly, and at the study visit at the end of the randomised phase.
- Tanner scales (see Appendix X) should be completed at week 0 and repeated every 24 weeks (unless previous scores of 5) until the study visit at the end of the randomised phase in children aged 8 or over.
- Lipodystrophy clinical assessment should be performed at week 0 and repeated at weeks 48 and 96 then 48 weekly and at the study visit at the end of the randomised phase.
- Pregnancy tests should be performed for all females of childbearing potential at screening, randomisation and all trial follow-up visits (including unscheduled visits), regardless of whether the participant has recently had her period. All boys and girls of reproductive age will be given continuing advice about avoiding pregnancy; information about contraception use will be recorded. If a pregnancy test performed during the trial is positive, please notify the appropriate CTU, following procedures detailed in Sections 6.8 and 7.2.1.

In addition at each visit the following should be recorded:

- Assessment of adherence to ART by adherence questionnaire while the participant is on treatment
- Changes in ART and other concomitant medication
- All adverse events since the last protocol visit, including haematological abnormalities, pancreatitis, diarrhoea, clinical lipodystrophy, acute illnesses
- Change in HIV disease stage since last protocol visit
- Inpatient and outpatient attendances with any documented test results

The next supply of drugs to last until the next clinic visit will be dispensed. Prescriptions of ART and any alterations to prescribed doses should be recorded on the CRF. Doses should be checked at every visit and adjusted for body surface area, or weight as appropriate.

Additional study visits, for example if the child develops drug toxicity or other clinical events should be recorded using appropriate forms. At such visits, laboratory tests should be performed as clinically indicated. Participants will also be given a patient card with the contact details for the trial research team at their site and information on ABC hypersensitivity if receiving ABC.

For the frequency of the assessments after week 96, see the Trial Assessment Schedule.

6.1.2 Extended Follow-up of ODYSSEY Participants

When participants attend for their study visit at the end of the randomised phase (after the last patient reaches 96 weeks for children recruited weighing ≥14kg or the 96 week visit for children <14kg), consent/assent will be requested in order for them to enter into a period of extended follow-up. The purpose of this extended follow-up is to collect further safety data for participants who will continue to receive ViiV Healthcare supplied dolutegravir (where the formulation that they are taking is not available through the country's national HIV treatment programme) and also to monitor long-term safety and effectiveness of dolutegravir versus standard of care (at selected sites, subject to sufficient funding). The child's visit schedule and care will be as per local clinic guidelines with a small amount of data to be collected in addition to this. Please see Appendix XX for further details on the arrangements for extended follow-up.

6.2 PROCEDURES FOR ASSESSING EFFICACY

6.2.1 Clinical:

A symptom checklist and targeted physical examination (to evaluate any reported symptoms) will be performed at each visit during the randomised phase. Hospital admissions will be solicited at all visits,

regardless of the trial phase. Where there is any clinical suspicion of a WHO Stage 3 or 4 disease event, centres will endeavour to investigate to the full extent possible given local availability of imaging and laboratory investigations (particularly microbiology) in order to establish a clear diagnosis of the event. The lists of WHO stages and diagnostic criteria are provided (see Appendices VII-IX). The site will report the event and the clinical investigations that support the diagnosis on the Event form in order to enable an independent evaluation of the event. An endpoint review committee will review all clinical endpoints occurring during the randomised phase to ensure that they satisfy the diagnostic criteria.

6.2.2 IMMUNOLOGY:

Blood will be collected according to the appropriate trial assessment schedule, depending on whether the participant is in the randomised phase or extended follow-up period of the trial, for the determination of total and percentage CD4 and CD8 T cell counts. The T cell subsets will be measured using the standard assay in the laboratory operating at each site according to quality-assured procedures.

6.2.3 VIRAL LOAD TESTING:

At sites where plasma HIV viral load (VL) is routinely measured every 12-16 weeks, VL should be measured at screening, week 4, 12, 24 and then every 12 weeks until the study visit at the end of the randomised phase.

At the sites where VLs are not routinely measured every 12-16 weeks, real-time viral load should be measured at the screening visit for participants in ODYSSEY B, unless one has been done within 4 weeks prior to screening. Viral loads should then be done according to local routine practice. Viral loads will be measured retrospectively on EDTA-plasma samples stored at screening, enrolment (ODYSSEY A), week 4, 12, 24, and then every 12 weeks until the end of the randomised phase. Retrospective VL measurements will be done in batches using the same assay (lower limit of detection of no greater than 50 c/ml) in one or more designated PENTA laboratories. The Independent Data Monitoring Committee (IDMC) (Section 14.3) will review VL results on all patients during the randomised phase.
If the participant meets the definition of treatment failure during the trial (WHO 2016 guidelines), and the treating physician wishes to modify treatment, they may perform a VL test at their site, to confirm treatment failure prior to switch. In this situation the management of the participant will be discussed with the relevant CTU and the trial Clinical Advice Group.

6.2.4 RESISTANCE TESTING

At sites where genotypic resistance testing is part of routine care, for children experiencing virological failure tests should be run on the latest sample while the child is still on the same treatment. At sites where genotypic resistance testing is not a part of routine care baseline samples will be tested retrospectively using stored EDTA-plasma to assess background regimen activity at baseline and batched genotypic resistance testing will be performed on the samples with viral load reaching current threshold for resistance assays. Additional resistance tests will be performed on stored plasma samples in selected participants at the end of the randomised phase of the trial to define in more detail the pattern of resistance development. Samples may be assayed locally where possible, or moved to another country.
Drug resistance mutations will be classified using the Stanford database algorithm. The results of all resistance tests performed in individual participants will be given to the treating physician after the last participant has completed 96 weeks follow-up, or as soon thereafter as results become available.

6.3 PROCEDURES FOR ASSESSING SAFETY

The clinical examination 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 per the appropriate Trial Assessment Schedule depending on whether the participant is in the randomised phase or extended follow-up period of the trial. Additional safety blood tests or investigations may be performed to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated.

Adverse events will be reported on the case report form. Adverse events (clinical and laboratory) will be graded using the 2014 Division of AIDS toxicity grading scale (see Appendix IX). Grade 1 and 2 clinical events do not need to be reported unless resulting in a change of ART regimen. Serious adverse events will be defined according to ICH GCP, and should be reported to the CTU within 24 hours of the site being aware (see Section 7 - Safety Reporting). All adverse events meeting the definitions above should be reported on study CRFs, regardless of their relationship to HIV.

6.4 PROCEDURES FOR ASSESSING QUALITY OF LIFE

Quality of life questionnaire adapted from EQ-5D questionnaires [48] should be completed by all children aged 8 or over, regardless of which arm they are in, at randomisation (week 0), 12, 24, 48 weeks and then every 48 weeks and at the study visit at the end of the randomised phase.

6.5 ADHERENCE ASSESSMENTS

Adherence issues should be addressed with potential participants in ODYSSEY B before screening for the trial and an adherence questionnaire should be completed at the screening visit. At 4 and 12 weeks and thereafter every 12 weeks until the end of the randomised phase, carers and children, where appropriate, will be asked to complete an adherence questionnaire. This will include questions about adherence to all the antiretrovirals.

6.6 MANAGEMENT OF PARTICIPANTS WITH TREATMENT FAILURE

- In settings where viral load measurement is part of routine care, viral loads will be measured locally. Participants experiencing virological failure should have reasons for virological failure investigated as per local practice (addressing problems with adherence, adequate dosing, drug interactions, and if available, drug levels, resistance mutations) prior to decisions being made about switching ART. ART management decisions (discontinuation of the previous regimen, change to the new regimen) should also be made by the treating clinician as per accepted local practice. Advice from the Clinical Advice Group should be sought during the randomised phase of the trial and the CTU also contacted. The participant should continue to be seen 12 weekly until the end of the randomised phase (see Trial Assessment Schedule for randomised phase of the trial). Participants should follow local practice at subsequent visits. CRFs should be completed at each follow up visit.

- In settings where viral load measurement is not routine care, the efficacy of treatment will be monitored using clinical assessment and local CD4 cell counts/percentage. During the randomised phase, therapy will be maintained according to the randomised strategy until there is clinical or immunological failure, defined for the protocol as after at least 36 weeks on the allocated regimen. Where available, a targeted viral load should be done to confirm treatment failure prior to switch. If the treating clinician decides to switch therapy, then the

next regimen should be given according to guidelines and paediatrician choice and based on the local availability of antiretrovirals; advice can also be obtained from the Clinical Advice Group. The clinician can at any stage give alternative treatment to that specified in the protocol if it is considered to be in the participant's best interest. However this should be discussed first with the CTU if the participant is in the randomised phase of the trial.

6.7 MANAGEMENT OF CHILDREN DIAGNOSED WITH TUBERCULOSIS (TB)

Participants with TB at enrolment or who develop TB during the trial should receive TB treatment following national guidelines (usually rifampicin, isoniazid, pyrazinamide, and ethambutol). Where available, cultures should be tested for sensitivity to first-line anti-TB drugs and regimens modified on the basis of these results.

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.

6.7.1 MANAGEMENT OF CHILDREN WITH TUBERCULOSIS INFECTION IN THE DTG ARM

DTG pharmacokinetics are influenced by concomitant treatment with rifampicin. This interaction can be overcome by giving the weight-appropriate dose of DTG twice daily, i.e. the protocol daily dose is doubled.

Therefore, in a child on rifampicin, the DTG dose needs to be increased from QD to BID and remain BID until 2 weeks after the last dose of rifampicin has been given (the enzyme inducing effect of rifampicin slowly fades away after discontinuing the drug).

Although not compulsory, at least 12 children in the DTG arm receiving rifampicin as part of anti-TB treatment or TB prevention therapy will be invited to participate in the TB substudy for children on DTG and rifampicin (see Section 10.1.3 and Appendix XIV).

6.7.2 MANAGEMENT OF CHILDREN WITH TUBERCULOSIS IN THE SOC ARM

As rifampicin interacts with some ARVs, including PIs and NNRTIs, change of regimen may be needed for co-infected children in SOC arm. Guidance on the choice of ART for children with TB can be found in the WHO 2016 guidelines and in national guidelines and may differ between countries. Children who are on EFV-based ART can continue on the same regimen while those (>3 years) receiving NVP should be switched to EFV. Children receiving 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), or they can be switched to EFV (if >3 years). As an alternative, children receiving NVP or LPV/r with rifampicin may change to triple NRTI (ZDV + 3TC + ABC) [49] or the NVP dose should be increased to the maximum recommended, i.e. 200 mg/m^2 BID. In order to obtain better exposure in younger children, the maintenance dose can be further increased by 20-30% after two weeks of starting (H Lyall, S Welch, unpublished data). CTUs should be notified and advice sought from the Clinical Advice Group.

6.8 MANAGEMENT OF PREGNANCY

Reproductive toxicology animal studies, including embryofoetal development studies in rats and rabbits, showed no evidence of adverse developmental outcomes [34].

A National Institutes of Health (NIH)-funded observational surveillance study in Botswana (TSEPAMO) evaluating the safety of ART regimens in pregnancy has recently identified an increased risk of neural

tube defects (NTD) amongst infants of women who initiated DTG-based regimens prior to pregnancy (see Background). This study and other surveillance studies are ongoing and other reproductive studies on DTG safety have been initiated. More data on safety of DTG for women of childbearing age and their infants are expected in the next year.

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 on the infant. If the girl then chooses to enter the trial, she will be advised to use highly effective contraception and to report to the study site staff as soon as possible if there is a possibility of pregnancy.

Following the safety alert, ODYSSEY sites were advised that all female participants who are sexually active must use highly effective contraception [38]. This includes:

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 (eg. containing 75 micrograms desogestrel)
    b. injectable
    c. implantable
3. Intrauterine device (IUD)
4. Intrauterine hormone-releasing system (IUS)

DTG has no interaction with hormonal contraceptives, and therefore any hormonal contraceptives inhibiting ovulation can be used in female participants in the DTG arm. For participants in the SOC arm, the site clinician should consider drug interactions between some third agents (nevirapine and protease inhibitors) and a number of hormonal contraceptives. Please refer to the table 'Recommendations for co-administration of different types of contraception with antiretrovirals in the MOP for guidance on prescribing hormonal contraceptives for participants.

Pregnancy testing will be undertaken at screening and randomisation in girls who have reached menses. If pregnant, she will be ineligible for the trial. For randomised females who have reached menses, pregnancy tests will be repeated at all trial follow-up visit 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.

Female participants taking DTG who are intending to become pregnant or are identified to be pregnant, need to discuss the risks and benefits of their current regimens with their health care providers. The neural tube closes within 4 weeks of conception and therefore switching off DTG is particularly relevant for women diagnosed with pregnancy early. If women are in very early pregnancy (within 8 weeks from last menstrual period) and there are other good options to replace DTG, then switching to a non-DTG ART regimen is strongly recommended as per DHHS guidance [50].

Those who are pregnant and are 8 weeks or greater from last menstrual period may continue DTG-based regimens. Discontinuing DTG-based regimens is unlikely to confer any benefits after the neural tube has formed, and medication changes during pregnancy could increase the risk of viremia and transmission of HIV to the infant.
There is also a risk that a young person may become non-adherent if their DTG-based ART regimen is well tolerated but this is then changed. The clinician should therefore use his/her judgement about whether benefits of continuing a pregnant woman on DTG-containing products are deemed to outweigh the risks (e.g., individual cases from study populations with limited treatment options, or

risk of poor adherence on alternative ART regimen, especially if pregnancy comes to light late and near to the time of delivery). Where local regulatory regulations allow, the woman may continue DTG and the case should be discussed with MRC CTU. 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 about their options and receive support to make decisions about continuing pregnancy. Folic acid should be provided to be taken throughout the first trimester. For females on DTG who become pregnant, advice on breast-feeding will be given according to local or national lactation and treatment guidelines and standard of care. All infants will receive infant prophylaxis according to the current local standard of care.

Reporting of pregnancy and pregnancy-related events are outlined in section 7.1.5.D.

6.9 EARLY STOPPING OF FOLLOW-UP

If a participant or their carer chooses to discontinue the trial treatment, the participant should continue to be followed until the end of the trial providing the participant and their carer are willing; that is, they should be encouraged not to leave the trial. However, if the participant and/or carer do not wish to remain on trial follow-up, they should be offered the option of continuing with routine follow up and permission to collect minimal routine outcomes from the patient's notes should be requested. If they do not wish to provide information about routine follow up, their decision must be respected and the patient will be withdrawn from the trial completely. The CTU should be informed of this in writing using the appropriate documentation. Participants stopping early have a negative impact on a trial's data.

If the medical data collected during the participant's time in the trial are kept for research and analysis purposes, they can be further anonymised if necessary. Consent for future (but not past) use of stored samples already collected can be refused when leaving the trial early (but this should be discouraged and should follow a discussion with the patient/carer).

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

Participants who stop trial follow-up early will not be replaced, as the total sample size includes an adjustment for losses to follow-up.

6.10 PARTICIPANT TRANSFERS

If a participant moves from the area, reasonable efforts should be made to continue their follow-up, e.g. by them continuing to come for visits providing the site has sufficient resources, or by conducting nurse only visits over the telephone and providing drugs and clinical care at a local clinic. If a local site is conducting the trial, the participant can be transferred there; a copy of the participant's CRFs should be provided to the new site and the parent/carer will need to sign a new consent form. 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 none of the above options are possible, then the participant should be considered as lost to follow-up. The participant and/or carer may or may not choose to formally register this as a withdrawal of consent.

6.11 END OF TRIAL

After target accrual is reached (see Section 3.4 and Analysis Plan Section 9.5) the *end of main* trial *recruitment date* will be defined. Recruitment will then stop for children ≥14kg. Recruitment will continue in the 3 lower weight bands (3-<6kg, 6-<10kg and 10-<14kg) until at least 20 children are recruited in each weight band. Follow-up for children recruited up to the *end of main trial recruitment date* will continue during the randomised phase until the last child recruited has completed 96 weeks follow-up; all such participants will attend a study visit for the end of the randomised phase after the last child reaches 96 weeks.

Analysis of the main trial will be conducted at this time. Results will not be available until approximately 6 months after children in the main trial have attended their final study visit (in the randomised phase), retrospective viral load testing is complete and the database has been locked. Each of the children recruited in the lower weight bands after the *end of main trial recruitment date* will continue to be followed up for 96 weeks. Children in the lower weight bands should attend for their study visit for the end of the randomised phase at or after 96 weeks; they should not attend for this visit prior to the '*diary date'* given in the participant's visit schedule.

After the end of the randomised phase DTG will be provided by ViiV for those children randomised to the DTG arm until it is available and recommended for children in their country of residence. Where DTG is available locally, a short supply of trial stock will be provided to enable participants to transition smoothly onto the national antiretroviral treatment programme. Participants receiving Triumeq should be switched to DTG 50mg plus a separate fixed dose combination of ABC/3TC 600/300mg (Kivexa or generic equivalent) on the national programme if Triumeq is not available locally.

Children weighing <20kg at sites in South Africa, Uganda and Zimbabwe still receiving DTG 5mg at the end of the randomised phase will continue into extended follow-up until they reach 20kg (and can switch to DTG 50mg, available locally) or generic dispersible DTG becomes available locally. Children weighing ≥20kg randomised to the DTG arm at these sites are expected to have access to DTG 50mg through their country's national antiretroviral treatment programme by the end of the randomised phase of the trial.

Children in Thailand randomised to the DTG arm will continue into extended follow-up so that DTG 50mg can continue to be provided. Participants receiving Triumeq will be switched to (DTG 50mg provided by ViiV) plus a separate fixed dose combination of ABC/3TC 600/300mg (Kivexa or generic equivalent available through the national antiretroviral treatment programme) for this period.

All children in DTG and SOC arms at sites in Africa and Thailand may continue into extended follow-up, subject to sufficient funding. Children in extended follow-up will attend clinic visits as per local practice (see Appendix XX for more details). SAEs will continue to be reported as per trial requirements (Section 7).

The ODYSSEY trial comprises a randomised phase and an extended follow-up phase. The end of the trial will be when all children have attended their final study visit (in randomised or extended follow-up phase, any retrospective viral load testing is complete and the database has been locked for the end of trial. The date of the expected end of the trial will be communicated to the participating centres approximately 3-6 months before the trial ends. The sponsor, or the sponsor's representative in each country, will notify the national regulatory body and ethics committee of the end of the trial. The

Principal Investigator at each site will be responsible for notifying local ethics boards and any other local bodies, such as R&D departments.

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 7.2** gives details of the investigator responsibilities and **Section 7.3** provides information on MRC CTU responsibilities.

7.1 DEFINITIONS

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 5.

Table 5: Definitions

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject 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 subject 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). In ODYSSEY DTG, Triumeq and 3rd agent comparators prescribed in the SOC arm are the IMP.

Adverse reactions include any untoward or unintended response to drugs. Reactions to the IMP or the other antiretrovirals 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 trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

Adverse events which do not require reporting in this trial:

- Overdose of medication without signs or symptoms
- Grade 1 or 2 events which do not result in any changes to ART

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

7.1.3 DISEASE-RELATED EVENTS

All adverse events meeting the definitions above should be reported on study CRFs, regardless of their relationship to HIV and should be graded. In particular, all deaths should be reported as fatal SAEs.

7.1.4 OTHER NOTABLE EVENTS

7.1.4.A Liver events

All suspected cases of drug induced liver injury in both arms should be reported as a notable event and AE or SAE as appropriate on an Event form and, during the randomised phase, should be sent to the relevant CTU within 24 hours of the site becoming aware. Reporting timelines during extended follow-up for notable events which don't constitute a SAE are outlined in Appendix XX. Additional information will be then requested from the sites. Any results of liver investigations, including liver biopsy and/or imaging should be reported.

7.1.4.B ABC Hypersensitivity reaction (HSR)

Clinically suspected ABC HSR should be reported as a notable event and AE or SAE as appropriate on an Event form and, during the randomised phase, should be sent to the relevant CTU within 24 hours of the site becoming aware. Reporting timelines during extended follow-up for notable events which don't constitute a SAE are outline in Appendix XX. Additional information will be requested from the sites and should be completed within one week of the onset of the hypersensitivity reaction.

7.1.4.C Suicidal Ideation or Behaviours

A possible suicidality-related adverse event (PSRAE) should be reported as a notable event and AE or SAE as appropriate on an Event form and, during the randomised phase, should be sent to the relevant CTU within 24 hours of the site becoming aware. Reporting timelines during extended follow-up for notable events which don't constitute a SAE are outline in Appendix XX. 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. Following receipt of the report, the Investigator will be requested to collect additional information which should be reported to the relevant CTU within one week of the investigator diagnosing a possible suicidality-related adverse event.

7.1.4.D Pregnancy

Pregnancy occurring during participation in ODYSSEY should be reported as a notable event on an Event form and sent to the relevant CTU (see Section 6.8). All pregnancies will be reported to ViiV and registered with 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, which must also be reported to the CTU on a Pregnancy Outcome form. The clinical team responsible will be informed of the mother's participation in the trial and will be asked to inform the relevant CTU if there is any suspicion of any adverse effect of the trial medication.

Spontaneous abortions, pregnancy complications and elective terminations for medical reasons must be reported on an Event form if the event meets the criteria of a reportable AE or SAE.

Any adverse event occurring in an infant born to a female trial participant within 30 days of delivery should be reported in order to evaluate any possible adverse reaction related to *in utero* exposure to the study drugs [51].

Any SAE occurring in association with a pregnancy brought to the investigator´s attention after the participant has completed the study and considered by the investigator as possibly related to the investigational product, should also be reported as an SAE. Any event fulfilling the criteria of an SAE (e.g. congenital abnormality or birth defect) should be reported within 24 hours of the Investigator becoming aware of the event.

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.

At the end of pregnancy, the investigator will complete an Outcome of Pregnancy CRF.

Reporting timelines during extended follow-up for notable events which don't constitute a SAE are outline in Appendix XX.

7.2 INVESTIGATOR RESPONSIBILITIES

All grade 3 and above clinical and laboratory AEs should be reported in the relevant section of the Event Form. Grade 1 and 2 clinical and laboratory AEs should be reported only if they result in change of ART. All ARs, whether expected or not, should be recorded in the participant's medical notes and reported on the Follow-up Form. SAEs and SARs and notable events should be reported to the relevant CTU within 24 hours of the site becoming aware of the event. Reporting timelines during extended follow-up for reportable events which don't constitute a SAE are outline in Appendix XX.

7.2.1 INVESTIGATOR ASSESSMENT

7.2.1.A Seriousness

When an AE or AR occurs, the investigator responsible for the care of the patient must first assess whether or not the event is serious using the definition given in Table 5. If the event is serious, then an Event Form must be completed and the CTU notified within 24 hours.

7.2.1.B Severity or Grading of Adverse Events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity grading in Appendix IX.

7.2.1.C Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 6. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

Table 6: Assigning Type of SAE through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	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).	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 SAE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE

If an SAE is considered to be related to an antiretroviral and drug is stopped or the dose modified, refer to Section 5.5.

7.2.1.D Expectedness

If there is at least a possible involvement of the trial treatment (or comparator), the investigator may make an initial assessment of the expectedness of the event, however the Sponsor has the overall responsibility for determination of expectedness. An unexpected adverse reaction is one not previously reported in the current Reference Safety Information (i.e. the Investigator's Brochure (for

DTG and DTG-containing products), or Summary of Product Characteristics (SPC; for all other ARVs)), that should be accessed through the ODYSSEY reserved area on the Penta website (https://penta-id.org/reserved-area/#odyssey), or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in Table 5. If a SAR is assessed as being unexpected, it becomes a SUSAR. If there is at least a possible involvement of the trial treatment, the Investigator should make an initial assessment of the expectedness of the event. The Sponsor will have the final responsibility for determination of expectedness (for reporting purposes), and this decision will be made on the basis of the above definition and the information provided by the Investigator. Please see the Manual of Operations for a summary of expected toxicities for ARVs.

7.2.1.E Notification

The relevant CTU should be notified of all SAEs and notable events within 24 hours of the investigator becoming aware of the event. Reporting timelines during extended follow-up for notable events which don't constitute a SAE are outlined in Appendix XX.

Investigators should notify the relevant CTU of all reportable AEs (section 7.2), SAEs and notable events occurring from the time of randomisation until the end of the trial or end of extended follow up, whichever is later. Any subsequent events that may be attributed to treatment should also be reported to national reporting schemes where relevant.

7.2.2 NOTIFICATION PROCEDURE

1. The Event Form must be completed by an investigator (a clinician 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, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed and signed by a member of the site trial team and faxed or emailed as appropriate. The responsible investigator should subsequently check the Event Form, make changes as appropriate, sign and then re-fax to the CTU as soon as possible. The initial report must be followed by detailed, written reports as appropriate.

2. The minimum information required for reporting an AE, SAE or notable event are the trial number and partial date of birth, name of investigator reporting, the event and why the event is considered serious or meets the criteria of a reportable event.

3. Follow-up: participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. A further Event Form, indicated as 'Follow-up' should be completed and faxed to the relevant CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately. The participant must be identified by trial number, anonymous code, and date of birth only. The participant's name should not be used on any correspondence and should be deleted from any test results.

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

SAE REPORTING

Within 24 hours of becoming aware of an SAE or notable event, please fax or email a completed Event form to the relevant CTU. Please ensure that an acknowledgment of receipt by the CTU is received.

MRC CTU: fax: +44 (0) 20 7670 4814 or email: mrcctu.trial-odyssey@ucl.ac.uk

Inserm-ANRS: fax: + 33 1 46 58 72 93 or email: penta.sc10@inserm.fr

PHPT: fax: +66 53 240 913 or email: suwalai.chalermpantmetagul@phpt.org

7.3 CTU RESPONSIBILITIES

Medically-qualified staff at the CTUs and/or the Chief Investigator (or a medically-qualified delegate) will review all event reports received. The causality assessment given by the local investigator at the hospital cannot be overruled; in the case of disagreement, both opinions will be provided in any subsequent reports.

The CTUs are undertaking the duties of trial sponsor and are responsible for the reporting of SAEs to the relevant regulatory authorities (MHRA and competent authorities of other European member states and any other countries in which the trial is taking place) and research ethics committees of any countries in which the trial is taking place, as appropriate. This responsibility may be delegated to country principal investigators for relevant reporting requirements in individual countries. Fatal and life-threatening SUSARs must be reported to the competent authorities within 7 days of the relevant CTU becoming aware of the event; other SUSARs must be reported within 15 days.

The relevant CTU will also keep all investigators informed of any safety issues that arise during the course of the trial.

MRC CTU will prepare annual Development Safety Update Reports (DSURs) on behalf of the sponsor which will be submitted to the Competent Authorities and Ethics Committees in each country participating in the trial.

Any drug companies involved will also be notified of reportable (serious and unexpected and drug-related/unknown relationship) events as per the requirements outlined in the individual contract.

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 ICH 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 Research Governance Committee (RGC) and has led to the development of a Data Management Plan (DMP), Safety Reporting Plan and Monitoring Plan which will be separately reviewed by the Quality Management Advisory Group (QMAG).

8.2 CENTRAL MONITORING AT CTU

Where local staff have successfully completed training on the trial database, data will be entered into the trial database directly at the clinical site. The site will retain the original CRF. Data stored on the central database will be checked at the CTU 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 contacted and asked to verify or correct the entry. Changes will be made on the original CRF and entered into the database at the site. The CTU will also send reminders for any overdue and/or missing data with the regular inconsistency reports of errors.

Alternatively sites can send completed CRFs to the CTU for data entry. Data received at CTUs will be checked and if problems are identified, a missing data report of the problematic data will be sent to the local site by secure e-mail for checking and confirmation or correction, as appropriate – any data which are changed should be crossed through with a single line, dated and initialled. The amended data should be returned to the appropriate CTU and the amended data should also be filed in the notes at site. The CTUs will send reminders for any overdue and missing data.

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

8.3 ON-SITE MONITORING

Staff from the CTUs or local monitors will visit clinical sites to validate and monitor data. 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. All monitoring will adhere to the principles of ICH GCP.

Monitors will:

- verify completeness of the Investigator Site File
- confirm adherence to protocol
- review procedures and resources
    - in the trial clinic
    - in the trial pharmacy

- in the trial laboratories

- advise on additional training as needed

The investigator (or delegated deputy) should work with the monitor to ensure that any problems detected are resolved.

8.3.1 DIRECT ACCESS TO PARTICIPANT RECORDS

Participating investigators will allow trial-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. If required locally, consent for this should be obtained from parents/carers and children, if appropriate. Such information will be treated as strictly confidential and will in no circumstances be made publicly available.

The following data should be verifiable from source documents:

- all signed consent forms
- all Eligibility and clinical and laboratory data at enrolment
- all clinical endpoints and all SAEs
- routine patient clinical and laboratory data
- trial drug accountability

8.3.2 CONFIDENTIALITY

We plan to follow the principles of the UK DPA regardless of the countries where the trial is being conducted.

The investigator must assure that the participants' anonymity will be maintained i.e. their identities are protected from unauthorised parties. Participants will be assigned a trial identification number to be used on all CRFs and no names will be used beyond the clinical care of the participant, in order to maintain confidentiality. All trial records, including a participant trial register linking identification numbers and names, will be kept in secure locations at each site.

9 STATISTICAL CONSIDERATIONS

9.1 METHOD OF RANDOMISATION

Randomisation of children weighing ≥14kg will be stratified by:

- antiretroviral treatment: naïve or experienced (ODYSSEY A or ODYSSEY B)
- routine availability at site of resistance tests vs. non availability of resistance tests, for children failing treatment
- bPI vs. non-bPI ART offered as SOC
- NRTI backbone : ABC/3TC or ABC/3TC/ZDV vs. TDF/3TC or TDF/FTC or TAF/3TC or TAF/FTC vs. Other

Randomisation of children weighing 3-<14kg will ***be performed separately*** stratified by

- antiretroviral treatment: naïve or experienced (ODYSSEY A or ODYSSEY B)
- weight band at randomisation: 3-<6kg vs. 6-<10kg vs. 10-<14kg

The randomisation lists will be prepared by staff at the MRC CTU under the direction of the trial statistician. The randomisation lists will be generated by random permuted blocks and will be securely incorporated within the web-enabled trial database. Randomisation will not take place until after informed consent has been confirmed and the participant is ready to receive therapy.

9.2 OUTCOME MEASURES

The primary comparison for the study is to compare DTG-based regimen versus SOC for the primary efficacy outcome in the combined population (naïve and experienced); subpopulation analyses (ODYSSEY A and ODYSSEY B) are key secondary comparisons. Outcomes are described below for the randomised phase.

9.2.1 PRIMARY EFFICACY OUTCOME (OVER 96 WEEKS)

Difference in the probability of virological or clinical failure by 96 weeks, estimated by Kaplan-Meier methods using time to the first occurrence of any of the following components (note, this does not mean VL must be performed in real time):

- Insufficient virological response defined as <1 $\log_{10}$ drop at week 24 (or VL≥50c/mL at week 24 in a participant with VL<500c/mL at baseline) and switch to second/third line ART for treatment failure
- VL ≥400 c/ml at or after 36 weeks confirmed by next visit
- Death due to any cause
- Any new or recurrent AIDS defining event (WHO 4) or severe WHO 3 events, confirmed by the Endpoint Review Committee

9.2.2 SECONDARY EFFICACY OUTCOMES

- Difference in proportion with clinical or virological failure (as defined above) by 48 weeks
- Time to any new or recurrent AIDS defining event (WHO 4) or severe WHO 3 events, confirmed by the Endpoint Review Committee
- Proportion of children with VL <50 c/ml at 48 and 96 weeks
- Proportion of children with VL <400 c/ml at 48 and 96 weeks
- Rate of clinical events over 96 weeks: WHO 4, severe WHO 3 events and death
- Change in CD4 count and percentage and CD4/CD8 ratio from baseline to weeks 48 and 96

- Proportion developing new resistance mutations

9.2.3 SECONDARY SAFETY OUTCOMES

- Change in total cholesterol, triglycerides and lipid fractions (LDL, HDL) from baseline to weeks 48 and 96 (change in total cholesterol from baseline to week 96 will be used to formally assess superiority of DTG based regimen vs. SOC)
- Incidence of serious adverse events
- Incidence of new clinical and laboratory grade 3 and 4 adverse events
- Incidence of adverse events (of any grade) leading to treatment modification

9.2.4 OTHER SECONDARY OUTCOMES

- Quality of life
  Adherence and acceptability

Outcomes in extended follow-up will focus on safety and possible long-term toxicities. See Appendix XX for further details.

9.3 SAMPLE SIZE

Based on previous HIV studies a non-inferiority margin (delta) of 10-12% is considered acceptable. Assuming a failure rate of 18% overall (both first-line and second-line children combined) in the DTG arm and SOC arm by 96 weeks and allowing for 10% loss to follow up, 700 children will provide 90% power to exclude (at two-sided 5% significance level) a difference of more than 10% between the two arms. If the upper bound of the two-sided 95% confidence limit for the difference in the proportion failing (DTG – SOC) is less than 10% (the margin of non-inferiority) the DTG-regimen will be considered to be non-inferior to the SOC.
Enrolling 310 first-line ART and 390 second-line ART children will provide 80% power to exclude a difference of more than 12% between the DTG and SOC arms in both subgroups, assuming a failure rate of 15% in ART-naïve (based on previous trials, including the recent ARROW trial [49] in Africa), and 20% in ART-experienced with loss to follow up of 10%.

9.4 INTERIM MONITORING & ANALYSES

An IDMC Charter will be drawn up that describes the membership of the IDMC, 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 IDMC will meet within 6 months after the trial opens; although the IDMC will in general meet annually, the frequency of subsequent meetings will be determined by the IDMC and could be more frequent if they deem necessary. The IDMC can recommend premature closure or reporting of the trial, or that recruitment be discontinued or modified. Such recommendations would be made if, in the view of the IDMC, there is proof beyond reasonable doubt that one of the allocated strategies is better than its comparator in terms of a difference of clinically significant magnitude in a primary outcome. The guiding statistical criteria for “proof beyond reasonable doubt” is a Haybittle-Peto type rule based on the 99.9% confidence interval of the relative hazard of death in each interim analysis.

9.5 ANALYSIS PLAN (BRIEF)

For the primary analysis of main trial participants, the two treatment groups (DTG and SOC) will be compared in terms of the cumulative probability of clinical or virological failure by week 96 (CPF96) (as defined above) as estimated by the Kaplan-Meier method, adjusting for stratification factors. DTG

will be considered non-inferior to SOC if the upper limit of the 95% confidence interval of the difference in CPF96 (DTG-SOC) is less than the non-inferiority margin of 10%. The number and percentage of participants with at least one component of the primary endpoint and the number and percentage for each component will be summarised.

Secondary analyses will summarise the rate of the composite primary endpoint per 100 person years by treatment group, and a treatment hazard ratio (HR: DTG to SOC) plus two-sided 95% confidence interval estimated by a Cox proportional hazards model. The primary analysis is by intention to treat and includes all randomised participants. A sensitivity analysis will be done with the per protocol population, censoring events after a participant stops the initial randomised trial treatment.

Participants with VL<50 (or <400) c/ml at 48 and 96 weeks will be compared between arms based on (i) crude proportions and (ii) using the FDA snapshot algorithm to determine the proportion of participants with VL<50 (or <400) c/ml.

The secondary endpoints of change in total cholesterol, triglycerides and lipid fractions (LDL, HDL) from baseline to weeks 48 and 96 will be analysed using analysis of covariance to compare the change in mean level between the two arms, adjusting for baseline value and stratification factors. These analyses will be carried out on all randomised participants (intention to treat) and change in total cholesterol from baseline to week 96 will assess the superiority of DTG compared to SOC for this parameter.

There will be a secondary analysis of primary and secondary endpoints in all children recruited weighing<14kg (where DTG dose is determined) when this group has completed 96 weeks follow-up. The primary endpoint will be re-evaluated in all children including those in the main trial and children recruited <14kg (where DTG dose is determined) when follow-up to a minimum of 96 weeks is complete.

Intention to treat analyses including all randomised participants will be performed for all other endpoints 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 using an in-house coding system.

Full details of all analyses will be provided in the Statistical Analysis Plan (SAP). This will include any additional pre-planned subgroup analyses.

A second SAP will be written for the extended follow-up phase.

10 ANCILLARY STUDIES

10.1 PHARMACOKINETIC SUBSTUDIES

10.1.1 WB-PK1

PHARMACOKINETICS OF DOLUTEGRAVIR IN WHO WEIGHT BANDS 3 TO <6KG, 6 TO <10KG, 10 TO <14KG, 14 TO <20KG AND 20 TO <25KG

Children weighing 3 to <25kg randomised to DTG will be recruited to the substudy until at least 8 children per weight band have evaluable PK curves on the investigated dose/formulation. Children will have a single 24h PK curve at least 1 week after starting DTG-based ART or changing to a new dose/formulation. Additional children may be recruited if a large interpatient variability in the PK parameters (i.e. >50% in AUC_{0-24}, C_{trough} or C_{max}) within the weight band is seen. PK, safety and tolerability will be assessed.
The substudy will be undertaken at clinical sites in Uganda, South Africa and Zimbabwe. For further information see Appendix XIII.

10.1.2 WB-PK2

A CROSSOVER PHARMACOKINETICS SUBSTUDY OF DOLUTEGRAVIR IN CHILDREN WEIGHING 25 TO <40KG WITH DOSE CHANGE TO DTG 50MG QD (the substudy is completed)
Children weighing 25 to <40kg taking DTG according to the previous version of the protocol (25mg for 25-<30kg weight band and 35mg for 30-<40kg weight band) were enrolled in the substudy until at least 8 children per weight band had evaluable PK curves. Participants had two 24h PK curves performed: the first curve on dosing they received prior to the dose change for at least 1 week and the second curve at least 1 week after changing to a 50mg tablet. Following the review of the PK results, clinical and laboratory adverse events and treatment discontinuations, children 25-<40kg in the main trial were switched to DTG 50mg film-coated tablet QD (Section 5.3).

The substudy was undertaken at clinical sites in Uganda and Zimbabwe. For further information see Appendix XIII.

10.1.3 TB-PK SUBSTUDY

PHARMACOKINETICS OF DOLUTEGRAVIR CO-ADMINISTERED WITH RIFAMPICIN IN HIV/TB CO-INFECTED CHILDREN
The substudy will evaluate the pharmacokinetics of DTG co-administered with rifampicin in HIV/TB co-infected children and estimate the impact of rifampicin on DTG plasma concentrations. Children aged 6 to <18 years treated for TB with rifampicin-containing regimen are enrolled. At least six children per age band 6 to <12 years and 12 to <18 years will be enrolled; the number may be increased if intersubject variability of DTG PK parameters in children appears much larger than that reported in non HIV-infected adults or if less than 2 children per WHO weight band have complete PK data. We anticipate few children <6 years being treated for TB with a rifampicin-containing regimen during ODYSSEY; however any who receive rifampicin treatment for TB or TB infection will be approached for recruitment. Participants will have two PK curves performed: the first curve (12h) during the last

month of rifampicin-containing TB treatment and the second curve (24h) four weeks after discontinuation of rifampicin (two weeks after changing DTG from BID to QD). Pharmacokinetics of BID DTG and QD DTG within participants will be compared and evaluated against the available data in children and adults.

The substudy will be undertaken at clinical sites in Uganda, South Africa and Zimbabwe. For further information see Appendix XIV.

10.2 IMMUNOLOGY/VIROLOGY SUBSTUDY

The substudy will assess the impact of DTG on the mechanisms of CD4 reconstitution, immune activation and HIV reservoir and replication. The study aims to collect samples from at least 350 children (as many as possible from ODYSSEY A). Blood samples for plasma will be collected at each study visit according to the trial assessment schedule for the randomised phase of the ODYSSEY trial, PBMCs will be collected at enrolment, and at 12, 48 and 96 weeks for sites participating in the substudy. Samples will be stored locally and later transferred to the Institute of Child Health, UCL or the African Health Research Institute (AHRI) Laboratories for analyses. Changes in thymic output, immune activation biomarkers and viral reservoirs and replication will be compared between DTG and SOC arms.

The substudy will be undertaken at clinical sites in Uganda, South Africa and Zimbabwe and Europe. For further information see Appendix XII.

10.3 QUALITATIVE SUBSTUDY: OPTIMISING ADHERENCE TO SECOND-LINE TREATMENT.

The qualitative substudy will explore how moving onto second-line treatment affects young people's treatment engagement and identify how best to support them to maintain optimal treatment adherence. Participants enrolled in ODYSSEY B aged 10-18 years who have known about their HIV status for a minimum of six months will be recruited. Two ODYSSEY trial sites, JCRC in Uganda and the University of Zimbabwe, Harare in Zimbabwe, will be involved; each site will recruit 20 participants (40 in total). Two in-depth individual interviews and a series of focus group discussions with trial participants at different stages of the trial will be conducted. Consultations with a Youth Trial Board (see below) to assist with the dissemination materials will be arranged.

The substudy will be undertaken at clinical sites in Uganda and Zimbabwe. For further information see Appendix XV.

10.4 YOUTH TRIAL BOARD PROJECT

A MULTI-COUNTRY MODEL OF USER INVOLVEMENT TO ENGAGE ADOLESCENTS LIVING WITH HIV IN THE DEVELOPMENT AND DELIVERY OF PAEDIATRIC CLINICAL TRIALS

The project will develop a model of meaningful engagement and participation of adolescent patient representatives in paediatric clinical trials and research studies. It will take place in 4 countries participating in ODYSSEY: the UK, South Africa, Uganda and Zimbabwe. Children living with HIV, aged 15-≤19 years will be included. At least half of the children involved will be ODYSSEY trial participants. Youth Trial boards (YTB), groups of at least 6 young people in each of the four sites, will be established. Each YTB will receive training to ensure understanding of clinical trials and their role. Once trained,

they will provide feedback to the ODYSSEY trial investigators on different aspects of the trial, including provision of the trial information, consent process, engagement with children and adolescents and retention of the participants during the trial. The YTB will be involved in dissemination of the ODYSSEY trial materials and the results. They will also participate at the development stage of new clinical trials as opportunities arise. At the end of the project the model will be adopted for a wider use in paediatric HIV trials and studies.

The substudy will be undertaken at clinical sites in South Africa, Uganda, Zimbabwe and the UK. For further information see Appendix XVI.

10.5 FOLATE AND VITAMIN B12 SUBSTUDY

DOLUTEGRAVIR AND FOLATE AND B12 LEVELS AMONG CHILDREN AND ADOLESCENTS IN THE ODYSSEY TRIAL

Recent concerns have been raised about the use of dolutegravir (DTG) in pregnant women. In a preliminary unscheduled analysis of an ongoing NIH-funded birth surveillance study in Botswana, an increased risk of neural tube defects (NTDs) among infants of women who became pregnant while taking DTG-based regimens has been reported. It is well known that maternal folate deficiency increases the risk of NTDs, however it is unknown whether DTG may affect folate levels.

The substudy will compare the folate levels among children and adolescents randomized to DTG versus those on a SOC ART regimen. The study aims to collect samples from children enrolled in ODYSSEY in sub Saharan sites and to determine whether there is a potential association between DTG and folate status.

Folate plasma levels will be assayed at baseline and 4 weeks after commencing trial treatment using plasma that is routinely stored as part of the main ODYSSEY protocol (see Trial Assessment Schedule). In addition, red cell folate and vitamin B12 levels will be assayed using the same blood draw as for plasma isolation at week 96 (or the next clinic visit after this timepoint if collection at week 96 is not possible). Where assays cannot be done in real time, the blood samples or lysates will be stored for subsequent testing.

The substudy will be undertaken at selected sites in Uganda. For further information see Appendix XVIII.

11 REGULATORY & ETHICAL ISSUES

11.1 COMPLIANCE

11.1.1 REGULATORY COMPLIANCE

The trial complies with the principles of the Declaration of Helsinki of 2013.

It will also be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP) as laid down by the European Commission Directive 2005/28/EC* with the implementation in national legislation in countries in the EU and subsequent amendments and appropriate data protection and regulatory legislation in participating countries, the UK Data Protection Act (DPA UCL's number Z6364106), and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF).

*Until the Clinical Trials Regulation EU No 536/2014 becomes applicable, the trial will be conducted in accordance with the Clinical Trials Directive as implemented in the UK statutory instrument. When the directive is repealed on the day of entry into application of the Clinical Trial Regulation the trial will work towards implementation of the Regulation (536/2014) following any transition period.

11.1.2 SITE COMPLIANCE

The site will comply with the above and with the principles of GCP as laid down by the ICH topic E6 (Note for Guidance on GCP), Commission Directive 2005/28/EC (the European Directive 2001/20/EC [where applicable]) and applicable national regulations. An agreement will be in place between the site, PENTA and the appropriate CTU, setting out respective roles and responsibilities (see Section 13 - Finance).

The site will inform the relevant CTU as soon as they are aware of a possible serious breach of compliance, so that the CTU 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

CRFs, clinical notes 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 in to application in 2020 and, if still applicable to ODYSSEY 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, with suitable notice, to the competent or equivalent authorities, the Sponsor, and other relevant parties in accordance with the applicable regulations. 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 toxicities are different by arm; this will be explained to children/families. The risks of HIV-1 viral load rebound due to a possibly less potent regimen and the use of a novel agent will be explained to children/families. Consent will be sought from parents/carers and from participants where allowed by national regulations. Participants not able to consent for themselves, but deemed able to understand about the trial, will be asked to assent.

As described above, the main risks to the participants are from the potential toxicity from integrase inhibitors. However, this possibility needs to be balanced against the risks from SOC ART. In addition, the trial will evaluate the net clinical/virological risk-benefit comparing DTG with SOC.

11.2.1.A Safety Profile of DTG

DTG has been taken by large numbers of adults in Phase III trials, and is licensed for the treatment of HIV infection in adults and children aged 6 and above weighing at least 15 kg.

The most common side effects of DTG in adults are headache, diarrhoea, abdominal pain, feeling sick, light headed or weak, worrying often and having sleep problems. Some adults taking dolutegravir have reported feeling depressed or having suicidal thoughts; these may not be related to this medicine in all cases. There is a small chance that dolutegravir may cause a rash, itching, vomiting, stomach pain, sleep problems, lack of energy, an increase in weight, feeling light headed, sad or worried or may cause serious liver problems (with signs of vomiting, jaundice or stomach pain).

In May 2018, an 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 DTG-based regimens prior to pregnancy (0.9%, which compares to a risk of ~0.1% in infants born to women on non-DTG based regimens; see Background). In a further report including all data through to March 2019 there were 5 cases of NTD in 1683 deliveries where their mother was taking DTG at conception (0.3% of deliveries) (36), suggesting the increased risk is ~3-fold, lower than the 10-fold risk initially estimated. To protect female participants and their unborn infants from this potential risk, all female participants who are sexually active must use highly effective contraception (see section 6.8). Females on DTG identified to be pregnant within 8 weeks after LMP should be changed to an alternative non-DTG ART regimen provided optimal options to replace DTG are available for them.

At the present time there is limited experience with the use of this drug in the paediatric population. Standard procedures are in place to record Serious Adverse Events arising from the use of DTG (or any study drug) in the trial, and such events will be evaluated and reported to ethics committees and regulatory agencies within specified timelines. The IDMC will closely monitor Serious Adverse Events and grade 3 and 4 events occurring during the randomised phase of the trial in all treatment groups and will be able to advise appropriate action if there is a pattern of serious toxicity emerging from one or more of the drugs.

11.2.1.B Burden of investigations

The follow-up study visits coincide with the usual frequency of visits for routine clinical care. Two extra visits are scheduled at the start of the trial to monitor participant's safety and adherence to medication. Additional tests (over and above routine care) may be required.

11.2.1.C Post-trial treatment

Provision of DTG will continue after the randomised phase of the trial, for participants randomised to receive DTG who are still receiving it, until it is locally approved and available for the child's age and weight band. Safety follow-up of those participants receiving DTG after the randomised phase will be performed.

11.2.1.D Informing potential trial participants of possible benefits and known risks

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

11.2.1.E Confidentiality

Participants' confidentiality will be maintained throughout the trial. Patient data will be identified by the trial number and a 3 letter computer generated anonymous code, date of birth and sex; samples sent to central testing facilities will be identified only by the trial number and a 3 letter computer generated anonymous code, date of collection, type of sample and visit number.

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 and carer will be submitted to national/local ethics committees for approval as required. Any further amendments will be submitted and approved by each ethics committee.

The rights of the participant and carer 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 carer/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 in each country where the trial will be conducted.

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the EU. In countries outside of the EU, local and national regulatory requirements will be followed.

The EudraCT number for the trial is 2014-002632-14.

The progress of the trial and safety issues will be reported to the competent authority, 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 authorities in accordance with each authority's requirements in a timely manner.

11.4 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 (CF) on local headed paper should be forwarded to the relevant CTU before any participants are screened for eligibility.

12 INDEMNITY

In consideration of the agreement by the Principal Investigator at each centre to supervise the trial, the PENTA Foundation 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 arises 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 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.

13 FINANCE

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.

DTG (including Triumeq, as appropriate) will be provided by ViiV for the duration of the randomised phase of the ODYSSEY trial. DTG 5mg dispersible tablets will only be provided to sites in South Africa, Uganda and Zimbabwe, and Triumeq will only be supplied in countries where it is licensed. For sites outside Europe, the following NRTIs will also be provided by ViiV where required for the duration of the ODYSSEY trial: ABC, 3TC, Kivexa and Combivir. After the end of the randomised phase, DTG will be provided by ViiV for those children randomised to the DTG arm until it is available and recommended for children in their country of residence. For sites in sub-Saharan Africa the Mylan formulation of ABC/3TC 120/60mg will be provided for the duration of the randomised phase, if required.

14 OVERSIGHT & TRIAL COMMITTEES

There are a number of committees involved with the oversight of the trial. These committees are detailed below, and the relationship between them is shown (see Appendix XVII).

14.1 TRIAL MANAGEMENT GROUP (TMG)

A Trial Management Group (TMG) will be formed comprising Chief Investigator(s), other lead investigators (clinical and non-clinical) and members of the CTUs: MRC CTU, INSERM-ANRS and PHPT. The TMG will be responsible for the day-to-day running and management of the trial. It will meet monthly during the recruitment phase and thereafter at least every other month. Part of this trial includes a Youth Trial Board (YTB) substudy (see Appendix XVI) and the YTB work with the TMG.

14.2 TRIAL STEERING COMMITTEE (TSC)

The trial will be supervised by the ODYSSEY TMG who will report to the ODYSSEY Trial Steering Committee (TSC). The TSC has membership from the TMG plus independent members, including a PPI representative and the Chair. 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 ODYSSEY TSC may decide to terminate the trial for any reason including the recommendation of the Independent Data Monitoring Committee (IDMC).

14.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC]

The Independent Data Monitoring Committee (IDMC) which oversees all PENTA trials will be the only group who sees the confidential, accumulating data for the trial. Reports to the IDMC will be produced by the CTU statisticians. The IDMC will meet within 6 months of the trial opening; the frequency of meetings will be dictated in the IDMC charter. The IDMC will consider data using the statistical analysis plan (see Section 9.5) and will advise the TSC. The IDMC can recommend premature closure or reporting of the trial, or that recruitment to any research arm is discontinued.

Further details of IDMC functioning and the procedures for interim analysis and monitoring are provided in the IDMC Charter.

14.4 ENDPOINT REVIEW COMMITTEE

An Endpoint Review Committee will be appointed whose remit will be to determine the validity of potential clinical endpoints in terms of meeting the standard criteria, as defined by the protocol. It will have an independent Chair. No member will review endpoints from their own site. Terms of reference for the Endpoint Review Committee will be drawn up.

14.5 ROLE OF STUDY SPONSOR

The sponsor of the trial is the PENTA Foundation. The management of the trial is delegated by the sponsor to the CTUs: MRC CTU, INSERM-ANRS and PHPT.

15 PUBLICATION

15.1 PUBLICATION

The ODYSSEY TMG will be responsible for preparing the manuscript for rapid publication. High priority will be given to this and it would be anticipated that a report would be completed within six months of the latter of database lock or receipt of retrospective viral loads for participants recruited weighing ≥14kg into the main trial. The final publication will require the approval of the ODYSSEY TMG and TSC. No other publications, including all or any part of the results, either written or verbal, will be made before the definitive manuscript has been agreed and accepted for publication without the prior approval of the ODYSSEY TMG and TSC. Individual clinicians must not publish data concerning their participants that are directly relevant to questions posed by the trial until the TMG has published its report. Responsibility for data analysis and publication for ODYSSEY will reside within the PENTA network and be governed by PENTA policies.

The trial will be registered with the internationally accepted clinical trials register, clinicaltrials.gov. The ISRCTN number will be attached to all publications resulting from this trial. The ODYSSEY TSC is the custodian of the data and specimens generated from the ODYSSEY trial; ODYSSEY trial data are not the property of individual participating investigators or health care facilities where the data were generated.

- The data derived from this clinical trial are considered the property of the ODYSSEY TSC. The presentation or publication of any data collected by the participating investigators on participants entered into this trial is under the direct control of the TMG and TSC (and the IDMC 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.

- 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 IDMC 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.

15.2 FEEDBACK TO PARTICIPANTS

At the end of the study, letters will be sent by trial sites to participants and families to inform them when the trial will be closing.

When the trial results are available, an information sheet in lay terms will be provided for every trial participant and carers to explain the results of the trial. This will be distributed to the Principal Investigators at each site so that the paediatrician can discuss it with the child and/or parent/carer to explain the outcome of the trial.

16 DATA AND/OR SAMPLE SHARING

Data will be shared according to the MRC CTU's controlled access approach, 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.

Researchers wishing to access ODYSSEY data should contact the Trial Management Group in the first instance.

17 PROTOCOL AMENDMENTS

Changes to protocol version 5.0 creating protocol version 6.0 8th November 2019

Major changes

1. The following sections have been amended to include information on extended follow-up and to clarify the differing requirements between the randomised phase and the extended follow-up phase:
    - Trial Summary: Clarified that trial outcomes are for randomised phase.
    - Trial Assessment Schedule for Randomised Phase of the Trial: Renamed to clarified that it is to be used for the randomised phase of the trial; End of Study visit renamed for clarity; footnote added to explain when participants should have their study visit for the end of the randomised phase and continue in extended follow-up.
    - Treatment of patients (including sub-sections 5.1, 5.1.1, 5.5.1): Clarified drug supply arrangements for the randomised phase and extended follow-up; clarified that a participant's NRTI backbone may be changed after completion of the randomised phase; differences in approach to ART modifications, interruptions and discontinuations between the randomised phase and extended follow-up described.
    - Assessments & Follow-Up (including sub-sections 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.11): Described assessments required during randomised phase and directed to Appendix XX for those required during extended follow-up.
    - Safety reporting (including subsections 7.1.4.A, 7.1.4.B, 7.1.4.C, 7.1.4.D, 7.2, 7.2.1.E): Clarified that reporting timeframes outlined for events that are not SAEs are for those occurring during the randomised phase; reporting timeframes for non-SAEs occurring during extended follow-up are outlined in Appendix XX.
    - Statistical considerations (including subsections 9.2, 9.5): Updated to clarify that trial outcomes documented are for the randomised phase; outcomes in extended follow-up will focus on safety and possible long-term toxicities; a second SAP will be written for the extended follow-up phase.
    - Ancillary studies (subsection 10.2): Clarified that time-points for collection of PBMCs for immunology virology substudy can be found in the Trial Assessment Schedule for the Randomised Phase of the Trial.
    - Regulatory & Ethical Issues (including subsections 11.2.1.A, 11.2.1.C): Clarified that the IDMC will only review events occurring during the randomised phase; clarified drug supply arrangements for the randomised phase and extended follow-up.
    - Finance: Clarified drug supply arrangements for the randomised phase and extended follow-up.
    - Appendix I: Added parent/carer PIS, participant PIS and simplified PIS for younger children for extended follow-up.
    - Appendix II: Added parent/carer ICF, participant ICF and participant assent forms for extended follow-up.
    - Appendix XIII: Clarified that the IDMC will review PK and safety data from the randomised phase of the trial.
    - Appendix XX: New appendix added to describe the arrangements for the extended follow-up of ODYSSEY participants
2. The following section has been amended to describe an update to the end of trial definition:
    - Assessments & Follow-Up (subsection 6.11): End of Trial definition updated.
3. Safety Reporting (Section 7.1.1): Correction of trial IMP definition

Minor changes

1. Front page: Logos updated
2. General Information: Compliance and safety information updated to comply with newly released MRC CTU protocol template; Penta, MRC CTU and PHPT details updated, including contact details for SAE reporting for PHPT sites.
3. Trial Assessment Schedule: Clarified that Sleep and Mood section of the Acceptability, Sleep and Mood questionnaire should only be completed for children aged 6 years and over, and that lipids/glucose tests after week 96 should also be should be performed under fasted conditions.
4. Introduction: Updated information on DTG and pregnancy based on more recent data from the TSEPAMO study.
5. Section 5.3.1: Clarified that DTG dose should be adjusted if a child moves weight band (removed reference to moving up a weight band); removed reference to WB-PK1 part III; removed that DTG dosing would *initially* be dependent on age for participants weighing 3-<6kg; removed that recruitment to lower weight bands may be opened at all sites; removed that DTG doses may change again based on PK data.
6. Section 5.9: Added reference to Section 6.9 for further information if a patient is withdrawn from follow-up.
7. Section 6.1.1: Minor updates to ensure consistency with Trial Assessment Schedule for Randomised Phase of the Trial
8. Section 6.9: Added statement on impact on trial data if participants stop trial follow-up early .
9. Section 7: Minor corrections throughout.
10. Section 7.1.2: Clarification of adverse event definition and those that require reporting.
11. Section 7.1.4.D – The timeframe for AEs in infants born to female participants to be collected increased to 30 days after delivery.
12. Section 7.2.1.C: Table 6 reordered to align with that in recently updated MRC CTU protocol template.
13. Section 7.2.1.D: Updated to clarify that the site investigator should make an initial assessment of expectedness but that Sponsor has overall responsibility; location of current RSI documentation added.
14. Section 7.2.2: Clarified that the "investigator" reporting events does not need to be the PI, it can be another medically qualified person with delegated responsibility for event reporting; contact details for event reporting added to this section
15. Section 7.3: Clarified that medically-qualified staff at the CTUs and/or the Chief Investigator (or a medically-qualified delegate) will review all event reports received, clarified to whom SAEs may be reported (regulatory authorities) and applicable timelines; MRC CTU produce the annual DSUR, clarified events will be reported to drug companies involved as per the individual contract requirements
16. Section 8: Minor updates throughout as per recently released MRC CTU protocol template.
17. Section 10.5: Minor correction to folate substudy appendix number
18. Section 11.1: Updated throughout to reference Clinical Trials Regulation EU No 536/2014
19. Section 11.2.1.A: Updated information on DTG and pregnancy following recent release of results from TSEPAMO study.
20. Section 14: Minor updates to include information on Patient and Pubic Involvement, as per MRC CTU protocol template.
21. Section 15: Updated to include timeline for reporting trial results.
22. Section 16: Added as per MRC CTU protocol template.
23. Appendix II: Corrections made to Participant Re-Consent to ODYSSEY trial.

24. Appendix XIII: WB-PK1 part III removed; removed that DTG dosing would *initially* be dependent on age for participants weighing 3-<6kg.
25. Appendix XIX: Removed DTG dosing for WB-PK participants relating to WB-PK1 part III; removed that DTG dosing would *initially* be dependent on age for participants weighing 3-<6kg.

Changes to protocol version 4.0 creating protocol version 5.0 1st March 2019

Major changes

1. Summary: Virological response component of primary outcome measure updated so that children who do not respond virologically will not be included as failures unless their clinician switches them from first to second-line treatment (ODYSSEY A) or second to third-line treatment (ODYSSEY B) or they have confirmed viral load ≥400 c/ml at or after 36 weeks; addition of folate substudy.
2. Trial assessment schedule and section 6.1: RBC folate/RBC storage and B12/serum storage for folate substudy added and footnotes updated accordingly.
3. Section 5.3.1: Updated to describe changes to DTG dosing within the main trial, based on latest PK and safety data, and also ongoing WB-PK doses. Detailed WB-PK substudy information removed to avoid duplication as included in Appendix XIII.
4. Section 5.5.1: Recommended switching female participants on DTG-based regimen identified to be pregnant within the first 8 weeks after the last menstrual period to a non-DTG ART regimen if there are other good options available to replace DTG.
5. Section 9.2.1: Virological response component of primary outcome measure updated so that children who do not respond virologically will not be included as failures unless their clinician switches them from first to second-line treatment (ODYSSEY A) or second to third-line treatment (ODYSSEY B) or they have confirmed viral load ≥400 c/ml at or after 36 weeks.
6. Section 10: Addition of folate substudy; minor updates to other substudies.
7. Appendix I: Updates to main trial PISs to include updated safety information, collection of information on babies born to female participants, information on data collection and storage; additional Qualitative substudy PISs to include in-depth interviews with caregivers, and in-depth interviews with participants on DTG following the safety alert; added PIS for YTB facilitators.
8. Appendix II: Addition of parent/carer and participant re-consent to the ODYSSEY trial and participant re-assent to the ODYSSEY trial; additional Qualitative substudy consent forms to include in-depth interviews with caregivers and consent/assent forms for in-depth interviews with participants on DTG following the safety alert; added consent form for YTB facilitators.
9. Appendix XV: Updated following DTG safety alert and to include caregiver interviews.
10. Appendix XVIII: Added for folate substudy.
11. Appendix XIX: Added for tabulation of dolutegravir dosing in the ODYSSEY trial across different protocol versions.

Minor changes

1. General information: Updated email address for contacting MRC CTU regarding randomisations & SAE reporting; staff details; collaborating centre details
2. Summary: Removed that participants 3-<14kg may contribute to the 700 children in the main trial as main trial finished recruitment before lower weight bands opened and therefore at least 60 additional children will be recruited; clarification of recruitment period for children 3-<14kg.

3. Trial schema: Added footnote to briefly describe enrolment and follow up of children 3-<14kg;
4. Trial assessment schedule: Pregnancy tests to be performed at all trial visits, and other time-points if required, for all females of childbearing potential.
5. Abbreviations: Updated
6. Section 1.3: Minor update (WHO 2016 no longer most recent guidelines)
7. Section 1.4: Updated to reference recent study.
8. Section 1.5: Section added to include information on TSEPAMO study and dolutegravir safety alert. Subsequent sections renumbered accordingly.
9. Section 1.6: Added information on DTG formulations available.
10. Section 3.1.1: Footnote amended for clarification.
11. Section 3.4: Clarification and update of recruitment period for children 3-<14kg.
12. Section 4.1: Updated email address for contacting MRC CTU regarding randomisations.
13. Section 5.1: Removed US as no longer participating; updated that DTG-containing FDCs may be sourced through national programmes where available.
14. Section 5.3.2: Updated to clarify that participants 25-<40kg whose DTG dose is increased to 50mg following the results of WB-PK2 and are already receiving ABC 600mg + 3TC 300mg may switch to Triumeq.
15. Section 5.5.2.A: Updated to enable possiblity of restarting DTG if alternative cause for explanation of raised liver enzymes is more likely.
16. Section 5.5.2.C: Updated for clarification.
17. Section 5.10: Sodium valproate added to list of drugs with significant interactions; update to information regarding concomitant calcium/iron/vitamin supplements; added reference to link to University of Liverpool HIV Drug Interactions website added.
18. Section 6.1: Pregnancy tests to be performed at all trial visits, and other time-points if required, for all females of childbearing potential; information about contraception use to be recorded; RBC folate/RBC storage and B12/serum storage for folate substudy added.
19. Section 6.7.1: Children in the DTG arm receiving rifampicin as part of TB prevention therapy may also participate in the TB-PK substudy.
20. Section 6.8: Updated to include information on TSEPAMO study; list of highly effective contraception that must be used if female participants are sexually active; updated guidance to sites if female participants taking DTG are intending to/become pregnant during the trial.
21. Section 7.1.5.D: Reporting of events in infants born to female trial participants added; other minor update for clarification.
22. Section 7.2.1.D: Updated to clarify that the most recently approved IB should be used for assessing expectedness for DTG and DTG-containing products but that SPC should be used for all other ARVs.
23. Section 9.5: Clarified primary analysis refers to main trial participants; clinical and adverse events will be summarised using an in-house coding system
24. Section 11.2.1.A: Updated with information on common side effects and dolutegravir in pregnancy safety alert.
25. Section 13: Clarification of the drugs provided for the trial and to which sites/countries.
26. Appendix I: Updates to WB-PK1 PISs to include children 3-<14kg; updates to Qualitative substudy focus group PISs; updates to YTB PIS.
27. Appendix II: Updates to parent/carer main study consent to randomisation, participant main study consent to continued participation for young people who reach the age of consent whilst in the trial; updates to WB-PK1 consent/assent forms to include children 3-<14kg; update to title of consent form for Qualitative focus group discussions (young people 18-19 years); updated YTB consent/assent forms.

28. Appendix XIII: Updated to include results and outcomes of the WB-PK substudies to date and to fully describe updates to the WB-PK1 substudy (parts II & III). Rearrangement of some sections and other minor amendments for clarification purposes; Table 10 moved to appendix XIX.
29. Appendix XIV: Children in the DTG arm receiving rifampicin as part of TB prevention therapy may also participate in the TB-PK substudy; clarified that children <6 years may be recruited.
30. Appendix XVI: Updated to include interviews and to clarify that ≥32 young people will take part.
31. Appendix XVII: Odyssey structure updated with sites added/deleted as appropriate.

Changes to protocol 3.0 creating version 4.0 22nd December 2017

Major changes

1. Summary: In the number of patients, added that 60 additional children 3-<14kg will be enrolled, some of whom may contribute to the 700 children in the main trial (see below changes in sections 9.1 and 9.5).
2. Section 6.1 and Trial assessment schedule footnote t: Clinical assessment, haematology and biochemistry tests at week 2 are required for all children 3-<14kg.
3. Section 3.1.1: Inclusion criteria expanded to include children aged ≥28 days and weighing 3-<14kg.
4. Section 3.4: Explanation that 60 additional children 3-<14kg will be enrolled as a separate group, some of whom may contribute to the 700 children in the main trial. Recruitment period increased to 96-120 weeks, to allow recruitment of younger/lighter children.
5. Section 5.3.1: Table 3 and the text are updated to include formulations and dosing information on children 3-<14kg recruited via an updated WB-PK1 substudy. Added information about the lead-in PK substudy for the weight band 3 to <14kg. Children 14-<20kg will receive DTG 25mg to simplify the dosing to one DTG 25mg tablet QD instead of two DTG 10mg tablets QD and to avoid confusion with two different dosing for this weight band in the trial. Added that ViiV Healthcare is confirming the suggested dose for children 3-<6kg. Also added that children 14-<25kg who are able to swallow tablets will be taking DTG 25mg tablets and those who cannot swallow will take dispersible tablets. Information on WB-PK1 is removed as repeated in Appendix XIII.
6. Section 6.11: The *end of the main trial recruitment* is defined. Explained that recruitment of children 3-<14kg may be continued after *the end of the main trial recruitment* reached and that all children will be followed up for a minimum of 96 weeks.
7. Section 9.1: Added that children 3-<14kg will be recruited and randomised as a separate group stratified by A/B and the 3 weight bands. Randomisation of children ≥14kg continues as previously.
8. Section 9.5: Added that children recruited in the 3 lower weight bands before recruitment targets have been achieved will contribute to the total accrual numbers for the main trial if their doses are confirmed to be optimal doses. Added that there will be a separate secondary analysis of all children <14kg when this group has completed 96 weeks follow-up.
9. Appendix XIII: WB-PK1 substudy is updated to include children 3-<14kg. Table 9 updated. References updated.

Minor changes

1. General information: Updated staff details; CTU address; added address of new collaborating centre.
2. Summary: Recruitment period increased to 96-120 weeks.

3. Trial assessment schedule footnote d: For clarity and consistency added that the screening viral load test for ODYSSEY B participants may be omitted if a result of ≥500 copies is available up to 4 weeks prior to the screening visit. (This change was included as part of the previous protocol version 3.0 and the details can be found elsewhere in sections 3.1.3 and 3.6.1. and for completeness and consistency is now added to the assessment schedule footnotes).
4. List of abbreviations: DT (dispersible tablet) added
5. Section 1.5: Information on marketing authorisation is updated.
6. Section 2.3: Deleted sites no longer participating, including Brazil and an IMPAACT-supported site in South Africa.
7. Section 3.1.3: TAF added to the list of drugs in the additional inclusion criteria for ODYSSEY B.
8. Section 3.3.1: TAF added to section on considerations of use of different NRTI.
9. Section 4 and Section 5.7 and Trial assessment Schedule: Updated that the Sleep and mood section of Acceptability, Sleep and Mood Questionnaire is to be completed at enrolment.
10. Section 5.1: Added TAF to list of NRTIs.
11. Section 5.2: – Added ATV/c to list of bPIs and added *"e.g.*" in order to clarify other less common drugs not listed may also be included.
12. Section 5.2.1 Table 1 and Section 5.2.2 Table 2: ATV/c, DRV/c and TDF or TAF are added in the examples of ART regimens for the SOC arm.
13. Section 5.3: TAF is added in the examples of NRTI backbone for the DTG arm.
14. Section 5.3.1: For children 20-<25kg added that doses in this weight band will be reviewed and, if necessary, modified based on PK and safety data from ODYSSEY and/or P1093. Clarified information on all weight bands in the WBPK substudies. Information on WB-PK1 is removed as repeated in Appendix XIII.
15. Section 5.5.1: Added that in exceptional circumstances study drug may be provided as third-line treatment for children in the SOC arm who have failed second-line treatment.
16. Section 5.5.2.C: Added that prompt clinical evaluation should be done (instead of considered) for participants who experience signs of suicidal ideation or behaviour.
17. Section 6.3: – Corrected typo - version of DAIDS from 2010 to 2014
18. Section 6.8: Information on reporting of pregnancy moved to the relevant section on safety reporting 7.1.5.
19. Section 7.1.5: Reporting of notable events is clarified. Added that the suspected cases of drug induced liver injury should be reported in both arms.
20. Section 7.2: clarified reporting of laboratory AEs, SAEs, SARs and notable events.
21. Sections 7.2.1 and 7.2.2: Clarified that notable events should be reported within 24 hours of the investigator becoming aware of the event.
22. Section 7.3: Clarified that the CTUs will review all reported notable events.
23. Section 8.3: Updated to clarify monitoring processes. Removed repetition on permission and consent to access patient data.
24. Section 8.3.2: Confidentiality section clarified.
25. Section 10.1: Updated information on PK substudies.
26. Section 17: References updated.
27. Appendix I: Titles of Patient Information Sheets are updated to include children weighing ≥3kg.
28. Appendix II: Titles of Template Consent and Assent Forms are updated to include children weighing ≥3kg. Main study consent to continued participation for young people who reach the age of consent whilst in the trial added.
29. Appendix XIII: Updated list of sites participating in WB-PK substudies.
30. Appendix XIV: Clarified that younger children <6 years may be recruited once the appropriate DTG doses are confirmed for them in WB-PK1 substudy. Updated information

in *study design* paragraph and Figure 1 that the 1st PK day (TB-PK1, 12h curve) may be performed within the last month of co-administration. Removed details of specific sites as the TB-PK will take place at all sites in Uganda, South Africa and Zimbabwe.

31. Appendix XVII: Odyssey structure updated with sites added/deleted as appropriate.

Minor corrections

Changes to protocol version 2.0 creating version 3.0 18th January 2017

Major changes

10. Summary of Trial and section 5.2: Added that INSTIs (other than DTG) can be included as a SOC third agent option. Clarified that PI means a boosted PI.
11. Summary of Trial secondary outcomes: Changed from ≥50 and ≥400 copies to <50 and <400 copies.
12. Summary of Trial and section 10 Ancillary substudies: Added WB-PK1 and WB-PK2 substudies. Renamed TB-PK substudy to differentiate from new PK substudies. Added Qualitative and Youth Trial Board substudies.
13. Updated Trial Schema to include INSTI in SOC Arm for ODYSSEY A and replace RAL with INSTI in SOC for ODYSSEY B.
14. Trial Assessment Schedule and accompanying notes: Added that the glucose test can be optional at the randomisation visit if there is a medical justification to limit the amount of blood drawn. Renamed EQ-5D questionnaire as Quality of Life questionnaire (as using an adapted version of the EQ-5D). Changed frequency of plasma storage after 96 weeks from every 24 weeks to every 12 weeks. Removed PBMC storage at screening, week 2 and the end of study visit. Changed acceptability questionnaire to acceptability, sleep and mood questionnaire and added that this will be done at week 12. Revised volumes for blood collection, differentiating for blood to be used for tests and for storage. Added that lipodystrophy and bone profile (optional) to be done at the end of study visit. Added clarifications regarding mandatory and optional tests. Clarified that adherence questionnaire for ODYSSEY B at screening visit only to be done if participant is currently on treatment. Added that BIA measurements will be done at selected sites. Added that, if not already scheduled, plasma storage, adherence and acceptability questionnaires should be done at point of treatment failure, and adherence and acceptability questionnaires if ART regimen changes.
15. Background: Updates and clarifications made.
16. Section 3.1.1 Patient inclusion criteria all patients: Replaced DTG dose known for age/weight band with “weighing ≥14 kg and DTG dose known for the child’s weight-band”, and added details regarding the inclusion criteria for children weighing 14 to <20kg.
17. Section 3.1.3 Additional criteria for ODYSSEY B: Additional definition of starting second-line ART as switch of only the third agent due to treatment failure where resistance tests show no NRTI mutations. Clarification that reasons for substitutions could also include changes in national guidelines or drug availability. Removed time period for cumulative results of resistance testing. Replaced viral load of >1000 copies with >500 copies at screening visit, and added that can also be within 4 weeks prior to screening.
18. Section 3.6.1: Removed words “for screening” and “screening” in order to comply with local requirements for consent procedures.
19. Section 3.6.1: Added viral load for ODYSSEY B may be done at screening or within 4 weeks prior to screening.
20. Section 4: Amended wording “written informed consent… must then be obtained” with “Continued agreement… must be confirmed” in order to comply with local requirements for consent procedures.

21. Section 5: Major reorganisation to this section: Added a general information section to clarify information relevant to all participants, regardless of treatment allocation. Moved text previously in either ODYSSEY A or B sections to this section as applicable to all participants (e.g. ABC warning cards).
22. Section 5.1.1: Added section 5.1.1 to clarify that participants must be prescribed the NRTI backbone selected prior to randomisation and added further guidance regarding changes to the NRTI backbone during the trial.
23. Section 5.1 and 5.2: Updated SOC drug options to include RPV and INSTIs. Tables 1 and 2 updated and moved to sections 5.2.1 and 5.2.2. Added for clarification that participants randomised to SOC must be prescribed the class of non-NRTI drug that was chosen prior to randomisation.
24. Section 5.2.2: Added further guidance regarding addressing adherence issues.
25. Section 5.2.2: Further guidance on interpretation of resistance test results added. Added that ddi or d4T may be used in second-line where no other drugs are available.
26. Section 5.3.1: Added information about DTG dosing according to the following weight bands: 14 to <20kg, 20 to <25kg, 25 to <40kg, and >40kg. Added information about the lead-in PK substudy (WB-PK1) for the weight bands 14 to <20kg and 20 to <25kg; and about the cross-over PK substudy (WB-PK2) for the weight band 25 to <40kg. Added table 3 summarising DTG dosing and formulations to be used in ODYSSEY.
27. Section 5.3.2: Added that (subject to satisfactory PK results) children ≥25kg in the main trial on DTG+ABC+3TC would be able to move to an FDC.
28. Added Section 5.5.2.C Suicidal Ideation Behaviours and Sleep Disorders.
29. Section 5.7: Acceptability questionnaire now incorporates questions on sleep and mood and week 12 now added (which was previously missing in error).
30. Section 5.10: Added information and table 4 on significant drug interactions with DTG.
31. Section 6.1 and 6.2.3: Added that for ODYSSEY B the viral load can be done at screening or 4 weeks prior.
32. Section 6.1: Removed PBMC storage at screening.
33. Section 6.2.4: Clarification that for children experiencing virological failure. Replaced >1000 c/ml with current threshold for resistance assays.
34. Section 6.4: Renamed EQ-5D questionnaire as Quality of Life questionnaire (as using an adapted version of the EQ-5D).
35. Section 6.7.1: Changed from at least '10' children to '12'.
36. Section 7.2: Added that Grade 1 clinical AEs should be reported only if they result in change of ART, (as well as Grade 2).
37. Section 9.1: Clarification that availability of resistance tests is for each particular site and is with respect to children who are failing treatment.
38. Section 9.1: Added TAF/3TC and TAF/FTC to TDF stratification group.
39. Section 9.1: Added that randomisation will be stratified by NRTI backbone.
40. Section 9.2.2: Changed, (<50 and <400 copies rather than ≥). Deleted "with a subgroup analyses according to the activity of the background regimen".
41. Appendix I Template information sheets Main study: Reworded explanation of second-line treatment. Updated volumes of blood collection from 2 to 3 teaspoons to 3 to 6 teaspoons. Deleted the visit schedule. Added sentence regarding depression or having suicidal thoughts in possible disadvantages of taking part. Added more detail on section "what will happen to information about me/my child collected during the study".
42. Appendix I: Added information sheet for the WB-PK 1 substudy (also incorporating the main trial).
43. Appendix I: Added information sheet for the WB-PK 2 substudy (also incorporating the main trial).

44. Appendix I: Renamed information sheet for TB PK substudy. Added further details to "what will happen to information about me/my child collected during this substudy". Reduced number of samples collected from 10 to 7. Changed wording from hospital to clinic.
45. Appendix I: Added information sheets for Qualitative substudy.
46. Appendix I: Added information sheets for Youth Trial Board substudy.
47. Appendix II: Added consent and assent forms for WB-PK 1 and WB-PK 2 substudies.
48. Appendix II: Added consent and assent forms for Qualitative substudy.
49. Appendix II: Added consent and assent forms for Youth Trial Board substudy.
50. Appendix IV: Updated adherence questionnaires.
51. Appendices V and VI: Updated acceptability questionnaires and also incorporated additional questions on sleep and mood. No longer different questionnaires for ODYSSEY A and B therefore Appendix VI deleted.
52. Added Appendix XI and Table 7 on safe limits of blood sample volumes in children.
53. Updated Appendix XII on the Immunology/virology substudy.
54. Added Appendix XIII on the Weight band pharmacokinetics substudies WB-PK 1 & 2.
55. Updated Appendix XIV on the TB PK substudy.
56. Added Appendix XV on the Qualitative Substudy.
57. Added Appendix XVI on the Youth Trials Board project.

Minor changes

1. Cover page: Mylan logo added.
2. General information: Updated phone number and e-mail address for MRC CTU randomisations.
3. General information: Updated e-mail address for SAE reporting for MRC CTU coordinated sites.
4. General information: Updated staff details at PENTA foundation, MRC CTU, INSERM-ANRS and PHPT.
5. General information: Updated details of staff at collaborating centres and removed countries and centres no longer participating. Updated and added new collaborating centres.
6. General information: Added e-mail addresses for David Burger, Nigel Klein and Maria Munoz Ferndandez.
7. Summary of Trial: Clarified that PI means a boosted PI.
8. Summary of Trial and sections 9.2.1 to 9.2.3; Primary and secondary outcomes: clarifications made to how endpoints will be assessed.
9. Summary of Trial: Secondary outcome measures, deleted word "suppression".
10. Summary of Trial and sections 9.2.3 and 9.5 Added that change in total cholesterol from baseline to week 96 will be used to assess superiority of DTG arm vs SOC arm.
11. Summary of Trial and section 10, ancillary substudies: Added "see section 10 for participating countries". Reworded summary Immunology/virology substudy for clarity and consistency.
12. Abbreviations: List updated. Removed EQ-5D and replaced with QoL.
13. Section 2.3 Site Management: Removed countries no longer participating.
14. Section 3.2 Patient exclusion criteria. Minor rewording for clarification regarding history of presence of known allergy or contraindications to DTG, proposed available SOC third agent or NRTI backbone.
15. Section 4 Registration & Randomisation: Minor rewording for clarity. Updated the MRC CTU contact details for randomisations. Clarified that family also can mean household for enrolment of multiple participants.

16. Section 5.1: Clarifications regarding drug supply added, and that that the Mylan formulation of ABC/3TC 120/60mg will be provided in sub-Saharan Africa if required.
17. Section 5.4: Clarification that refers to trial drugs.
18. Section 5.5: Renamed section title for clarity (deleted word “dose”).
19. Section 5.5.1: Renamed section title for clarity. Moved sentence on “if simplification…is deemed necessary” to the end of the section. Added word “treatment”. Minor clarification regarding recommendations if possible drug induced liver injury.
20. Section 5.5.2: Renamed section title for clarity. Added word “appropriate” before CTU.
21. Section 5.7 Heading reworded for clarity from Compliance and adherence to adherence and acceptability. Deleted words “participant-reported” in first sentence for clarity.
22. Section 5.8: Reworded “pills” as may include liquid formulations.
23. Section 6.1: Clarification that if previous Tanner scores of 5, no need to continue doing Tanner scores at subsequent visits. Added “and then 48 weekly” and “and at end of study” to those measurements where this was missing, in order to match the Trial Assessment Schedule.
24. Section 6.2.4: Added that samples may be assayed locally where possible, or moved to another country.
25. Section 6.4 Added “and at end of study” for the quality of life questionnaire”.
26. Sections 6.7 to 6.7.2. Clarification that participants may either have TB at enrolment or develop TB during the trial. Clarification that not compulsory to enter the substudy if participant has TB. Other minor rewording for clarification.
27. Section 6.11: Clarification that the trial will be considered closed when the last patient to be enrolled reaches 96 weeks.
28. Sections 7.1, 7.1.5 and 7.2.1: Table 4 renumbered as Table 5.
29. Section 7.2.1: Table 5 renumbered as Table 6.
30. Section 7.1.5: Renamed section title as other notable events, renumbered some section titles from 7.3.*x* to 7.2.*x*
31. Section 7.3: Corrected spelling error.
32. Section 8.2: Deleted MRC as relevant to all CTUs.
33. Section 9.1: Clarification that availability of resistance testing is relevant to “before switch to second line”.
34. Section 9.2.3: Added “change in total cholesterol from baseline to week 96”.
35. Section 9.2.4: Removed “as assessed by patient completed questionnaires”.
36. Section 9.5: Added paragraph on how the proportion of participants with VL <50 or <400 will be determined.
37. Section 10: Added a short summary of the ancillary studies details of which countries are participating.
38. Section 11.2.1.E: Corrected that computer generated anonymous codes will be three letters not four. Corrected that full date of birth, not just month and year of birth will be used. Added further details on identifiers for stored samples.
39. Section 13: Clarification regarding arrangements for drug supply.
40. Appendix I: Grammar correction in patient/carer information sheet “what happens at the end of the study” section.
41. TB-PK information sheet – changed wording from “Rifampicin” to “anti-TB medicine” to make easier to understand. Changed blood sample amount from “less than” half a teaspoon to “about” half a teaspoon.
42. Appendix II: Parent/carer – main trial consent to screening, corrected typo on last statement.
43. Appendix II: Added screening assent form.
44. Appendix II: Added participant consent to storage of blood samples for future testing form.
45. Appendix II: Renamed consent form for TB PK substudy (added “TB”).

46. Renumbering of Appendices throughout document following deletion of appendix VI.
47. Appendix IX: Updated DAIDS Tables to 2014 version.
48. Appendix XVII updated ODYSSEY structure to remove countries and collaborating sites no longer participating and to include new collaborating sites.

Changes to protocol version 1.1 creating version 2.0 6th March 2015
Cover page: IMPAACT logo updated.
General Information: Details for collaborating centres in Klerksdorp, South Africa (PHRU) and Memphis, US (St Jude Children's Research Hospital) added
General Information & Section 2.3 Site Management: US removed in relation to IMPAACT and added as a MRC collaborator.
General Information: MRC CTU at UCL staff details updated.
Trial Assessment Schedule: Timing of urine dipstick tests corrected – tests at end of study visit added.
Trial Assessment Schedule & Section 6.4 Procedures for Assessing Quality of Life: Removal of reference to EQ-5D-Y questionnaire, replaced with EQ-5D. EuroQol website link added to section 6.4.
Trial Assessment Schedule: Total blood volume to be collected clarified.
Abbreviations: List updated to include EQ-5D.
Section 6.8 Management of Pregnancy: Clarified that pregnant participants should be encouraged to remain in the study even if ART regimen is changed.
Section 7.3.1.D Expectedness: Updated information on responsibilities for determination of expectedness of serious adverse events.

Changes to protocol version 1.0 creating version 1.1 11 December 2014 (the protocol was still a draft document at this stage but a "final" version was required for review by Viiv resulting in version numbers taking this format. Neither protocol version 1.0 nor version 1.1 have been reviewed by an ethics committee or competent authority).
General Information, Summary of Trial, Section 2 Selection of Sites/Clinicians & Section 14 Oversight & Trial Committees: Details of IMPAACT involvement added.
General Information: Funding information corrected to reflect current status.
General Information: Sponsor details added.
General Information: Immunology/Virology Committee member details updated.
Summary of Trial: Updated for consistency and minor amendments for clarification.
Trial Schema, Section 5.1 Introduction & Section 5.2 SOC Arm: Addition of raltegravir to SOC arm of ODYSSEY B.
Trial Assessment Schedule & Section 6.1 Trial Assessment Schedule: Addition of urine dipstick tests.
Trial Assessment Schedule, Section 3.1.1 Patient Inclusion Criteria, Section 6.1 Trial Assessment Schedule & Section 6.8 Management of Pregnancy: Pregnancy test requirements clarified.
Trial Assessment Schedule: Timing of Tanner scale measurements, lipodystrophy assessments and study drug supply clarified.
Trial Assessment Schedule: Timing of screening and randomisation visits clarified.
Abbreviations: List updated accordingly.
Section 1 Background: Updated
Section 2 Selection of Sites: General wording updated and update to laboratory requirements. Clarified that a site and lab risk assessment will be carried out prior to site activation.
Section 3.2 Patient Exclusion Criteria: Bilirubin must be ≥2xULN.
Section 5 Treatment of Patients & Section 13 Finance: Triumeq can be provided by Viiv Healthcare as appropriate.

Section 5.5.2.A Liver Toxicity: Stopping criteria updated to include that DTG should be substituted if ALT ≥3xULN and bilirubin ≥2xULN, or that ALT ≥5xULN for more than 2 weeks with bilirubin <2xULN and no symptoms of acute hepatitis or hypersensitivity.
Section 6.2.2 Immunology, Section 8.3.1 Direct Access to Participant Records & Section 9.2.2 Secondary Efficacy Outcomes: Clarification that total and percentage CD8 T cell counts should also be measured and access will be required to a random sample of this data. This data will be used to provide CD4/CD8 ratios required as a secondary efficacy outcome.
Section 6.2.4 Resistance Testing: At sites where genotypic resistance testing is not performed as standard of care baseline samples will be tested retrospectively and batched genotypic resistance testing will be performed on samples with viral load >1000 c/ml.
Section 6.7.1 Management of Children with Tuberculosis in the DTG Arm & Section 10.2 Pharmacokinetic Substudy in Participants Developing TB while on DTG: At least 10 children with TB receiving DTG and rifampicin will be invited to participate in the PK substudy.
Section 6.8 Management of Pregnancy: Clarification that all infants born to female participants will receive infant prophylaxis according to current local standard of care.
Section 6.8 Management of Pregnancy: Clarification that any pregnancy that occurs during study participation must be reported as a notable event.
Section 6.10 Participant Transfers: Patients can continue to attend visits at original site if sufficient resources are available, or nurse only telephone visits can be conducted with drugs and clinical care provided at a local clinic. Participant should be considered lost to follow-up if none of the options are possible.
Section 7.4 CTU Responsibilities: Modified for general applicability. CTUS are responsible for reporting of SAEs to relevant regulatory authorities and research ethics committees. This responsibility may be delegated to country principal investigators.
Section 8.3 On-Site Monitoring: Monitors will evaluate laboratory procedures and sample storage.
Section 9 Statistical Considerations: Randomisation will be stratified by bPI/non-bPI-base ART offered as SOC (to include RAL).
Section 13 Finance: Drugs provided by Viiv Healthcare corrected.
Minor corrections

18 REFERENCES

1. UNAIDS. Aids by the Numbers. 2016. http://www.unaids.org/sites/default/files/media_asset/AIDS-by-the-numbers-2016_en.pdf.
2. UNAIDS. Children and HIV. 2016. http://www.unaids.org/sites/default/files/media_asset/FactSheet_Children_en.pdf.
3. Stellbrink HJ, Reynes J, Lazzarin A, Voronin E, Pulido F, Felizarta F, et al. Dolutegravir in antiretroviral-naive adults with HIV-1: 96-week results from a randomized dose-ranging study. AIDS. 2013;27(11):1771-8.
4. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. The Lancet infectious diseases. 2013;13(11):927-35.
5. Eron JJ, Clotet B, Durant J, Katlama C, Kumar P, Lazzarin A, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. The Journal of infectious diseases. 2013;207(5):740-8.
6. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutierrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. The New England journal of medicine. 2013;369(19):1807-18.
7. Tebas P KP, Hicks C. 48 week bone marker changes with dolutegravir plus abacavir/lamivudine vs. tenofovir/emtricitabine/efavirenz: the SINGLE trial. In: al. e, editor. 53rd ICAAC; Denver2013.
8. Yazdanpanah Y, Khuong-Josses MA, Hocqueloux L, Pialoux G, Durant J, Wynne B, et al. 48 week bone marker changes with Dolutegravir (DTG) plus Abacavir/Lamivudine (ABC/3TC) vs. Tenofovir/Emtricitabine/Efavirenz (EFV/TDF/FTC): the SINGLE trial. BMC Infectious Diseases. 2014;14(Suppl 2):P72-P.
9. Molina JM, Clotet B, van Lunzen J, Lazzarin A, Cavassini M, Henry K, et al. Once-daily dolutegravir is superior to once-daily darunavir/ritonavir in treatment-naive HIV-1-positive individuals: 96 week results from FLAMINGO. Journal of the International AIDS Society. 2014;17(4 Suppl 3):19490.
10. Kanters S, Vitoria M, Doherty M, Socias ME, Ford N, Forrest JI, et al. Comparative efficacy and safety of first-line antiretroviral therapy for the treatment of HIV infection: a systematic review and network meta-analysis. Lancet HIV. 2016;3(11):e510-e20.
11. Patel DA, Snedecor SJ, Tang WY, Sudharshan L, Lim JW, Cuffe R, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naive HIV-1-infected patients: a systematic review and network meta-analysis. PLoS One. 2014;9(9):e105653.
12. Cahn P, Pozniak AL, Mingrone H, Shuldyakov A, Brites C, Andrade-Villanueva JF, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet. 2013;382(9893):700-8.
13. Castagna A, Maggiolo F, Penco G, Wright D, Mills A, Grossberg R, et al. Dolutegravir in Antiretroviral-Experienced Patients With Raltegravir- and/or Elvitegravir-Resistant HIV-1: 24-Week Results of the Phase III VIKING-3 Study. The Journal of infectious diseases. 2014.
14. Weller S, Borland J, Chen S, Johnson M, Savina P, Wynne B, et al. Pharmacokinetics of dolutegravir in HIV-seronegative subjects with severe renal impairment. European journal of clinical pharmacology. 2014;70(1):29-35.
15. Demarest J, Underwood M, St Clair M, Dorey D, Almond S, Cuffe R, et al. DTG-containing regimens are active in INI-naïve patients with a history of NRTI resistance. Oral abstract (TUAB0104) presented at: Antiretroviral therapy: not all strategies are created equal, 20th International AIDS Conference; 2014 July 20-25; Melbourne, Australia. http://pag.aids2014.org/Abstracts.aspx?AID=6331

16. Wiznia A et al, editor IMPAACT 1093: Dolutegravir in 6- to 12-Year-Old HIV-Infected Children: 48-Week Results. CROI; 2016; Boston, USA.
17. Viani RM, Alvero C, Fenton T, Acosta EP, Hazra R, Townley E, et al. Safety, Pharmacokinetics and Efficacy of Dolutegravir in Treatment-experienced HIV-1 Infected Adolescents: Forty-eight-week Results from IMPAACT P1093. Pediatr Infect Dis J. 2015;34(11):1207-13.
18. Wiznia A, Alvero C, Fenton T, George K, Townley E, Hazra R, et al. IMPAACT 1093: Dolutegravir in 6- to 12-Year-Old HIV-Infected Children: 48-Week Results. Poster abstract (816) presented at Pharmacokinetics: efficacy and safety of new ARVs in children; Conference of Retroviruses and Opportunistic Infections (CROI); 2016 Feb 22-25; Boston, Ma. http://www.croiconference.org/sessions/impaact-1093-dolutegravir-6-12-year-old-hiv-infected-children-48-week-results.
19. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection - recommendations for a public health approach (second edition). June 2016. http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1
20. LePrevost M, Green H, Flynn J, Head S, Clapson M, Lyall H, et al. Adherence and acceptability of once daily Lamivudine and abacavir in human immunodeficiency virus type-1 infected children. Pediatr Infect Dis J. 2006;25(6):533-7.
21. PENTA. Pharmacokinetic study of once-daily versus twice-daily abacavir and lamivudine in HIV type-1-infected children aged 3-<36 months. Antivir Ther. 2010;15(3):297-305.
22. Musiime V, Kasirye P, Naidoo-James B, Nahirya-Ntege P, Mhute T, Cook A, et al. Once vs twice-daily abacavir and lamivudine in African children. AIDS. 2016;30(11):1761-70.
23. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. The New England journal of medicine. 2008;359(21):2233-44.
24. Harrison L, Melvin A, Fiscus S, Saidi Y, Nastouli E, Harper L, et al. HIV-1 Drug Resistance and Second-Line Treatment in Children Randomized to Switch at Low Versus Higher RNA Thresholds. J Acquir Immune Defic Syndr. 2015;70(1):42-53.
25. Germanaud D, Derache A, Traore M, Madec Y, Toure S, Dicko F, et al. Level of viral load and antiretroviral resistance after 6 months of non-nucleoside reverse transcriptase inhibitor first-line treatment in HIV-1-infected children in Mali. The Journal of antimicrobial chemotherapy. 2010;65(1):118-24.
26. Ruel TD, Kamya MR, Li P, Pasutti W, Charlebois ED, Liegler T, et al. Early virologic failure and the development of antiretroviral drug resistance mutations in HIV-infected Ugandan children. J Acquir Immune Defic Syndr. 2011;56(1):44-50.
27. Hamers RL, Sigaloff KC, Wensing AM, Wallis CL, Kityo C, Siwale M, et al. Patterns of HIV-1 drug resistance after first-line antiretroviral therapy (ART) failure in 6 sub-Saharan African countries: implications for second-line ART strategies. Clin Infect Dis. 2012;54(11):1660-9.
28. Paton NI, Kityo C, Hoppe A, Reid A, Kambugu A, Lugemwa A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. The New England journal of medicine. 2014;371(3):234-47.
29. Fox MP, Ive P, Long L, Maskew M, Sanne I. High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa. J Acquir Immune Defic Syndr. 2010;53(4):500-6.
30. Sigaloff KC, Hamers RL, Wallis CL, Kityo C, Siwale M, Ive P, et al. Second-line antiretroviral treatment successfully resuppresses drug-resistant HIV-1 after first-line failure: prospective cohort in Sub-Saharan Africa. The Journal of infectious diseases. 2012;205(11):1739-44.
31. Song IH, Borland J, Savina PM, Chen S, Patel P, Wajima T, et al. Pharmacokinetics of Single-Dose Dolutegravir in HIV-Seronegative Subjects With Moderate Hepatic Impairment Compared to Healthy Matched Controls. Clin Pharmacol Drug Dev. 2013;2(4):342-8.
32. Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once

daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013;62(1):21-7.
33. Dooley K, Kaplan R, Mwelase T, Grinsztejn B, Ticona E, Lacerda M, et al., editors. Safety and efficacy of dolutegravir-based ART in TB/HIV co-infected adults at week 48. 22nd International AIDS Conference; 2018 23-27 July; Amsterdam, The Netherlands.
34. Ltd VHU. Tivicay film-coated tablets: summary of product characteristics: ViiV Healthcare UK Ltd; [Available from: https://www.medicines.org.uk/emc/product/5248/smpc
35. Dorward J, Lessells R, Drain PK, Naidoo K, de Oliveira T, Pillay Y, et al. Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research. Lancet HIV. 2018;5(7):e400-e404.
36. Zash R. HL, Diseko M., Jacobson D.L., et al. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. The New England journal of medicine. 2019(381):827-40.
37. Zash R, Jacobson DL, Diseko M, Mayondi G, Mmalane M, Essex M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. The Lancet Global health. 2018;6(7):e804-e810.
38. Heads of Medicines Agencies, C.T.F.G. Recommendations related to contraception and pregnancy testing in clinical *trials*. 15 Sep 2014; Available from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf.
39. Patel P, Song I, Borland J, Chen S, Peppercorn A, Wajima T, et al. Relative bioavailability of a paediatric granule formulation of the HIV integrase inhibitor dolutegravir in healthy adult subjects. Antivir Ther. 2014;19(3):229-33.
40. Buchanan AM HM, Conn I, Davies M, Choukour M, Wynne BR. . Relative Bioavailability of a Dolutegravir Dispersible Tablet and the Effects of Low- and High-Mineral-Content Water on the Tablet in Healthy Adults. Clin Pharmacol Drug Dev. 2017;6(6):577-583.
41. Penazzato M, Prendergast A, Tierney J, Cotton M, Gibb D. Effectiveness of antiretroviral therapy in HIV-infected children under 2 years *of age.* Cochrane Database Syst Rev, 2012. **7**: p. CD004772.
42. Abers MS, Shandera WX, Kass JS. Neurological and psychiatric adverse effects of antiretroviral drugs. CNS Drugs, 2014. **28**(2): p. 131-45.
43. Bollen P, Turkova A, Mujuru H, Musiime V, Amuge P, Lugemwa A, et al., editors. Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing 14 to <25kg on film-coated dolutegravir 25mg tablets in the ODYSSEY trial. 10th International Workshop on HIV Pediatrics. 2018. Amsterdam, the Netherlands.
44. Bollen P, Turkova A, Mujuru H, Kaudha E, Lugemwa A, Amuge P, Colbers A, Moore C,Parker A, Musiime V, Hakim JG, Ford D, Gibb D, Burger D, and the ODYSSEY trial team, Adult dolutegravir 50mg film-coated tablets in children living with HIV weighing 20 to <25kg, in Conference of Retroviruses and Opportunistic Infections (CROI*)*. 2019: Seattle, WA.
45. Turkova A, Bollen P, Kaudha E, Chidziva E, Lugemwa A, Kekitiinwa A, Parker A, Shakeshaft C, Montero S, Colbers A, Nanduudu A, Mujuru H, Makumbi S, Amuge P, Rojo P, Ford D, Burger DM, Gibb DM, and the ODYSSEY trial team. Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing ≥25kg after switching to 50mg film-coated dolutegravir tablets in the ODYSSEY trial, in 10th International Workshop on HIV Pediatrics. 2018: Amsterdam, The Netherlands.
46. WHO, Paediatric Antiretroviral Drug Optimization (PADO) Meeting 3. WHO.
47. Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serrano J, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf, 2009. **32**(1): p. 55-68.
48. Wille N, Badia X, Bonsel G, Burstrom K, Cavrini G, Devlin N, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res, 2010. **19**(6): p. 875-86.

49. Kekitiinwa A, Cook A, Nathoo K, Mugyenyi P, Nahirya-Ntege P, Bakeera-Kitaka S, et al. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. Lancet. 2013;381(9875):1391-403.
50. AIDSinfo. Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child-Bearing Potential. 2018 May 30, 2018; Available from: https://aidsinfo.nih.gov/news/2109/recommendations-regarding-the-use-of-dolutegravir-in-adults-and-adolescents-with-hiv-who-are-pregnant-or-of-child-bearing-potential.
51. EMA. Guideline on good pharmacovigilance practices (GVP) Module VI – Collection, management and submission of reports of suspected adverse re*actions to medicinal products (Rev 2)*, in *Guideline on good pharmacovigilance practices (GVP)*. 2017: EMA.

19 APPENDIX I TEMPLATE PATIENT INFORMATION SHEETS

PARENT/CARER INFORMATION SHEET - MAIN STUDY ONLY

ODYSSEY STUDY

We are inviting you and your child to take part in a research study

- Before you decide whether to take part, it is important for you and your child to understand why we want to carry out this study and what it will mean for you both.
- Please take time to read the following information and to discuss it with friends, family and with your doctor or clinic nurse if you wish.
- You are free to decide if you want your child to take part in this research study. If you choose not to take part, this will not affect the care your child gets from your doctor or nurse.
- If you decide to take part in the study you can stop taking part at any time without giving a reason.
- Ask your study doctor or nurse if anything is not clear or if you would like more information.
- Thank you for reading this information.

Important to know

- If you decide to take part your child will have some extra visits to the clinic at the beginning of the study.
- A computer program will choose which treatment your child will take. Neither you nor your doctor will be able to choose which group your child is in.

Contents

1 Why are we doing this study?

Dolutegravir is a new medicine being used to treat adults with HIV.

In adults it has been shown to be effective and safe, with few side effects, and it only needs to be taken once a day.

Sometimes a medicine works differently in growing children than in adults, so we need to check how it works in children as well. Dolutegravir could be an excellent option for children if the study finds it works as well as it does in adults.

ODYSSEY will see how children and adolescents taking dolutegravir as part of their anti-HIV medicines compare to others taking different anti-HIV medicines.

2 Why has my child been asked to take part?

We are aiming to ask 700 children and young people from many countries to take part.

Your child has been asked to participate because:

A. He/She is about to start taking anti-HIV medicine for the first time.

Or

B. He/She is already taking one set of anti-HIV medicine that is no longer working well and your doctor has decided it is time your child changes to a new combination. This is known as “second-line” treatment.

3 What will happen if we decide not to take part?

It is totally up to you and your child whether or not he/she takes part in this study.

It is your right to decide not to take part if you wish.

This will not affect your child’s care now or in the future in any way.

4 What will happen if my child takes part?

If you decide to take part, we will go through this information sheet together. We will give a copy to you to keep. You will be asked to sign a consent form to show you have understood the information and have agreed for your child to have some blood tests and a check-up to see whether they can go into the study.

If the results show that your child can participate, we will invite him/her to enter the study. We need to know that you have fully understood the study and then we will ask you to sign a second consent form for your child to join.

Your child’s health will be watched closely during the study.

In the first 2 months you will need to come for 3 appointments. Once your doctor is happy that your child has no side effects from the medicines and is doing well, they will change to having 3-monthly appointments.

These visits are to make sure your child is continuing to do well. If for any reason your doctor has any concerns, they will change your child's treatment in the normal way.

In addition to blood tests to check for any side effects, a small amount of extra blood will be collected at each visit. The total amount of blood taken will never exceed a safe limit and will be between 3 and 6 teaspoons depending upon the age of your child. Part of this sample will be stored to be used to check the amount of virus in the blood and to look at how the body fights HIV. We would like your agreement that we can store these samples anonymously (without your child's name or exact date of birth) for up to 15 years.

Your child will be in the study for at least 2 years. When the study ends, if your child is doing well they may be able to remain on the same anti-HIV medicines they have been taking during the study, but you will need to discuss this with your doctor.

It is important that you know that this is a voluntary study so if at any time you decide that your child does not want to be involved anymore, you can stop and it will not affect the care that your child receives in the future.

5 What medicines will my child be given if we take part?

If your child joins the study, a computer will choose which group he/she will be in so it is fair and we can truly compare the treatments.

There will be two groups in the study:

- **Standard of care group:** meaning your child will receive the usual, nationally approved anti-HIV medicine.
- **Dolutegravir group:** meaning your child will take a combination of anti-HIV medicines that includes the new medicine, dolutegravir.

6 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this study?

We cannot promise that participating in the study will directly help your child. Compared to other anti-HIV medicines dolutegravir may have fewer side effects and needs to be taken only once a day which may make it easier to take medicines long-term.

However, if your child is in the 'standard of care' group they will receive the same anti-HIV medicines as children not taking part in ODYSSEY, although your child will be watched very carefully for any side effects and responses to the treatment. All the information we get will help children and young people across the world with HIV and in the future it may mean your child has the chance to change to medicines that are easier to take.

What are the possible disadvantages and risks of taking part in this study?

Whichever group they are in your child will have 3 extra visits to the clinic.

Anti-HIV medicines, like all medicines, can have side effects; most common are nausea, vomiting, abdominal discomfort, diarrhoea, rash or may affect the liver. If your child feels unwell, you should contact the clinic as soon as possible.

The new medicine, dolutegravir, has been shown to be effective, with few side effects in adults, but we don't know if this will be the same in children (which is why we need to do this study). The most common side effects in adults are headache, diarrhoea, abdominal pain feeling sick, light headed or weak, worrying often and having sleep problems. Some adults taking dolutegravir have reported feeling depressed or having suicidal thoughts, these may not be related to this medicine in all cases. There is a small chance that dolutegravir may cause a rash, itching, vomiting, stomach pain, sleep problems, lack of energy, an increase in weight, feeling light headed, sad or worried or may cause serious liver problems (with signs of vomiting, jaundice or stomach pain), which is why the doctor needs to follow your child closely. If your child has these signs for more than a day you should inform your doctor straight away.

Risks in Pregnancy and anti-HIV medicines

There is very little information about the effect of dolutegravir in unborn babies. In a recent study from Botswana, approximately 1 in 100 women who were taking dolutegravir when they became pregnant had babies with serious brain and/or spine problems. In the same study, approximately 1 in 1000 women who were taking other antiretrovirals had babies with brain and/or spine problems, which is similar to what is seen in women without HIV. These problems happen very early in pregnancy, before many women even know that they are pregnant. We do not know for sure if these problems are because of dolutegravir. The study in Botswana and other similar studies are ongoing. We expect more information about this in the near future. In the meantime, we would like to tell you about this possible risk.

If your child could become pregnant, she will need a pregnancy test before entering the study. She will not be able to join the study if the test shows she is pregnant. She should avoid getting pregnant while in the study, and use effective contraceptives if she is having sex. While in the study, please let us know if she is thinking about having a baby before she starts trying, or if she thinks she is pregnant. Pregnancy tests will be done regularly during the study to find out early if she is pregnant or not and to give her the appropriate medical care. If she does get pregnant, she will be able to stay in the study and her doctor will talk to you both about whether she needs to change her medicine. Once she delivers, her baby will be assessed by a doctor for any problems and the baby will be followed for approximately 4 weeks to monitor their health. Health information, including HIV status, will be collected about the baby. If she has already had a baby whilst being on the study, health information captured by the hospital during this time period will be collected for the study.

7 Study questionnaires

We are very interested in finding out what children, young people and families feel about the study and how it is affecting their wellbeing. Over the course of the study we will ask you and your child to complete questionnaires asking how your child takes their medicines, what it's like taking medicine and how they feel in general.

8 More information about taking part

Additional studies

There are some additional studies that are part of ODYSSEY. If they are run at your clinic your doctor may talk to you and your child about taking part.

Who is organising the study?

ODYSSEY is organised by the PENTA Foundation, an independent organisation that concentrates specifically on treatment issues for children and young people infected with HIV.

Who has checked this study is safe?

The information about this study has been checked by an independent group of people (a Research Ethics Committee) to make sure that, as far as possible, the safety and wellbeing of anyone taking part in the study is protected.

A second group (the Independent Data Monitoring Committee) will meet regularly during the study to review the results as they come out and will recommend if the study is safe to continue. This is standard for all studies looking at medicines for adults or children.

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should your child come to any harm from participating in this study. If your child is harmed due to someone's negligence then you may have reasons for legal action for compensation against the clinic where this occurred.

With your permission your child's GP will be informed of his/her participation in the study. Your hospital doctor is not receiving any personal payment for carrying out this research. *[Country specific, delete if not applicable]*

What will happen to information about my child collected during the study?

The Fondazione PENTA Onlus, based in Italy and Sponsor for this study, is the owner of data and acts as Joint Data Controller. University College London (UCL) through the MRC Clinical Trial Unit at UCL, will be using information from your child and your child's medical records in order to undertake this study and will act, along with the Sponsor, as Joint Data Controller for this study and Data Processor. This means that PENTA and UCL are responsible for looking after your child's information and using it properly. UCL and the sponsor designated trial co-ordinating units will keep information about your child for a minimum of 15 years after the study has finished.

Your and your child's rights to access, change, move or erase their information are limited, as we need to manage information in specific ways in order for the research to be reliable and accurate. If your child withdraws from the study, we will keep the information about your child that we have already obtained. To safeguard your child's rights, we will use the minimum personally identifiable information possible.

All ODYSSEY study information received by the above organisations and other authorised independent individuals will be kept completely confidential and names will not be used. Your child will only be identified using a study number, an anonymous code and their date of birth.

Your child's clinic notes may be looked at by the above organisations and authorised independent individuals to make sure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published your child's name will not be used nor any information that could be used to identify your child. The study will be conducted in agreement with the country specific data protection regulations.

You can find out more about how we use your child's information at www.ctu.mrc.ac.uk/general/privacy-policy and www.penta-id.org/study-participants-privacy.

How your child's data will be stored and collected

Your child's clinic will collect information from your child and your child's medical records for this research study in accordance with our instructions.

Your child's clinic will keep your child's name, NHS Number and contact details confidential and will not pass this information to anyone outside of the clinic. Your child's clinic will use this information as needed, to contact your child about the research study, and make sure that relevant information about the study is recorded for your child's care, and to oversee the quality of the study. Certain individuals from UCL, authorised regulatory organisations and authorised independent individuals may look at your child's medical and research records to check the accuracy of the research study. They may also be seen by the companies who are supplying medicines for the study or relevant international regulatory authorities. The people who analyse the information will not be able to identify your child and will not be able to find out your child's name, NHS number or contact details.

UCL will collect information about your child for this research study from your child's clinic. This information will include health information. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.

How your data will be used in future & other research

When your child agrees to take part in a research study, the information about your child's health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your child's information will only be used by organisations and researchers to conduct research in accordance with the relevant legislation, ethics and NHS research policy requirements.

We won't share information with others that can identify your child. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your child's care. It will not be used to make decisions about future services available to your child, such as insurance.

What happens at the end of the study?

You and your child and their doctor will continue to make decisions about your child's medicines once the study has finished. If your child is in the dolutegravir group and treatment with dolutegravir appears to be a safe and effective way of treating children and young people with HIV then they may be able to stay on these medicines. We would also like to continue to collect routine information about your child after the study has ended so we can look at the long term effects of the new medicines.

What if new information about dolutegravir becomes available during the study?

Sometimes during a study, new information becomes available about the medicines that are being studied. An independent committee will look at any new information and will also look at the

information collected so far in the study and decide if any changes are needed. If this happens, your doctor will tell you about it and discuss whether you want your child to continue in the study. If you decide to stop taking part in the study, your doctor will continue your child's regular care.

How can my child join the study?

If your child would like to join the ODYSSEY study please speak to the staff at your nearest clinic where the study is run during your next appointment.

How to contact us?

Contact: _____

Tel: _____

PARTICIPANT INFORMATION SHEET - MAIN STUDY ONLY

ODYSSEY STUDY

We are inviting you to take part in a research study

- Before you decide whether to take part, it is important for you to understand why we want to carry out this study and what it will mean for you.
- Please take time to read the following information and to discuss it with friends, family and with your doctor or clinic nurse if you wish.
- You are free to decide if you want to take part in this research study. If you choose not to take part, this will not affect the care you get from your doctor or nurse.
- If you decide to take part in the study you can stop taking part at any time without giving a reason.
- Ask your study doctor or nurse if anything is not clear or if you would like more information.
- Thank you for reading this information.

Important to know

- If you decide to take part you will have some extra visits to the clinic at the beginning of the study.
- A computer program will choose which treatment you will take. Neither you nor your doctor will be able to choose which group you are in.

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ODYSSEY will see how children and adolescents taking dolutegravir as part of their anti-HIV medicines compare to others taking different anti-HIV medicines.

2 Why have I been asked to take part?

We are aiming to ask 700 young people like yourself, from many countries to take part.

You have been asked to participate because:

A: You are about to start taking anti-HIV medicine for the first time

or

B: You are already taking one set of anti-HIV medicine that is no longer working well and your doctor has decided it is time you change to a new combination. This is known as “second-line” treatment.

3 What will happen if I decide not to take part?

It is totally up to you whether or not you take part in this study.

It is your right to decide not to take part if you wish.

This will not affect your care now or in the future in any way.

4 What will happen if I take part?

If you decide to take part we will go through this information sheet together. We will give a copy to you to keep. Your parent/carer will be asked to sign a consent form to show you have both understood the information and agreed to have some blood tests and a check-up to see whether you can go into the study.

If the results show that you can participate we will invite you to enter the study. We need to know that you have fully understood the study and then we will ask your parent/carer to sign a second consent form for you to join. We will also ask you to sign a form giving your assent to join the study.

Your health will be watched closely during the study. In the first 2 months you will need to come for 3 appointments. Once your doctor is happy that you have no side effects from the medicines and you are doing well, you will change to having 3-monthly appointments.

These visits are to make sure you are continuing to do well. If for any reason your doctor has any

concerns, they will change your treatment in the normal way.

In addition to blood tests to check for any side effects, a small amount of extra blood will be collected at each visit. The total amount of blood taken will never exceed a safe limit and will be between 3 and 6 teaspoons depending on your age. Part of this sample will be stored to be used to check the amount of virus in the blood and to look at how the body fights HIV. We would like your agreement that we can store these samples anonymously (without your name or exact date of birth) for up to 15 years.

You will be on the study for at least 2 years. When the study ends, if you are doing well, you may be able to remain on the treatment you have been taking during the study, but you will need to discuss this with your doctor.

It is important that you know that this is a voluntary study so if at any time you decide that you do not want to be involved anymore, you can stop and it will not affect the care that you receive in the future.

5 What medicines will I be given?

If you join the study, a computer will choose which group you will be in so it is fair and we can truly compare the treatments.

There will be two groups in the study:
Standard of Care group: meaning you will receive the usual, nationally approved anti-HIV medicine.

Dolutegravir group: meaning you will take a combination of anti-HIV medicines that includes the new medicine, dolutegravir.

6 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this study?

We cannot promise that participating in the study will directly help you. Compared to other anti-HIV medicines, dolutegravir may have fewer side effects and needs to be taken only once a day which may make it easier to take medicines long-term.

If you are in the 'standard of care' group you will receive the same anti-HIV medicines as children not taking part in ODYSSEY although you will still be watched very carefully for any side effects and responses to the treatment. All the information we get will help children and young people across the world with HIV, and in the future it may mean you have the chance to change to medicines that are easier to take.

What are the possible disadvantages and risks of taking part in this study?

Whichever group you are in you will have 3 extra visits to the clinic.

Anti-HIV medicines, like all medicines, can have side effects; most common are nausea, vomiting, abdominal discomfort, diarrhoea, rash or may affect the liver. If you feel unwell, you should contact the clinic as soon as possible.

The new medicine, dolutegravir, has been shown to be effective with few side effects in adults, but we don't know if this will be the same in children (which is why we need to do this study). The most common side effects in adults are headache, diarrhoea, abdominal pain feeling sick, light headed or weak, worrying often and having sleep problems. Some adults taking dolutegravir have reported feeling depressed or having suicidal thoughts, these may not be related to this medicine in all cases. There is a small chance that dolutegravir may cause a rash, itching, vomiting, stomach pain, sleep

problems, lack of energy, an increase in weight, feeling light headed, sad or worried or may cause serious liver problems (with signs of vomiting, jaundice or stomach pain), which is why the doctor needs to follow you closely. If you have these signs for more than a day you should inform your doctor straight away.

Risks in Pregnancy and anti-HIV medicines

There is very little information about the effect of dolutegravir in unborn babies. In a recent study from Botswana, approximately 1 in 100 women who were taking dolutegravir when they became pregnant had babies with serious brain and/or spine problems. In the same study, approximately 1 in 1000 women who were taking other antiretrovirals had babies with brain and/or spine problems, which is similar to what is seen in women without HIV. These problems happen very early in pregnancy, before many women even know that they are pregnant. We do not know for sure if these problems are because of dolutegravir. The study in Botswana and other similar studies are ongoing. We expect more information about this in the near future. In the meantime, we would like to tell you about this possible risk.

If you are a girl who has started your period you will need a pregnancy test before entering the study. You will not be able to join the study if the test shows you are pregnant. You should avoid getting pregnant while in the study, and use effective if you are having sex. While in the study, please let us know if you are thinking about having a baby before you start trying, or if you think you are pregnant. Pregnancy tests will be done regularly during the study to find out early if you are pregnant or not and to give you the appropriate medical care. If you do get pregnant, you will be able to stay in the study and your doctor will talk to you about whether you need to change your medicine. Once you deliver, your baby will be assessed by a doctor for any problems and the baby will be followed for approximately 4 weeks to monitor their health. Health information, including HIV status, will be collected about the baby. If you have already had a baby whilst being on the study, health information captured by the hospital during this time period will be collected for the study.

7 Study questionnaires

We are very interested in finding out what children, young people and families feel about the study and how it is affecting their wellbeing. Over the course of the study we will ask you to complete questionnaires asking how you take your medicines, what it's like taking medicine and how you feel in general.

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There are some additional studies that are part of ODYSSEY. If they are run at your clinic your doctor may talk to you about taking part.

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ODYSSEY is organised by the PENTA Foundation, an independent organisation that concentrates specifically on treatment issues for children and young people infected with HIV.

Who has checked this study is safe?

The information about this study has been checked by an independent group of people (a Research Ethics Committee) to make sure that as far as possible, the safety and wellbeing of anyone taking part in the study is protected.

A second group (the Independent Data Monitoring Committee) will meet regularly during the study to review the results as they come out and will recommend if the trial is safe to continue. This is standard for all studies looking at medicines for adults or children.

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should you come to any harm from participating in this study. If you are harmed due to someone's negligence then you may have reasons for legal action for compensation against the clinic where this occurred.

With your permission your GP will be informed of your participation in the study. Your hospital doctor is not receiving any personal payment for carrying out this research. *[Country specific, delete if not applicable]*

What will happen to information about me collected during the study?

The Fondazione PENTA Onlus, based in Italy and Sponsor for this study, is the owner of data and acts as Joint Data Controller. University College London (UCL) through the MRC Clinical Trial Unit at UCL, will be using information from you and your medical records in order to undertake this study and will act, along with the Sponsor, as Joint Data Controller for this study and Data Processor. This means that PENTA and UCL are responsible for looking after your information and using it properly. UCL and the sponsor designated trial co-ordinating units will keep information about you for a minimum of 15 years after the study has finished.

You and your parent/carer's rights to access, change, move or erase your information are limited, as we need to manage information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about your child that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

All ODYSSEY study information received by the above organisations and other authorised independent individuals will be kept completely confidential and names will not be used. You will only be identified using a study number, an anonymous code and your date of birth.

Your clinic notes may be looked at by the above organisations and authorised independent individuals to make sure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published your name will not be used nor any information that could be used to identify you. The study will be conducted in agreement with the country specific data protection regulations.

You can find out more about how we use your information at www.ctu.mrc.ac.uk/general/privacy-policy and www.penta-id.org/study-participants-privacy.

How your data will be stored and collected

Your clinic will collect information from you and your medical records for this research study in accordance with our instructions.

Your clinic will keep your name, NHS Number and contact details confidential and will not pass this information to anyone outside of the clinic. Your clinic will use this information as needed, to contact you or your parent/carer about the research study, and make sure that relevant information about

the study is recorded for your care, and to oversee the quality of the study. Certain individuals from UCL, authorised regulatory organisations and authorised independent individuals may look at your medical and research records to check the accuracy of the research study. They may also be seen by the companies who are supplying medicines for the study or relevant international regulatory authorities. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

UCL will collect information about you for this research study from your clinic. This information will include health information, This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.

How your data will be used in future & other research

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the relevant legislation, ethics and NHS research policy requirements.

We won't share information with others that can identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

What happens at the end of the study?

You, your parent/carer and your doctor will continue to make decisions about your medicines once the study has finished.

If you are in the dolutegravir group and treatment with dolutegravir appears to be a safe and effective way of treating children and young people with HIV then you may stay on these medicines.

We would also like to continue to collect your routine information after the study has ended so we can look at the long term effects of the new medications.

What if new information about dolutegravir becomes available during the course of the study?

Sometimes during a study, new information becomes available about the medicines that are being studied. An independent committee will look at any new information and will also look at the data collected so far in the study and decide if any changes are needed. If this happens, your doctor will tell you about it and discuss whether you want to continue in the study. If you decide to stop taking part in the study, your doctor will continue your regular care.

How can I join the study?

If you would like to join the ODYSSEY study please speak to the staff at your nearest clinic where the study is run during your next appointment.

How to contact us?

Contact:_____

Tel:_____

CHILDREN'S INFORMATION SHEET - MAIN STUDY ONLY

ODYSSEY

ODYSSEY is a study. Studies take groups of people and ask them to do something and then see if there are any changes. This study is looking at some new medicine for children.

DOLUTEGRAVIR is the name of the new medicine, we know it works very well with adults but we don't know how it works with children.

YOU have been asked to take part because you need to start taking medicines or you need to change the medicines you are on.

SO why be involved? Well, this new medicine is exciting as it will mean a big difference for lots of children around the world, so you can be part of something that makes a big difference.

STUDIES run in different ways. This one has two groups: one will take the new medicine and the other will take the medicine your doctor has given to lots of children like you. This is so both groups can be watched to see any differences. This is decided randomly – like pulling names out of a hat – so you can't choose which one you are in.

EVERYONE taking part will be closely watched by doctors, so you will need to come to some extra clinic visits in the first two months and after that it'll be every three months.

YOU can say yes now, but if you change your mind at any point, you can stop being part of the study, it's up to you.

PARENT/CARER INFORMATION SHEET – EXTENDED FOLLOW-UP

ODYSSEY STUDY

Contents

1 Why are we requesting extended follow-up?

We are requesting extended follow-up so that we can continue to collect safety information from children and adolescents enrolled in ODYSSEY. This information is important as it will enable the long term safety and effectiveness of dolutegravir in children and adolescents to be assessed.

If your child is currently taking dolutegravir in a form that is not currently available through your country's national treatment programme, we are also required to collect further safety information.

2 Why has my child been asked to take part?

Your child has been asked to take part in extended follow-up because he/she is enrolled in the ODYSSEY trial and we would like to collect further information on the treatment that they receive in order to assess the safety of dolutegravir over a longer period of time.

3 What will happen if we decide not to take part?

It is totally up to you and your child whether or not he/she takes part in extended follow-up.

If you choose that your child will not take part, but your child is currently taking a form of dolutegravir that is not available through your country's national treatment programme, then it may be necessary for your doctor to change your child's anti-HIV medicine so that they will take another appropriate drug in place of dolutegravir. If your child is taking anti-HIV medicines that are available through your country's national treatment programme then their treatment may not need to be changed if you choose not to take part.

This will not affect your child's care now or in the future in any way.

4 What will happen if my child takes part?

If you decide to take part, we will go through this information sheet together. We will give you a copy to keep. You will be asked to sign a consent form to show you have understood the information and have agreed for your child to continue in extended follow-up.

Once your child is in the extended follow-up period they will attend for regular clinic visits which will be similar to routine care in your country. Blood tests will be performed as per local practice and, if your child could become pregnant, a pregnancy test will be performed at every visit. Sleep and Mood Questionnaire data will be collected annually. Your child will remain in extended follow-up for a period of up to 3 years (until May 2023)

It is important that you know that this is a voluntary study so if at any time you decide that you do not want to be involved anymore, you can stop and it will not affect the care that you receive in the future.

5 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in extended follow-up?

Although there may not be any direct benefits to you or your child of taking part, the information collected will help us to improve the treatment of other children and adolescents who are living with HIV.

If your child is taking a form of dolutegravir that is not available through your country's national HIV treatment programme then taking part will enable them to continue taking the same treatment. In these circumstances the medicine will continue to be provided to your clinic, by a drug company working with the study team, free of charge to your child.

What are the possible disadvantages and risks of taking part in this study?

Anti-HIV medicines, like all medicines, can have side effects; most common are nausea, vomiting, abdominal discomfort, diarrhoea, rash or may affect the liver. If your child feels unwell, you should contact the clinic as soon as possible.

Dolutegravir has been shown to be effective, with few side effects in adults, but we don't know if this will be the same in children (which is why we need to do this study). The most common side effects in adults are headache, diarrhoea, abdominal pain, feeling sick, light headed or weak, worrying often and having sleep problems. Some adults taking dolutegravir have reported feeling depressed or having suicidal thoughts, these may not be related to this medicine in all cases. There is a small chance that dolutegravir may cause a rash, itching, vomiting, stomach pain, sleep problems, lack of energy, an increase in weight, feeling light headed, sad or worried or may cause serious liver problems (with signs of vomiting, jaundice or stomach pain), which is why the doctor needs to follow your child closely. If your child has these signs for more than a day you should inform your doctor straight away.

Risks in Pregnancy and anti-HIV medicines

There is very little information about the effect of dolutegravir in unborn babies. In a recent study from Botswana, approximately 3 in 1000 women who were taking dolutegravir when they became pregnant had babies with serious brain and/or spine problems. In the same study, approximately 1 in 1000 women who were taking other antiretrovirals had babies with brain and/or spine problems, which is similar to what is seen in women without HIV. These problems happen very early in pregnancy, before many women even know that they are pregnant. We do not know for sure if these problems are because of dolutegravir. The study in Botswana and other similar studies are ongoing. We expect more information about this in the near future. In the meantime, we would like to tell you about this possible risk.

If your child could become pregnant, she should avoid getting pregnant while in extended trial follow-up, and use effective contraceptives if she is having sex. While in extended follow-up, please let us know if she is thinking about having a baby before she starts trying, or if she thinks she is pregnant. Pregnancy tests will continue to be done regularly during extended follow-up to find out early if she is pregnant or not and to give her the appropriate medical care. If she does get pregnant, she will be able to stay in extended follow-up and her doctor will talk to you both about whether she needs to change her medicine. Once she delivers, her baby will be assessed by a doctor for any problems and the baby will be followed for approximately 4 weeks to monitor their health. Health information, including HIV status, will be collected about the baby. If she has already had a baby whilst being on the study, health information captured by the hospital during this time period will be collected for the study.

6 More information about taking part

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should your child come to any harm from participating in this study. If your child is harmed due to someone's negligence then you may have reasons for legal action for compensation against the clinic where this occurred.

What will happen to information about my child collected during follow-up?

The Fondazione PENTA Onlus, based in Italy and Sponsor for this study, is the owner of data and acts as Joint Data Controller. University College London (UCL) through the MRC Clinical Trial Unit at UCL, will be using information from your child and your child's medical records in order to undertake this study and will act, along with the Sponsor, as Joint Data Controller for this study and Data Processor. This means that PENTA and UCL are responsible for looking after your child's information and using it properly. UCL and the sponsor designated trial co-ordinating units will keep information about your child for a minimum of 15 years after the study has finished.

Your and your child's rights to access, change, move or erase their information are limited, as we need to manage information in specific ways in order for the research to be reliable and accurate. If your child withdraws from the study, we will keep the information about your child that we have already obtained. To safeguard your child's rights, we will use the minimum personally identifiable information possible.

All ODYSSEY study information received by the above organisations and other authorised independent individuals will be kept completely confidential and names will not be used. Your child will only be identified using a study number, an anonymous code and their date of birth.

Your child's clinic notes may be looked at by the above organisations and authorised independent individuals to make sure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published your child's name will not be used nor any information that could be used to identify your child. The study will be conducted in agreement with the country specific data protection regulations.

You can find out more about how we use your child's information at www.ctu.mrc.ac.uk/general/privacy-policy and www.penta-id.org/study-participants-privacy.

How your child's data will be stored and collected

Your child's clinic will collect information from your child and your child's medical records for this research study in accordance with our instructions.

Your child's clinic will keep your child's name and contact details confidential and will not pass this information to anyone outside of the clinic. Your child's clinic will use this information as needed, to contact your child about the research study, and make sure that relevant information about the study is recorded for your child's care, and to oversee the quality of the study. Certain individuals from UCL, authorised regulatory organisations and authorised independent individuals may look at your child's medical and research records to check the accuracy of the research study. They may also be seen by the companies who are supplying medicines for the study or relevant international regulatory authorities. The people who analyse the information will not be able to identify your child and will not be able to find out your child's name or contact details.

UCL will collect information about your child for this research study from your child's clinic. This information will include health information. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.

How your data will be used in future & other research

When your child agrees to take part in a research study, the information about your child's health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, hospitals or companies involved in health and care research in this country or abroad. Your child's information will only be used by organisations and researchers to conduct research in accordance with the relevant legislation and ethics requirements.

We won't share information with others that can identify your child. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your child's care. It will not be used to make decisions about future services available to your child, such as insurance.

What happens at the end of extended follow-up?

You, your child and their doctor will continue to make decisions about your child's medicines once extended follow-up has finished. If, at the end of this follow-up period, dolutegravir is still not available through your country's national treatment programme, your child may have to change to different anti-HIV medicines.

How to contact us?

Contact: _____

Tel: _____

PARTICIPANT INFORMATION SHEET – EXTENDED FOLLOW-UP

ODYSSEY STUDY

Contents

1 Why are we requesting extended follow-up?

We are requesting extended follow-up so that we can continue to collect safety information from children and young people taking part in ODYSSEY. This information is important as it will enable the long term safety and effectiveness of dolutegravir in children and adolescents to be assessed.

If you are currently taking dolutegravir in a form that is not currently available through your country's national treatment programme, we are also required to collect further safety information.

2 Why have I been asked to take part?

You have been asked to take part in extended follow-up because you are taking part in the ODYSSEY trial and we would like to collect further information on the treatment that you receive in order to assess the safety of dolutegravir over a longer period of time.

3 What will happen if I decide not to take part?

It is totally up to you whether or not you take part in extended follow-up.

If you choose not to take part, but you are currently taking a form of dolutegravir that is not available through your country's national treatment programme, then it may be necessary for your doctor to change your anti-HIV medicine so that you will take another appropriate drug in place of dolutegravir. If you are taking anti-HIV medicines that are available through your country's national treatment programme then your treatment may not need to be changed if you choose not to take part.

This will not affect your care now or in the future in any way.

4 What will happen if I take part?

If you decide to take part, we will go through this information sheet together. We will give you a copy to keep. If you are not old enough to give consent yourself, your parent/carer will be asked to sign a consent

form to show you have both understood the information and have agreed to continue in extended follow-up.

Once you are in the extended follow-up period you will attend for regular clinic visits which will be similar to routine care in your country. Blood tests will be performed as per local practice and, if you could become pregnant, a pregnancy test will be performed at every visit. Sleep and Mood Questionnaire data will be collected annually. You will remain in extended follow-up for a period of up to 3 years (until May 2023)

It is important that you know that this is a voluntary study so if at any time you decide that you do not want to be involved anymore, you can stop and it will not affect the care that you receive in the future.

5 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in extended follow-up?

Although there may not be any direct benefits to you of taking part, the information collected will help us to improve the treatment of other children and adolescents who are living with HIV.

If you are taking a form of dolutegravir that is not available through your country's national HIV treatment programme then taking part will enable you to continue taking the same treatment. If this is the case, the medicine will continue to be provided to your clinic, by a drug company working with the study team, free of charge.

What are the possible disadvantages and risks of taking part in this study?

Anti-HIV medicines, like all medicines, can have side effects; most common are nausea, vomiting, abdominal discomfort, diarrhoea, rash or may affect the liver. If you feel unwell, you should contact the clinic as soon as possible.

Dolutegravir has been shown to be effective with few side effects in adults, but we don't know if this will be the same in children (which is why we need to do this study). The most common side effects in adults are headache, diarrhoea, abdominal pain, feeling sick, light headed or weak, worrying often and having sleep problems. Some adults taking dolutegravir have reported feeling depressed or having suicidal thoughts, these may not be related to this medicine in all cases. There is a small chance that dolutegravir may cause a rash, itching, vomiting, stomach pain, sleep problems, lack of energy, an increase in weight, feeling light headed, sad or worried or may cause serious liver problems (with signs of vomiting, jaundice or stomach pain), which is why the doctor needs to follow you closely. If you have these signs for more than a day you should inform your doctor straight away.

Risks in Pregnancy and anti-HIV medicines

There is very little information about the effect of dolutegravir in unborn babies. In a recent study from Botswana, approximately 3 in 1000 women who were taking dolutegravir when they became pregnant had babies with serious brain and/or spine problems. In the same study, approximately 1 in 1000 women who were taking other antiretrovirals had babies with brain and/or spine problems, which is similar to what is seen in women without HIV. These problems happen very early in pregnancy, before many women even know that they are pregnant. We do not know for sure if these problems are because of dolutegravir. The study in Botswana and other similar studies are ongoing. We expect more information about this in the near future. In the meantime, we would like to tell you about this possible risk.

If you are a girl who has started your period you should avoid getting pregnant while in extended trial follow-up, and use effective contraceptives if you are having sex. While in extended follow-up, please let us know if you are thinking about having a baby before you start trying, or if you think you are pregnant. Pregnancy tests will continue to be done regularly during extended follow-up to find out early if you are pregnant or not

and to give you the appropriate medical care. If you do get pregnant, you will be able to stay in extended follow-up and your doctor will talk to you about whether you need to change your medicine. Once you deliver, your baby will be assessed by a doctor for any problems and the baby will be followed for approximately 4 weeks to monitor their health. Health information, including HIV status, will be collected about the baby. If you have already had a baby whilst being on the study, health information captured by the hospital during this time period will be collected for the study.

6 More information about taking part

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should you come to any harm from participating in this study. If you are harmed due to someone's negligence then you may have reasons for legal action for compensation against the clinic where this occurred.

What will happen to information about me collected during the study?

The Fondazione PENTA Onlus, based in Italy and Sponsor for this study, is the owner of data and acts as Joint Data Controller. University College London (UCL) through the MRC Clinical Trial Unit at UCL, will be using information from you and your medical records in order to undertake this study and will act, along with the Sponsor, as Joint Data Controller for this study and Data Processor. This means that PENTA and UCL are responsible for looking after your information and using it properly. UCL and the sponsor designated trial co-ordinating units will keep information about you for a minimum of 15 years after the study has finished.

You and your parent/carer's rights to access, change, move or erase your information are limited, as we need to manage information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about your child that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

All ODYSSEY study information received by the above organisations and other authorised independent individuals will be kept completely confidential and names will not be used. You will only be identified using a study number, an anonymous code and your date of birth.

Your clinic notes may be looked at by the above organisations and authorised independent individuals to make sure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published your name will not be used nor any information that could be used to identify you. The study will be conducted in agreement with the country specific data protection regulations.

You can find out more about how we use your information at www.ctu.mrc.ac.uk/general/privacy-policy and www.penta-id.org/study-participants-privacy.

How your data will be stored and collected

Your clinic will collect information from you and your medical records for this research study in accordance with our instructions.

Your clinic will keep your name and contact details confidential and will not pass this information to anyone outside of the clinic. Your clinic will use this information as needed, to contact you or your parent/carer about the research study, and make sure that relevant information about the study is recorded for your care, and

to oversee the quality of the study. Certain individuals from UCL, authorised regulatory organisations and authorised independent individuals may look at your medical and research records to check the accuracy of the research study. They may also be seen by the companies who are supplying medicines for the study or relevant international regulatory authorities. The people who analyse the information will not be able to identify you and will not be able to find out your name or contact details.

UCL will collect information about you for this research study from your clinic. This information will include health information, This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.

How your data will be used in future & other research

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the relevant legislation, ethics and NHS research policy requirements.

We won't share information with others that can identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

What happens at the end of extended follow-up?

You, your parent/carer and your doctor will continue to make decisions about your medicines once extended follow-up has finished. If, at the end of this follow-up period, dolutegravir is still not available through your country's national treatment programme, you may have to change to different anti-HIV medicines.

How to contact us?

Contact:_____

Tel:_____

CHILDREN'S INFORMATION SHEET – EXTENDED FOLLOW-UP

ODYSSEY STUDY (PENTA 20)

You are taking part in a study called ODYSSEY. In ODYSSEY we have been looking at a new medicine for children called dolutegravir.

We would like to collect more information on dolutegravir and the other medicines that children in ODYSSEY are taking. To do this we would like you to stay in the ODYSSEY study until May 2023 (up to an extra 3 years after you would have finished taking part).

The information that we collect will help us find out if dolutegravir is still safe and working well even after children have been taking it for a long time.

The doctors will still watch you closely but now you will only need to attend for visits at the same times that you would if you were not taking part in the study.

Most of the tests that you will have are the same as those you would have outside of the study but you or your carer will sometimes also be asked to answer some questions on how easy you find it to take your medicine.

It is still up to you whether you take part in the study. If you say yes now you can change your mind at any time and stop being part of the study. It is up to you.

PARENT/CARER INFORMATION SHEET – MAIN STUDY & WEIGHT BAND PK 1 (3 TO <14KG)

ODYSSEY STUDY

We are inviting you and your child to take part in a research study

- Before you decide whether to take part, it is important for you and your child to understand why we want to carry out this study and what it will mean for you both.
- Please take time to read the following information and to discuss it with friends, family and with your doctor or clinic nurse if you wish.
- You are free to decide if you want your child to take part in this research study. If you choose not to take part, this will not affect the care your child gets from your doctor or nurse.
- If you decide to take part in the study you can stop taking part at any time without giving a reason.
- Ask your study doctor or nurse if anything is not clear or if you would like more information.
- Thank you for reading this information.

Important to know

- If you decide to take part your child will have some extra visits to the clinic at the beginning of the study.
- A computer program will choose which treatment your child will take. Neither you nor your doctor will be able to choose which group your child is in
- If your child is in the dolutegravir group they will be asked to come into the clinic and stay for a whole day at least 1 week after starting the new medicine. He/she will have up to 7 blood samples taken during the day (over a 24 hour period) to test the level of medicine in their blood. We will also need to take a blood sample the next morning. Your child can stay overnight or we will provide transport for you to come back the next day.

Contents

1 Why are we doing this study?

Dolutegravir is a new medicine being used to treat adults with HIV.

In adults it has been shown to be effective and safe, with few side effects, and it only needs to be taken once a day.

Sometimes a medicine works differently in growing children than in adults, so we need to check how it works in children as well. Dolutegravir could be an excellent option for children if the study finds it works as well as it does in adults.

ODYSSEY will see how children and adolescents taking dolutegravir as part of their anti-HIV medicines compare to others taking different anti-HIV medicines.

Weight band Pharmacokinetic (PK) Study (checking the level of medicine in the blood):

We need to check that the dose of the new medicine is correct for younger children. If your child joins the study and is put in the dolutegravir group he/she will come into the clinic for a PK blood sampling day.

2 Why has my child been asked to take part?

We are aiming to ask 700 children and young people from many countries to take part.

Your child has been asked to participate because:

A. He/She is about to start taking anti-HIV medicine for the first time.
Or

B. He/She is already taking one set of anti-HIV medicine that is no longer working well and your doctor has decided it is time your child changes to a new combination. This is known as “second-line” treatment.

3 What will happen if we decide not to take part?

It is totally up to you and your child whether or not he/she takes part in this study.

It is your right to decide not to take part if you wish.

This will not affect your child’s care now or in the future in any way.

4 What will happen if my child takes part?

If you decide to take part, we will go through this information sheet together. We will give a copy to you to keep. You will be asked to sign a consent form to show you have understood the information and have agreed for your child to have some blood tests and a check-up to see whether they can go into the study.

If the results show that your child can participate, we will invite him/her to enter the study. We need to know that you have fully understood the study and then we will ask you to sign a second consent form for your child to join.

Your child’s health will be watched closely during the study.

In the first 2 months you will need to come for 3 or 4 appointments. Once your doctor is happy that your child has no side effects from the medicines and is doing well, they will change to having 3-monthly appointments.

These visits are to make sure your child is continuing to do well. If for any reason your doctor has any concerns, they will change your child's treatment in the normal way.

In addition to blood tests to check for any side effects, a small amount of extra blood will be collected at each visit. The total amount of blood taken will never exceed a safe limit and will be between 3 and 6 teaspoons depending upon the age of your child. Part of this sample will be stored to be used to check the amount of virus in the blood and to look at how the body fights HIV. We would like your agreement that we can store these samples anonymously (without your child's name or exact date of birth) for up to 15 years.

Your child will be in the study for at least 2 years. When the study ends, if your child is doing well they may be able to remain on the same anti-HIV medicines they have been taking during the study, but you will need to discuss this with your doctor.

It is important that you know that this is a voluntary study so if at any time you decide that your child does not want to be involved anymore, you can stop and it will not affect the care that your child receives in the future.

PK (blood levels) Study (only to be done in children allocated to the dolutegravir group)
If your child is in the dolutegravir group they will be asked to come into the clinic and stay for a whole day at least 1 week after starting the new medicine. He/she will have up to 7 blood samples taken during the day (over a 24 hour period) to test the level of medicine in their blood. A local anaesthetic cream will be used to make the skin numb and a thin tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken. All blood samples will be taken from the cannula, so only one needle prick is required. Each blood sample will be small (less than half a teaspoon) and is an amount which is safe for your child's age and weight.

We will also need to take a blood sample the next morning. Your child can stay overnight or we will provide transport for you to come back the next day.

The laboratory needs to know exactly when your child took their medicine so you will be asked to record the time of giving the medicine the day before. Immediately after the first blood sample is taken your child will be given breakfast (we will provide all their meals during the day) with their usual dose of medicine.

5 What medicines will my child be given if we take part?

If your child joins the study, a computer will choose which group he/she will be in so it is fair and we can truly compare the treatments.

There will be two groups in the study:

- **Standard of care group:** meaning your child will receive the usual, nationally approved anti-HIV medicine.
- **Dolutegravir group:** meaning your child will take a combination of anti-HIV medicines that includes the new medicine, dolutegravir. Children in this group will also take part in PK (blood levels) study.

6 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this study?

We cannot promise that participating in the study will directly help your child. Compared to other anti-HIV medicines dolutegravir may have fewer side effects and needs to be taken only once a day which may make it easier to take medicines long-term.

However, if your child is in the 'standard of care' group they will receive the same anti-HIV medicines as children not taking part in ODYSSEY, although your child will be watched very carefully for any side effects and responses to the treatment. All the information we get will help children and young people across the world with HIV and in the future it may mean your child has the chance to change to medicines that are easier to take.

What are the possible disadvantages and risks of taking part in this study?

Whichever group they are in your child will have 3 or 4 extra visits to the clinic and if they are in the dolutegravir group, they will come in for a full day (and possibly an overnight stay) at clinic for the blood sampling day.

Anti-HIV medicines, like all medicines, can have side effects; most common are nausea, vomiting, abdominal discomfort, diarrhoea, rash or may affect the liver. If your child feels unwell, you should contact the clinic as soon as possible.

The new medicine, dolutegravir, has been shown to be effective, with few side effects in adults, but we don't know if this will be the same in children (which is why we need to do this study). The most common side effects in adults are headache, diarrhoea, abdominal pain feeling sick, light headed or weak, worrying often and having sleep problems. Some adults taking dolutegravir have reported feeling depressed or having suicidal thoughts, these may not be related to this medicine in all cases. In most of these cases the person had a history of similar problems before starting dolutegravir. There is a small chance that dolutegravir may cause a rash, itching, vomiting, stomach pain, sleep problems, lack of energy, an increase in weight, feeling light headed, sad or worried or may cause serious liver problems (with signs of vomiting, jaundice or stomach pain), which is why the doctor needs to follow your child closely. If your child has these signs for more than a day you should inform your doctor straight away.

Pregnancy and anti-HIV medicines

There is very little information about the effect of dolutegravir in unborn babies. If your child could become pregnant, she will need a pregnancy test before entering the study. She will not be able to join the study if the test shows she is pregnant. We encourage her to use effective contraceptives and for her to let us know straightaway if at any time she thinks she may have become pregnant. If this is confirmed with a pregnancy test her treatment will be reviewed by the doctor. She will be able to stay in the study if she becomes pregnant.

7 Study questionnaires

We are very interested in finding out what children, young people and families feel about the study and how it is affecting their wellbeing. Over the course of the study we will ask you and your child to complete questionnaires asking how your child takes their medicines, what it's like taking medicine and how they feel in general.

8 More information about taking part

Additional studies

There are some additional studies that are part of ODYSSEY. If they are run at your clinic your doctor may talk to you and your child about taking part.

Who is organising the study?

ODYSSEY is organised by the PENTA Foundation, an independent organisation that concentrates specifically on treatment issues for children and young people infected with HIV.

Who has checked this study is safe?

The information about this study has been checked by an independent group of people (a Research Ethics Committee) to make sure that, as far as possible, the safety and wellbeing of anyone taking part in the study is protected.

A second group (the Independent Data Monitoring Committee) will meet regularly during the study to review the results as they come out and will recommend if the study is safe to continue. This is standard for all studies looking at medicines for adults or children.

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should your child come to any harm from participating in this study. If your child is harmed due to someone's negligence then you may have reasons for legal action for compensation against the clinic where this occurred.

With your permission your child's GP will be informed of his/her participation in the study. Your hospital doctor is not receiving any personal payment for carrying out this research. *[Country specific, delete if not applicable]*

What will happen to information about my child collected during the study?

The Fondazione PENTA Onlus, based in Italy and Sponsor for this study, is the owner of data and acts as Joint Data Controller. University College London (UCL) through the MRC Clinical Trial Unit at UCL, will be using information from your child and your child's medical records in order to undertake this study and will act, along with the Sponsor, as Joint Data Controller for this study and Data Processor. This means that PENTA and UCL are responsible for looking after your child's information and using it properly. UCL and the sponsor designated trial co-ordinating units will keep information about your child for a minimum of 15 years after the study has finished.

Your and your child's rights to access, change, move or erase their information are limited, as we need to manage information in specific ways in order for the research to be reliable and accurate. If your child withdraws from the study, we will keep the information about your child that we have already obtained. To safeguard your child's rights, we will use the minimum personally identifiable information possible.

All ODYSSEY study information received by the above organisations and other authorised independent individuals will be kept completely confidential and names will not be used. Your child will only be identified using a study number, an anonymous code and their date of birth.

Your child's clinic notes may be looked at by the above organisations and authorised independent individuals to make sure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published your child's name will not be used nor any information that could be used to identify your child. The study will be conducted in agreement with the country specific data protection regulations.

You can find out more about how we use your child's information at www.ctu.mrc.ac.uk/general/privacy-policy and www.penta-id.org/study-participants-privacy.

How your child's data will be stored and collected

Your child's clinic will collect information from your child and your child's medical records for this research study in accordance with our instructions.

Your child's clinic will keep your child's name, NHS Number and contact details confidential and will not pass this information to anyone outside of the clinic. Your child's clinic will use this information as needed, to contact your child about the research study, and make sure that relevant information about the study is recorded for your child's care, and to oversee the quality of the study. Certain individuals from UCL, authorised regulatory organisations and authorised independent individuals may look at your child's medical and research records to check the accuracy of the research study. They may also be seen by the companies who are supplying medicines for the study or relevant international regulatory authorities. The people who analyse the information will not be able to identify your child and will not be able to find out your child's name, NHS number or contact details.

UCL will collect information about your child for this research study from your child's clinic. This information will include health information. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.

How your data will be used in future & other research

When your child agrees to take part in a research study, the information about your child's health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your child's information will only be used by organisations and researchers to conduct research in accordance with the relevant legislation, ethics and NHS research policy requirements.

We won't share information with others that can identify your child. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your child's care. It will not be used to make decisions about future services available to your child, such as insurance.

What happens at the end of the study?

You and your child and their doctor will continue to make decisions about your child's medicines once the study has finished. If your child is in the dolutegravir group and treatment with dolutegravir appears to be a safe and effective way of treating children and young people with HIV then they may be able to stay on these medicines. We would also like to continue to collect routine information about your child after the study has ended so we can look at the long term effects of the new medicines.

What if new information about dolutegravir becomes available during the study?

Sometimes during a study, new information becomes available about the medicines that are being studied. An independent committee will look at any new information and will also look at the information collected so far in the study and decide if any changes are needed. If this happens, your doctor will tell you about it and discuss whether you want your child to continue in the study. If you decide to stop taking part in the study, your doctor will continue your child's regular care.

How can my child join the study?

If your child would like to join the ODYSSEY study please speak to the staff at your nearest clinic where the study is run during your next appointment.

How to contact us?

Contact: _____

Tel: _____

CHILDREN'S INFORMATION SHEET – MAIN STUDY & WEIGHT BAND PK 1 (3 TO <14KG)

ODYSSEY STUDY

Odyssey is a study. Studies take groups of people and ask them to do something and then see if there are any changes. This study is looking at some new medicine for children

Dolutegravir is the name of the new medicine, we know it works very well with adults but we don't know how it works with children

You have been asked to take part because you need to start taking medicine or you need to change the medicine you are on.

So why be involved? Well, this new medicine is exciting as it will mean a big difference for lots of children around the world, so you can be part of something that makes a big difference.

Studies run in different ways. This one has two groups: one will take the new medicine and the other will take the medicine your doctor has given to lots of children like you. This is so both groups can be watched to see any differences. This is decided randomly – like pulling names out of a hat – so you can't choose which one you are in.

Everyone taking part will be closely watched by doctors, so you will need to come to some extra clinic visits in the first two months and after that it'll be every three months.

You can say yes now, but if you change your mind at any point, you can stop being part of the study, it's up to you.

BLOOD LEVELS STUDY

If you are in the group taking the new medicine, after at least one week of taking this new medicine you will be asked to spend a whole day at the clinic so we can check how much of the medicine is in your blood. We will take up to 7 small blood samples during the day (over a 24 hour period). Each blood sample will be small (less than half a teaspoon) and the amount of blood taken will be safe for your age and weight.

After the first blood sample is taken you will be given breakfast (we will provide all your meals during this day) with your usual dose of medicine.

We also need a sample the next morning. Your clinic team will let you know whether you need to stay overnight or come back the next day to have this sample taken.

PARENT/CARER INFORMATION SHEET –WEIGHT BAND PK 1 (3KG TO <25KG)

ODYSSEY WEIGHT BAND PK 1 – BLOOD LEVELS STUDY

1 Why are we doing this study?

We need to confirm that the dose of the new medicine is suitable for children who weigh 3kg to 25kg. If your child joins this study he/she will need to come into the clinic for a whole day (over a 24 hour period) when samples will be taken to check the pharmacokinetics (PK) which means the levels of medicine in their blood.

2 Why has my child been asked to take part?

Children being asked to take part in this study are taking part in ODYSSEY, weigh between 3kg to 25kg and are taking dolutegravir. We are aiming to ask a small group of children to take part.

Your child has been asked to take part either because:

A. he/she is already taking part in ODYSSEY

OR

B. you and your child may be thinking about taking part in ODYSSEY; in this case your child may only take part in this additional study if they join the ODYSSEY trial and they are allocated dolutegravir.

3 What will happen if we decide not to take part?

It is totally up to you and your child whether or not he/she takes part in this study.

If you or your child decides not to take part in the PK (blood levels) study this will not stop your child from taking part in ODYSSEY or affect your child's care now or in the future in any way.

4 What will happen if my child takes part?

If you decide to take part, we will go through this information sheet together. We will give you a copy to keep. You will be asked to sign a consent form to show you understand the information and agree to take part.
If your child does take part, blood samples will be taken from your child and stored so researchers can learn more about anti-HIV medicines. If at any point your child wants to stop

being in the study we hope that you will still allow us to use these samples. If, however, you do not give your permission then we will destroy them.

Your child's wellbeing will be monitored closely during the study. If for any reason his/her medicine needs to be changed this will be done by their doctor.

Important to know

- ***If your child is eligible and does take part they will need to spend one whole day in the clinic after at least 1 week of taking dolutegravir.***

On the day booked for the blood sampling visit your child will be asked to come to the clinic for a whole day. He/she will have up to 7 blood samples taken during the day (over a 24 hour period) to test the level of medicine in their blood. A cream with local pain-killing effect will be used to make the skin numb and a thin flexible tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken more easily. All blood samples will be taken from the cannula so only one needle prick is required. Each blood sample will be small (less than half a teaspoon), and the amount will be is safe for your child's age and weight.

We will also need to take a blood sample the next morning. Your child can stay overnight or we will provide transport for you to come back the next day.

At this point the PK (Blood Levels) study will end. However, usual clinic ODYSSEY visits will continue for routine monitoring of your child's health.

5 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this study?

We cannot promise that participating in the study will directly help your child but the results of this study will give us more information about the dosing of dolutegravir for children and young people. It is very important that we have this information so we can make sure that children are given the correct amount of medicine.

This information will help children and young people across the world with HIV and in the future it may mean your child has the chance to get the most appropriate amount of medicine.

What are the possible disadvantages and risks of taking part in this study?

It's important to think about these before deciding to take part.

This study will not result in any risk to your child's health. However, your child will have to spend one day at the clinic and may need to stay overnight on this day.

On the PK day, up to 7 small blood samples will be taken but only one needle prick will be needed.

6 More information about taking part

Who has checked this study is safe?

This study has been looked at by an independent group of people (a Research Ethics Committee) to make sure that, as far as possible, the safety and wellbeing of anyone taking part in the study is protected.

A second group (the Independent Data Monitoring Committee) will review the results as they come out and will recommend if the study is safe to continue. This is standard for all studies looking at medicines for adults or children.

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should your child come to any harm from participating in this study. However, if your child is harmed due to someone's negligence then you may have reasons for legal action for compensation against the hospital where the negligence occurred.

With your permission your child's GP will be informed of his/her participation in the study. Your hospital doctor is not receiving any personal payment for carrying out this research. *[Country specific, delete if not applicable]*

What will happen to information about my child collected during this study?

All information collected during the ODYSSEY study will be kept completely confidential and names will not be used. Your child will only be identified using a study number, an anonymous code and their date of birth. Your child's clinic notes may be looked at by study staff from the PENTA Foundation, the trials units co-ordinating the study or other independent people authorised to make sure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published no information will be included that could identify your child (no name or date of birth). The study will be conducted in agreement with the country specific data protection regulations.

7 Contacts for more information

If you would like more information about the study please ask the doctor or nurse at your clinic. If you still need more information please call:

Contact: _____
Tel: _____

CHILDREN'S INFORMATION SHEET – WEIGHT BAND PK 1 (3 TO <25KG)

ODYSSEY PK (BLOOD LEVELS) STUDY

We need to confirm that the dose of the new medicine is suitable for children who are about the same weight as you. If you join this study you will need to come into the clinic for a whole day when samples will be taken to check the levels of medicine in the blood.

You have been asked to take part because either

A. you are part of the ODYSSEY study and are taking the new medicine
   OR
B. you may be taking part in ODYSSEY and could be starting to take the new medicine if and when you start the study.

You can say yes now, but if you change your mind at any point, you can stop being part of the study, it's up to you.

After at least one week in the study and taking the new medicine you will be asked to spend a whole day at the clinic so we can check how much of the medicine is in your blood. We will take up to 7 small blood samples during the day (over a 24 hour period). Each blood sample will be small (less than half a teaspoon), and the amount will be is safe for your age and weight.

After the first blood sample is taken you will be given breakfast (we will provide all your meals during this day) with your usual dose of medicine.

We also need a sample the next morning. Your clinic team will let you know whether you need to stay overnight or come back the next day to have this sample taken.

PARENT/CARER INFORMATION SHEET – WEIGHT BAND PK 2 (25KG TO <40KG)

ODYSSEY WEIGHT BAND PK 2 – BLOOD LEVELS STUDY

1 Why are we doing this study?

We need to check that a different dose of dolutegravir is suitable for children who weigh 25kg to 40kg.

2 Why has my child been asked to take part?

Children being asked to take part in this study are taking part in ODYSSEY, weigh between 25kg and 40kg and are taking dolutegravir. We are aiming to ask a small group of children to take part.

Your child has been asked to take part either because:

A. he/she is already taking part in ODYSSEY

OR

B. you and your child may be thinking about taking part in ODYSSEY; in this case your child may only take part in this additional study if they join the ODYSSEY trial and they are allocated dolutegravir.

3 What will happen if we decide not to take part?

It is totally up to you and your child whether or not he/she takes part in this study.

If you or your child decides not to take part this will not stop your child from taking part in ODYSSEY or affect your child's care now or in the future in any way.

4 What will happen if my child takes part?

If you decide to take part, we will go through this information sheet together. We will give you a copy to keep. You will be asked to sign a consent form to show you understand the information and agree to take part.

If your child does take part, blood samples will be taken from your child and stored so researchers can learn more about anti-HIV medicines. If at any point your child wants to stop being in the study we hope that you will still allow us to use these samples. If, however, you do not give your permission then we will destroy them.

Your child's wellbeing will be monitored closely during the study. If for any reason his/her medicine needs to be changed this will be done by their doctor.

Important to know

- ***If your child is eligible and does take part in the blood levels study they will need to spend one whole day at the clinic after at least 1 week of taking dolutegravir.***

- ***Your child's dose will be changed after the first PK (blood sampling) day.***

- ***At least 1 week after your child has been changed to the new dose of dolutegravir, he/she will spend a second day at the clinic.***

- ***Your child will also have to come in for a clinic visit at 2, 4 and 12 weeks after starting the new dose of dolutegravir. Where possible these visits will be timed to coincide with scheduled ODYSSEY study visits to minimise additional clinic visits.***

On the day booked for the first blood sampling visit your child will be asked to come to the clinic for a whole day. He/she will have up to 7 blood samples taken during the day (over a 24 hour period) to test the level of medicine in their blood. A cream with local pain-killing effect will be used to make the skin numb and a thin flexible tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken more easily. All blood samples will be taken from the cannula so only one needle prick is required. Each blood sample will be small (less than half a teaspoon), and the amount will be is safe for your child's age and weight.

We will also need to take a blood sample the next morning. Your child may stay overnight or we will provide transport for you to come back the next day.

At least one week after your child has switched to the new dose of dolutegravir he/she will be asked to spend a second day at the clinic and another set of blood samples will be taken. Like for the first PK day this may also require an overnight stay in hospital.

2, 4 and 12 weeks after starting the new dose of dolutegravir your child will be asked to come to clinic for clinical assessment, some blood tests and we will ask you and your child to complete a short questionnaire. These visits are to make sure that your child is doing well and is healthy whilst taking the new dose.

At this point the PK (Blood Levels) study will end. However, usual clinic ODYSSEY visits will continue for routine monitoring of your child's health.

5 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this study?

We cannot promise that participating in the study will directly help your child but the results of this study will give us more information about which dose of dolutegravir works better for children and young people. It is very important that we have this information so we can make sure that children are given the correct amount of medicine.

This information will help children and young people across the world with HIV and in the future it may mean your child has the chance to get the most appropriate amount of medicine.

What are the possible disadvantages and risks of taking part in this study?

It's important to think about these before deciding to take part.

This study will not result in any risk to your child's health. However, your child will have to spend two days at the clinic and may need to stay overnight on these days.

On each PK day, up to 7 small blood samples will be taken but only one needle prick will be needed.

Your child will have to attend at least 1 or 2 additional visits after starting the new dose in order to check they are doing well.

6 More information about taking part

Who has checked this study is safe?

This study has been looked at by an independent group of people (a Research Ethics Committee) to make sure that, as far as possible, the safety and wellbeing of anyone taking part in the study is protected.

A second group (the Independent Data Monitoring Committee) will review the results as they come out and will recommend if the study is safe to continue. This is standard for all studies looking at medicines for adults or children.

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should your child come to any harm from participating in this study. However, if your child is harmed due to someone's negligence then you may have reasons for legal action for compensation against the hospital where the negligence occurred.

With your permission your child's GP will be informed of his/her participation in the study. Your hospital doctor is not receiving any personal payment for carrying out this research. *[Country specific, delete if not applicable]*

What will happen to information about my child collected during this study?

All information collected during the ODYSSEY study will be kept completely confidential and names will not be used. Your child will only be identified using a study number an anonymous code and their date of birth. Your child's clinic notes may be looked at by study staff from the PENTA Foundation, the trials units co-ordinating the study or other independent people authorised to make sure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published no information will be included that could identify your child (no name or date of birth). The study will be conducted in agreement with the country specific data protection regulations.

7 Contacts for more information

If you would like more information about the study please ask the doctor or nurse at your clinic. If you still need more information please call:

Contact: _____
Tel: _____

PARTICIPANT INFORMATION SHEET –WEIGHT BAND PK 2 (25KG TO <40KG)

ODYSSEY WEIGHT BAND PK 2 - BLOOD LEVELS STUDY

1 Why are we doing this study?

We need to check that a different dose of the new medicine is suitable for children who weigh about the same as you.

2 Why have I been asked to take part?

You have been asked to take part because either

A. you are part of the ODYSSEY study and are taking the new medicine
OR
B. you may be taking part in ODYSSEY and could be starting to take the new medicine if and when you start the study.

3 What will happen if we decide not to take part?

It is totally up to you whether or not to take part in this study.

If you decide not to take part this will not stop you from taking part in ODYSSEY or affect your care now or in the future in any way.

4 What will happen if I take part?

If you decide you would like to take part, we will go through this information sheet together. We will give you a copy to keep. You will be asked to sign an assent form to show you understand the information and agree to take part.

Important to know

- ***If you do take part you will need to spend one whole day in the clinic after at least 1 week of taking the new medicine.***
- ***Your dose will be changed after the first blood sampling day.***
- ***After at least 1 week of being on the new dose of your medicine you will spend a second day at the clinic.***
- ***You will also have to come in for a clinic visit at 2, 4 and 12 weeks after starting the new dose of medicine.***

On the day booked for the first blood sampling visit you will be asked to come to the clinic for a whole day.

You will have up to 7 blood samples taken during the day (over a 24 hour period) to test the level of medicine in your blood. A cream will be used to make the skin numb and a thin flexible tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken more easily. All blood samples will be taken from the cannula so only one needle prick is required.

Each blood sample will be small (less than half a teaspoon), and the amount will be is safe for your age and weight.

We will also need to take a blood sample the next morning. You can stay overnight or we will provide transport for you to come back the next day.

At least one week after you have switched to the new dose of medicine you will be asked to spend a second day at the clinic and another set of blood samples will be taken. Like the first blood sampling day, this may also require an overnight stay in the clinic.

2, 4 and 12 weeks after starting the new dose you will be asked to come to clinic to make sure that you are doing well and are healthy whilst taking the new dose.

At this point the blood levels study will end. However, usual clinic ODYSSEY visits will continue for routine monitoring of your health.

PARENT/CARER INFORMATION SHEET FOR TB PHARMACOKINETIC (PK) SUBSTUDY

ODYSSEY TB PK STUDY:
DOLUTEGRAVIR + anti-TB medicines

1 Why are we doing this study?

Many people taking dolutegravir also need to take anti-TB medicines.

Studies looking at this in adults have shown the amount of dolutegravir needs to be doubled if anti-TB medicines are taken at the same time.

In children there isn't enough information about how much we need to increase the amount of dolutegravir if anti-TB medicines are taken.

We hope this study will help us to find the best treatment for children like yours.

2 Why has my child been asked to take part?

Your child has been asked to participate because he/she is part of the ODYSSEY study and is taking dolutegravir and anti-TB medicines.

We are asking at least 12 children and young people to take part.

3 What will happen if we decide not to take part?

It is totally up to you and your child whether or not he/she takes part in this study. It is your right to decide not to take part if you wish.

If you or your child decides not to take part this will not stop your child from taking part in ODYSSEY or affect your child's care now or in the future in any way.

If you do decide to take part, blood samples will be taken and stored from your child so researchers can learn more about anti-HIV medicines. If at any point your child wants to stop being in the study we hope that you will still allow us to use these samples. If, however, you do not give your permission then we will destroy them.

4 What will happen if my child takes part?

If you do decide to take part, we will go through this information sheet together. We will give you a copy to keep. You will be asked to sign a consent form to show you understand the information and agree to take part.

Your child's wellbeing will be monitored closely during the study. If for any reason his/her medicine needs to be changed this will be done by their doctor in the usual way.

Important to know

- ***If you decide to take part your child will need to spend one day in clinic while taking anti-TB medicines.***
- ***At least a month after your child stops taking anti-TB medicines, he/she will spend a second day at the clinic and may need to stay overnight.***

At the start of the study your child will be taking dolutegravir and anti-TB medicines. At this point we will take some blood samples to measure the level of dolutegravir in the blood.

Your child will be asked to come into clinic for a whole day. He/she will have up to 7 blood samples taken during the day (over a 12 hour period) to test the level of dolutegravir and anti-TB medicine in their blood. A cream with local pain-killing effect will be used to make the skin numb and a thin flexible tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken. All blood samples will be taken from the cannula so only one needle prick is required. Each blood sample will be small (about half a teaspoon), and the amount will be is safe for your child's age and weight.

At least a month after your child has completed his/her anti-TB treatment he/she will be asked to spend a second day at the clinic and another 7 blood samples will be taken (over 24 hours). This may require an overnight stay in hospital.

At this point the dolutegravir-anti-TB medicines study will end. However, usual clinic ODYSSEY visits will continue for routine monitoring of your child's health.

5 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this study?

We cannot promise that participating in the study will directly help your child but the results of this study will give us more information about how dolutegravir and anti-TB medicines work together in children. It is very important that we have this information so we can make sure that children are given the correct amount of medicine.
This information will help children and young people across the world with HIV and TB and in the future it may mean your child has the chance to get the most appropriate amount of medicines.

What are the possible disadvantages and risks of taking part in this study?

It's important to think about these before deciding to take part.
This study will not result in any risk to your child's health. However, your child will have to spend separate two days at the clinic and may need to stay overnight on the second day.
Each day, up to 7 small blood samples will be taken but only one needle prick will be needed each day.

6 More information about taking part

Who has checked this study is safe?

This study has been looked at by an independent group of people (a Research Ethics Committee) to make sure that, as far as possible, the safety and wellbeing of anyone taking part in the study is protected.

A second group (the Independent Data Monitoring Committee) will meet regularly during the study to review the results as they come out and will recommend if the study is safe to continue. This is standard for all studies looking at medicines for adults or children.

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should your child come to any harm from participating in this study. However, if your child is harmed due to someone's negligence then you may have reasons for legal action for compensation against the hospital where the negligence occurred.

With your permission your child's GP will be informed of his/her participation in the study. Your hospital doctor is not receiving any personal payment for carrying out this research. *[Country specific, delete if not applicable]*

What will happen to information about my child collected during this study?

All information collected during the ODYSSEY study will be kept completely confidential and names will not be used. Your child will only be identified using a study number, an anonymous code and their date of birth. Your child's clinic notes may be looked at by study staff from the PENTA Foundation, the trials units co-ordinating the study or other independent people authorised to ensure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published no information will be included that could identify your child (no name or date of birth). The study will be conducted in agreement with the country specific data protection regulations.

7 Contacts for more information

If you would like more information about the study please ask the doctor or nurse at your clinic. If you still need more information please call:

Contact: _____
Tel: _____

PARTICIPANT INFORMATION SHEET FOR TB PHARMACOKINETIC (PK) SUBSTUDY

ODYSSEY TB PK STUDY:
DOLUTEGRAVIR + anti-TB medicines

1 Why are we doing this study?

Many people taking dolutegravir also need to take anti-TB medicines.

Studies looking at this in adults have shown the amount of dolutegravir needs to be doubled if anti-TB medicines are taken at the same time.

In children there isn't enough information about how much we need to increase the amount of dolutegravir if anti-TB medicines are taken.

We hope this study will help us to find the best treatment for young people like you.

2 Why have I been asked to take part?

You have been asked to participate because you are part of the ODYSSEY study and are taking dolutegravir and anti-TB medicines.

We are asking at least 12 young people to take part.

3 What will happen if I decide not to take part?

It is totally up to you whether or not you take part in this study. It is your right to decide not to take part if you wish.

If you decide not to take part this will not stop you from taking part in ODYSSEY or affect your care now or in the future in any way.

If you do decide to take part, blood samples will be taken and stored from you so researchers can learn more about anti-HIV medicines. If at any point you want to stop being in the study we hope that you will still allow us to use these samples. If, however, you do not give your permission then we will destroy them.

4 What will happen if I take part?

If you do decide to take part, we will go through this information sheet together. We will give a copy to you to keep. Your parent/carer will then be asked to sign a consent form to show you both understand the information and agree to take part. We will also ask you to sign a form giving your assent to join the study.

Your wellbeing will be monitored closely during the study. If for any reason your medicine needs to be changed this will be done by your doctor in the usual way.

Important to know

- ***If you decide to take part you will need to spend one day in clinic while taking anti-TB medicines.***
- ***At least a month after you stop taking anti-TB medicines, you will spend a second day at the clinic and may need to stay overnight.***

At the start of the study you will be taking dolutegravir and anti-TB medicines. At this point we will take some blood samples to measure the level of dolutegravir in the blood.

You will be asked to come into hospital for a whole day. You will have up to 7 blood samples taken during the day (over a 12 hour period) to test the level of dolutegravir and anti-TB medicine in your blood. A cream with local pain-killing effect will be used to make the skin numb and a thin flexible tube (called a cannula) will be inserted into a vein for the day to enable the blood samples to be taken. All blood samples will be taken from the cannula, so only one needle prick is required. Each blood sample will be small (about half a teaspoon), and the amount will be is safe for your age and weight.

At least a month after you have completed your anti-TB treatment you will be asked to spend a second day at the clinic and another 7 blood samples will be taken (over a 24 hour period). This may require an overnight stay in hospital.

At this point the dolutegravir-anti-TB medicines study will end. However, usual clinic ODYSSEY visits will continue for routine monitoring of your health.

5 What are the possible benefits and disadvantages of taking part?

What are the possible benefits of taking part in this study?

We cannot promise that participating in the study will directly help you but the results of this study will give us more information about how dolutegravir and anti-TB medicines work together in children and young people. It is very important that we have this information so we can make sure that children and young people are given the correct amount of medicine.
This information will help children and young people across the world with HIV and TB and in the future it may mean you have the chance to get the most appropriate amount of medicines.

What are the possible disadvantages and risks of taking part in this study?

It's important to think about these before deciding to take part.

This study will not result in any risk to your health. However, you will have to spend two days in the clinic and may need to stay overnight on the second day.
Each day, up to 7 small blood samples will be taken but only one needle prick will be needed each day.

6 More information about taking part

Who has checked this study is safe?

This study has been looked at by an independent group of people (a Research Ethics Committee) to make sure that, as far as possible, the safety and wellbeing of anyone taking part in the study is

protected.

A second group (the Independent Data Monitoring Committee) will meet regularly during the study to review the results as they come out and will recommend if the study is safe to continue. This is standard for all studies looking at medicines for adults or children.

What if something goes wrong?

The PENTA Foundation has made arrangements for compensation should you come to any harm from participating in this study. However, if you are harmed due to someone's negligence then you may have reasons for legal action for compensation against the hospital where the negligence occurred.

With your permission your GP will be informed of your participation in the study. Your hospital doctor is not receiving any personal payment for carrying out this research. *[Country specific, delete if not applicable]*

What will happen to my information collected during this study?

All information collected during the ODYSSEY study will be kept completely confidential and names will not be used. You will only be identified using a study number, an anonymous code and their date of birth. Your clinic notes may be looked at by study staff from the PENTA Foundation, the trials units co-ordinating the study or other independent people authorised to ensure that the ODYSSEY study is being properly carried out. They may also be seen by the companies who are supplying medicine for the study or relevant international regulatory authorities. Confidentiality will be maintained at all times.

If the results of this study are reported or published no information will be included that could identify you (no name or date of birth). The study will be conducted in agreement with the country specific data protection regulations.

7 Contacts for more information

If you would like more information about the study please ask the doctor or nurse at your clinic. If you still need more information please call:

Contact: _____
Tel: _____

INFORMATION SHEETS FOR QUALITATIVE SUBSTUDY

Information sheets for in-depth interviews (IDIs)- 10-18 year olds

- Information sheets – IDIs- young people (15- 18 year olds)
- Information sheets- IDIs – young people (10-14 year olds)
- Information sheets- IDIs- parents/ guardians
- Information sheets – IDIs- caregivers
- Information sheets – IDIs- young people (15- 19 year olds) - DTG alert
- Information sheets- IDIs – young people (10-14 year olds) - DTG alert
- Information sheets- IDIs- parents/ guardians - DTG alert

Information sheets for focus group discussions (FGDs) 10-18 year olds

- Information sheets- FGDs- young people (15-18 year olds)
- Information sheets- FGDs- young people (10-14 year olds)
- Information sheets- FGDs- parents/ guardians

ODYSSEY QUALITATIVE STUDY:

PARTICIPANT INFORMATION SHEET FOR IN-DEPTH INTERVIEWS 15-18 YEAR OLDS

(Insert version no and date)

We are doing a study to hear from young people (aged 10-18 years) about their experiences of growing up with HIV. We would like you to join our study.
Before you decide if you want to take part please read this information sheet carefully and ask any questions you may have.

What is the purpose of the study?
This is a study to find out about what it is like for young people growing up with HIV and taking HIV treatment. In particular, we are looking to better understand what it is like to take second-line HIV treatment. Second-line means that you were already taking one set of anti-HIV medicine that were no longer working well and your doctor decided it was time for you change to a new combination. We are interested in learning from young people what can make it difficult to take their treatment and what might help make it easier. We will do this by talking with young people, like you, about their experiences. This is because we think that the best way to learn about the experiences of young people is to listen carefully to what they have to say. This type of research is called a qualitative study.

Why is the study being done?
Until now there hasn't been much research done which asks young people themselves about their experiences of being on second-line treatment. This is why we are doing the study. By listening to what young people tell us we hope to make some suggestions about how to improve support for young people to take their treatment.

Who is doing the study?
This study is being run in two of the sites, one in Uganda and one in Zimbabwe, where the ODYSSEY trial is being conducted. This qualitative study is being done by a small team of researchers from Uganda, Zimbabwe and the United Kingdom. We have done similar research before in these sites and are experienced in talking with young people.

Why are we asking you?
We are asking whether you would like to take part in this study because you are participating in the ODYSSEY trial and are aged between 10-18 years old.

What would I be asked to do?
We would like you to meet a researcher for two interviews. The first interview will be close to when you begin the ODYSSEY trial and the second interview would take place later on in the trial. Each interview will be like a conversation and will last for about an hour. There are no wrong or right answers. You do not have to talk about any topics that you do not want to. You can stop the interview at any time, without having to explain why.
We would like to audio record these interviews, if this is OK with you. The interview will take place somewhere that you feel comfortable, probably a private place at the clinic.

What will happen to any information collected about me during this study?
Any information that you share with us will only be seen by members of the research team. This means that whenever we write or talk about anything you have told us we never use your real name. All information about you will be stored securely.
The only exception to this is if you tell us something that makes us worried about you or another young person's safety, such as physical harm or neglect. If we think that we should tell someone else, we will talk to you about it first and ask if you would like us to do that.

How will the research be used?

The findings of this study will be reported to a wide range of people who are involved in providing treatment, care and support for children and young people living with HIV. The findings will be used to guide the way young people on second-line HIV treatment are supported in the future.

What are the benefits and risks of taking part?

You will be part of a study that aims to help young people live well with HIV and to support those taking second-line treatment. Some young people may find the opportunity to talk about their experiences of growing up with HIV and taking treatment to be a really good thing. Some young people though might find it a difficult subject to talk about. The researcher will take care to ask questions sensitively. It is up to you what you want to tell us. Also if you want there can be someone available from your clinic to talk to if you feel that you want to at any point during the study, including after the interview.

Do I have to take part?

No, you do not have to take part in the study. Your access to the clinic will not be affected in anyway if you decide not to take part. It will not affect any of the services that you currently receive. If you do decide to take part but later change your mind this is OK too.

Will I receive anything for taking part?

Yes, your travel expenses will be covered for the interviews. If you are accompanied to the interview then your escort's travel expenses will be covered too. You will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*

Yes, your travel expenses will be covered for the interviews. You will receive US$7 per interview or local equivalent. If you are accompanied to the interview then your escort's travel expenses will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before deciding the staff at your clinic can arrange for you to speak to one of the researchers more about it.

I'm happy to take part. Now what?

Once you have signed the assent or consent form and, if you are under 18 years old your carer has given their consent, the researcher will contact you and your carer, if necessary, to arrange the first interview.

What happens if you have questions?

If you or the person who takes care of you have any questions, you can contact: xxxxxxxx
If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this!

ODYSSEY QUALITATIVE STUDY:

PARTICIPANT INFORMATION SHEET FOR IN-DEPTH INTERVIEWS 10-14 YEAR OLDS

(Insert version no and date)

We are doing a study with young people (aged 10-18 years) about their experiences of growing up with HIV. We would like you to join our study.
Before you decide if you want to take part we would like you to read the information below carefully. Someone can help you read it if that is easier. It is important that you understand what we are asking you to do and you should feel comfortable to ask any questions, however big or small.

What is the purpose of the study?
This is a study to find out about what it is like for young people when they are growing up with HIV. We are really interested to understand more about what it is like for you and other young people to take your HIV treatment every day. We especially want to understand what it is like when your treatment has been changed to what is called second-line. Second-line means that you were already taking one set of anti-HIV medicine that were no longer working well and your doctor decided it was time for you change to a new combination. We want to know what can make it difficult to take treatment and what might help make it easier. We will do this by talking with young people, like you, about what it is like. This is because we think that the best way to learn about this is to listen carefully to what young people have to say.

Why is the study being done?
We don't at the moment know very much about what it is like for young people to take second-line treatment. So we are doing this study so that we can learn more about it. This will help us to make suggestions about how to help young people with taking their treatment.

Who is doing the study?
This study is being run in Uganda and Zimbabwe. The researchers working on this study are from Uganda, Zimbabwe as well as the United Kingdom. We have done lots of work like this before.

Why are we asking you?
We are asking whether you would like to take part in this study because you are already talking part in the ODYSSEY trial and are aged between 10-18 years old.

What would I be asked to do?
We would like you to meet a researcher for two interviews. The first interview will happen after you have started the ODYSSEY trial and the second interview will take place later on in the trial. The interviews will be like a conversation. They will last for about an hour. There are no wrong or right answers. You do not have to talk about anything that you don't want to and you will not need to say why.
As we want to listen very carefully to everything that you tell us we would like to audio record the interviews. We will only record them if you are OK with this.

The interview will take place somewhere that you feel comfortable. This will probably be at the clinic, somewhere private so that no one can overhear what we will be talking about.

What will happen to any information collected about me during this study?
Anything that you tell us will only be listened to by the research team. This means that whenever we write or talk about anything you have told us we never use your real name. We will be very careful to keep all the information about you locked away so that no one else can see it.
The only exception to this is if you tell us something that makes us worried about you or another young person's safety. If we are concerned and think that we should tell someone else, we will talk to you about it first and ask if you would like us to do that.

How will the research be used?

We will tell lots of people who look after children and young people living with HIV what we have learnt from our study. What we learn will be used to guide the way young people on second-line HIV treatment are supported in the future

What are the benefits and risks of taking part?

You will be part of a study that aims to help young people live well with HIV and to support those taking second-line treatment. Some young people may find the opportunity to talk about their experiences of growing up with HIV and taking treatment to be a really good thing. Some young people though might find it a difficult subject to talk about. The researcher will take care to ask questions thoughtfully. It is up to you what you want to tell us. Also if you want there can be someone available from your clinic to talk to if you feel that you want to at any point during the study, including after the interview.

Do I have to take part?

No, you do not have to take part in the study. If you say no, everything that you receive at the clinic will be just the same as before. If you do decide to take part but later change your mind this is OK too.

Will I receive anything for taking part?

Yes, your travel expenses will be covered for the interviews. If you are accompanied to the interview then the expenses of the person who comes with you will also be covered. You will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*

Yes, your travel expenses will be covered for the interviews. You will receive US$7 per interview or local equivalent. If you are accompanied to the interview then the person who comes with you will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before deciding the staff at your clinic can arrange for you to speak to one of the researchers more about it. We will be very happy to answer any of your questions.

I'm happy to take part. Now what?

Once you and your carer have signed the assent or consent form the researcher will contact you and your carer to arrange the first interview.

What happens if you have questions?

If you or the person who takes care of you have any questions you can contact: xxxxxxxx
If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this!

ODYSSEY QUALITATIVE STUDY:

PARENT/CARER INFORMATION SHEET FOR IN-DEPTH INTERVIEWS

(Insert version no and date)

We are doing a study to hear from young people (aged 10-18 years) about their experiences of growing up with HIV. We would like your child to join our study.
Before you decide if you want your child to take part please read this information sheet carefully and ask any questions you may have.

What is the purpose of the study?
This is a study to find out about what it is like for young people growing up with HIV and taking HIV treatment. In particular, we are looking to better understand what it is like to be on second-line HIV treatment. Second-line means that someone was already taking one set of anti-HIV medicine that were no longer working well and their doctor decided it was time for them change to a new combination. We are interested in learning from young people what can make it difficult to take treatment and what might help make it easier. This will be done by talking with young people, like your child, about their experiences. This is because we think that the best way to learn about the experiences of young people is to listen carefully to what they have to say. This type of research is called a qualitative study.

Why is the study being done?
Up until now there hasn't been much research done which asks young people themselves about their experiences of being on second-line treatment. This is why we are doing the study. By listening to what young people tell us we hope to make some suggestions about how to improve support for young people to take their treatment.

Who is doing the study?
This study is being run in two sites where the ODYSSEY trial is being conducted. One is at JCRC in Uganda and one is at the University of Zimbabwe in Harare, Zimbabwe. This qualitative study is being done by a small team of researchers from Uganda, Zimbabwe and the United Kingdom. We have done similar research before in these sites and are experienced in talking with young people about similar topics.

Why are we asking your child?
We are asking whether you are happy for your child to take part in this study because your child is already participating in the ODYSSEY trial and is aged between 10-18 years old.

What would my child be asked to do?
We would like your child to meet with a researcher for two interviews. The first interview will be close to when they begin the ODYSSEY trial and the second interview would take place later on in the trial. Each interview will be like a conversation and will last for about an hour. There are no wrong or right answers. Your child does not have to talk about anything that they do not want to. Your child can stop the interview at any time, without having to explain why.

We would like to audio record these interviews, if this is OK with you and your child. The interview will take place somewhere that your child feels comfortable, probably at the clinic where a private place will be found for them to meet the researcher.

What will happen to any information collected about my child during this study?
Any information that your child shares with us will only be seen by members of the research team. This means that whenever we write or talk about anything your child has told us we would never use their real name. All information about your child will be stored securely.

The only exception to this is if your child tells us something that makes us worried about your child or another young person's safety, such as physical harm or neglect. If we think that we should tell someone else, we will talk to them about it first and ask if they would like us to do that.

How will the research be used?

The findings of this study will be reported to a wide range of people who are involved in providing treatment, care and support for children and young people living with HIV. The findings will be used to guide the way young people on second-line HIV treatment are supported in the future

What are the benefits and risks of taking part?

Your child will be part of a study that aims to help young people live well with HIV and to support those taking second-line treatment. Some young people may find the opportunity to talk about their experiences of growing up with HIV and taking treatment to be a really good thing. Some young people though might find it a difficult subject to talk about. The researcher will take care to ask questions sensitively. It is up to your child what they want to tell us. Also if your child wants there can be someone available from their clinic to talk to if they feel that they want to at any point during the study, including after the interview.

Does my child have to take part?

No, they do not have to take part in the study. Their access to the clinic will not be affected in anyway if you or your child decides that you do not want them to take part. It will not affect any of the services that they currently receive. If your child does decide to take part but later changes their mind this is OK too.

Will my child receive anything for taking part?

Yes, their travel expenses will be covered for the interviews. If they are accompanied to the interview then their escort's travel expenses will be covered too. They will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*
Yes, their travel expenses will be covered for the interviews. They will receive US$7 per interview or local equivalent. If they are accompanied to the interview then their escort's travel expenses will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before you decide the staff at your clinic can arrange for you to speak to one of the researchers more about it.

I'm happy for my child to take part. Now what?

Once you have signed the consent form and, if your child has given their assent, the researcher will contact you and your child to arrange the first interview.

What happens if you have questions?

If you or your child have any questions you can contact: xxxxxxxxx

If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this!

ODYSSEY QUALITATIVE STUDY:

PARTICIPANT INFORMATION SHEET FOR IN-DEPTH INTERVIEWS - CAREGIVERS

(Insert version no and date)

As part of the Odyssey trial we are doing a study to hear from young people (aged 10-19 years) about their experiences of growing up with HIV and their caregivers. We would like you to join our study.
Before you decide if you want to take part please read this information sheet carefully and ask any questions you may have.

What is the purpose of the study?
This is a study to find out about what it is like for young people growing up with HIV and taking HIV treatment. In particular, we are looking to better understand what it is like for young people to grow up well with HIV, including being able to take their treatment well and access the information that they need. We are interested in learning from young people and their caregivers what can make it difficult for young people to grow up well with HIV and what might help make it easier. We will do this by talking with young people and their caregivers, like you, about their experiences. This is because we think that the best way to learn about the experiences of young people is to listen carefully to what they have to say. This type of research is called a qualitative study.

Why is the study being done?
Until now there hasn't been much research done which asks young people themselves about their experiences of growing up with HIV and also what it is like for their caregivers. This is why we are doing the study. By listening to what young people and their caregivers tell us we hope to make some suggestions about how to improve support for young people.

Who is doing the study?
This study is being run in two of the sites, one in Uganda and one in Zimbabwe, where the ODYSSEY trial is being conducted. This qualitative study is being done by a small team of researchers from Uganda, Zimbabwe and the United Kingdom. We have done similar research before in these sites and are experienced in talking with caregivers and young people.

Why are we asking you?
We are asking whether you would like to take part in this study because a young person that you care for is participating in the ODYSSEY trial. They have agreed that it is okay if we ask you if you would like to be involved in the caregiver part of our study.

What would I be asked to do?
We would like you to meet a researcher for an interview. The interview will be like a conversation and will last for about an hour. There are no wrong or right answers. You do not have to talk about any topics that you do not want to. You can stop the interview at any time, without having to explain why.
We would like to audio record these interviews, if this is OK with you. The interview will take place somewhere that you feel comfortable, probably a private place at the clinic.

What will happen to any information collected about me during this study?
Any information that you share with us will only be seen by members of the research team. This means that whenever we write or talk about anything you have told us we never use your real name. We will not reveal any information that you tell us that can be personally linked to you to anyone else, including the young person you care for. Nor shall we share anything with you that they have told us. All information about you will be stored securely. The only exception to this is if you tell us something that makes us worried about a young person's safety, such as physical harm or neglect. If we think that we should tell someone else, we will talk to you about it first and ask if you would like us to do that.

How will the research be used?

The findings of this study will be reported to a wide range of people who are involved in providing treatment, care and support for children and young people living with HIV. The findings will be used to guide the way young people on HIV treatment are supported in the future.

What are the benefits and risks of taking part?

You will be part of a study that aims to help young people live well with HIV as they grow up. Some people may find the opportunity to talk about what it is like to care for someone who is growing up with HIV to be a really good thing. Some though might find it a difficult subject to talk about. The researcher will take care to ask questions sensitively. It is up to you what you want to tell us. Also if you want there can be someone available from your clinic to talk to if you feel that you want to at any point during the study, including after the interview.

Do I have to take part?

No, you do not have to take part in the study. Your own or the young person's access to the clinic will not be affected in anyway if you decide not to take part. It will not affect any of the services that you or they currently receive. If you do decide to take part but later change your mind this is OK too.

Will I receive anything for taking part?

Yes, your travel expenses will be covered for the interview. You will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*

Yes, your travel expenses will be covered for the interview. You will receive US$7 per interview or local equivalent. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before deciding the staff at your clinic can arrange for you to speak to one of the researchers more about it.

I'm happy to take part. Now what?

Once you have signed the consent form the researcher will contact you to arrange the interview.

What happens if you have questions?

If you or the person who takes care of you have any questions, you can contact: xxxxxxxx
If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this!

ODYSSEY QUALITATIVE STUDY:

PARTICIPANT INFORMATION SHEET FOR IN-DEPTH INTERVIEW 15-19 YEAR OLDS (DTG alert)

(Insert version no and date)

We are doing a study to hear from young people (aged 10-19 years) about their experiences of growing up with HIV and the discussions they have within the HIV clinic. We would like to invite you to take part.

Before you decide if you want to take part please read this information sheet carefully and ask any questions you may have.

What is the purpose of the study?
This is a study to find out about what it is like for young people growing up with HIV, taking HIV treatment and being part of ODYSSEY. In particular, we are looking to better understand what you discuss about growing up with HIV with healthcare staff and others and what sorts of information you would like to have about growing up with HIV. We will do this by talking with young people, like you, about their experiences. This is because we think that the best way to learn about the experiences and attitudes of young people is to listen carefully to what they have to say. This type of research is called a qualitative study.

Why is the study being done?
Until now there hasn't been much research done which asks young people themselves about their experiences of being in trials and on HIV treatment. This is why we are doing the study. By listening to what young people tell us we hope to make some suggestions about how to improve support for young people to take their treatment and provide them with information that they would find helpful.

Who is doing the study?
This study is being run in two of the sites, one in Uganda and one in Zimbabwe, where the ODYSSEY trial is being conducted. This qualitative study is being done by a small team of researchers from Uganda, Zimbabwe and the United Kingdom. We have done similar research before in these sites and are experienced in talking with young people.

Why are we asking you?
We are asking whether you would like to take part in this study because you are participating in the ODYSSEY trial and are aged between 10-19 years old.

What would I be asked to do?
We would like you to meet a researcher for an interview. The interview will be like a conversation and will last for about an hour. There are no wrong or right answers. You do not have to talk about any topics that you do not want to. You can stop the interview at any time, without having to explain why.
We would like to audio record this interview, if this is OK with you. The interview will take place somewhere that you feel comfortable, probably a private place at the clinic.

What will happen to any information collected about me during this study?
Any information that you share with us will only be seen by members of the research team. This means that whenever we write or talk about anything you have told us we never use your real name. All information about you will be stored securely.
The only exception to this is if you tell us something that makes us worried about you or another young person's safety, such as physical harm or neglect. If we think that we should tell someone else, we will talk to you about it first and ask if you would like us to do that.

How will the research be used?

The findings of this study will be reported to a wide range of people who are involved in providing treatment, care and support for children and young people living with HIV. The findings will be used to guide the way young people on HIV treatment are supported in the future.

What are the benefits and risks of taking part?

You will be part of a study that aims to help young people live well with HIV and to provide them with the information that they need and can understand. Some young people may find the opportunity to talk about their experiences of growing up with HIV to be a really good thing. Some young people though might find it a difficult subject to talk about. The researcher will take care to ask questions sensitively. It is up to you what you want to tell us. Also if you want there can be someone available from your clinic to talk to if you feel that you want to at any point during the study, including after the interview.

Do I have to take part?

No, you do not have to take part in the study. Your access to the clinic will not be affected in anyway if you decide not to take part. It will not affect any of the services that you currently receive. If you do decide to take part but later change your mind this is OK too.

Will I receive anything for taking part?

Yes, your travel expenses will be covered for the interview. If you are accompanied to the interview then your escort's travel expenses will be covered too. You will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*

Yes, your travel expenses will be covered for the interview. You will receive US$7 per interview or local equivalent. If you are accompanied to the interview then your escort's travel expenses will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before deciding the staff at your clinic can arrange for you to speak to one of the researchers more about it.

I'm happy to take part. Now what?

Once you have signed the assent or consent form and, if you are under 18 years old your carer has given their consent, the researcher will contact you and your carer, if necessary, to arrange the first interview.

What happens if you have questions?

If you or the person who takes care of you have any questions, you can contact: xxxxxxxx
If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this!

ODYSSEY QUALITATIVE STUDY:

PARTICIPANT INFORMATION SHEET FOR IN-DEPTH INTERVIEW 10-14 YEAR OLDS (DTG alert)

(Insert version no and date)

We are doing a study with young people (aged 10-19 years) about their experiences of growing up with HIV. We would like you to join our study.

Before you decide if you want to take part we would like you to read the information below carefully. Someone can help you read it if that is easier. It is important that you understand what we are asking you to do and you should feel comfortable to ask any questions, however big or small.

What is the purpose of the study?
This is a study to find out about what it is like for young people when they are growing up with HIV. We are really interested to understand more about what it is like for you and other young people to take your HIV treatment every day. We especially want to understand what it is like to talk about growing up with HIV and being part of ODYSSEY trial, as well as what sorts of information you would like to have about growing up with HIV. We will do this by talking with young people. This is because we think that the best way to learn about this is to listen carefully to what young people have to say.

Why is the study being done?
We don't at the moment know very much about what it is like for young people who are on HIV treatment and in a clinical trial. So we are doing this study so that we can learn more about it. This will help us to make suggestions about how to help young people with taking their treatment and to have the information that they want to grow up well with HIV.

Who is doing the study?
This study is being run in Uganda and Zimbabwe. The researchers working on this study are from Uganda, Zimbabwe as well as the United Kingdom. We have done lots of work like this before.

Why are we asking you?
We are asking whether you would like to take part in this study because you are already talking part in the ODYSSEY trial and are aged between 10-19 years old.

What would I be asked to do?
We would like you to meet a researcher for an interview. This will be like a conversation and will last for about an hour. There are no wrong or right answers. You do not have to talk about anything that you don't want to and you will not need to say why.
As we want to listen very carefully to everything that you tell us we would like to audio record the interview. We will only record them if you are OK with this.
The interview will take place somewhere that you feel comfortable. This will probably be at the clinic, somewhere private so that no one can overhear what we will be talking about.

What will happen to any information collected about me during this study?

Anything that you tell us will only be listened to by the research team. This means that whenever we write or talk about anything you have told us we never use your real name. We will be very careful to keep all the information about you locked away so that no one else can see it.

The only exception to this is if you tell us something that makes us worried about you or another young person's safety. If we are concerned and think that we should tell someone else, we will talk to you about it first and ask if you would like us to do that.

How will the research be used?

We will tell lots of people who look after children and young people living with HIV what we have learnt from our study. What we learn will be used to guide the way young people on HIV treatment are supported in the future

What are the benefits and risks of taking part?

You will be part of a study that aims to help young people live well with HIV and to provide them with the information that they need and can understand. Some young people may find the opportunity to talk about their experiences of growing up with HIV to be a really good thing. Some young people though might find it a difficult subject to talk about. The researcher will take care to ask questions thoughtfully. It is up to you what you want to tell us. Also if you want there can be someone available from your clinic to talk to if you feel that you want to at any point during the study, including after the interview.

Do I have to take part?

No, you do not have to take part in the study. If you say no, everything that you receive at the clinic will be just the same as before. If you do decide to take part but later change your mind this is OK too.

Will I receive anything for taking part?

Yes, your travel expenses will be covered for the interview. If you are accompanied to the interview then the expenses of the person who comes with you will also be covered. You will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*

Yes, your travel expenses will be covered for the interview. You will receive US$7 per interview or local equivalent. If you are accompanied to the interview then the person who comes with you will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before deciding the staff at your clinic can arrange for you to speak to one of the researchers more about it. We will be very happy to answer any of your questions.

I'm happy to take part. Now what?

Once you and your carer have signed the assent or consent form the researcher will contact you and your carer to arrange the first interview.

What happens if you have questions?

If you or the person who takes care of you have any questions you can contact: xxxxxxxx

If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this!

ODYSSEY QUALITATIVE STUDY:

PARENT/CARER INFORMATION SHEET FOR IN-DEPTH INTERVIEW (DTG alert)

(Insert version no and date)

We are doing a study to hear from young people (aged 10-19 years) about their experiences of growing up with HIV and being part of a clinical trial. We would like your child to join our study.
Before you decide if you want your child to take part please read this information sheet carefully and ask any questions you may have.

What is the purpose of the study?
This is a study to find out about what it is like for young people growing up with HIV, taking HIV treatment and being part of ODYSSEY. In particular, we are looking to better understand what information they receive about growing up with HIV, whether they understand the information that they are given and their ideas about what forms of information would be helpful to them. . This will be done by talking with young people, like your child, about their experiences. This is because we think that the best way to learn about the experiences of young people is to listen carefully to what they have to say. This type of research is called a qualitative study.

Why is the study being done?
Up until now there hasn't been much research done which asks young people themselves about their experiences of being in a trial, on HIV treatment and what information they want about growing up with HIV. This is why we are doing the study. By listening to what young people tell us we hope to make some suggestions about how to improve support for young people to take their treatment and to have the information that they want to grow up well with HIV.

Who is doing the study?
This study is being run in two sites where the ODYSSEY trial is being conducted. One is at JCRC in Uganda and one is at the University of Zimbabwe in Harare, Zimbabwe. This qualitative study is being done by a small team of researchers from Uganda, Zimbabwe and the United Kingdom. We have done similar research before in these sites and are experienced in talking with young people about similar topics.

Why are we asking your child?
We are asking whether you are happy for your child to take part in this study because your child is already participating in the ODYSSEY trial and is aged between 10-19 years old.

What would my child be asked to do?
We would like your child to meet with a researcher for an interview. This interview will be like a conversation and will last for about an hour. There are no wrong or right answers. Your child does not have to talk about anything that they do not want to. Your child can stop the interview at any time, without having to explain why.

We would like to audio record this interview, if this is OK with you and your child. The interview will take place somewhere that your child feels comfortable, probably at the clinic where a private place will be found for them to meet the researcher.

What will happen to any information collected about my child during this study?
Any information that your child shares with us will only be seen by members of the research team. This means that whenever we write or talk about anything your child has told us we would never use their real name. All information about your child will be stored securely.

The only exception to this is if your child tells us something that makes us worried about your child or another young person's safety, such as physical harm or neglect. If we think that we should tell someone else, we will talk to them about it first and ask if they would like us to do that.

How will the research be used?

The findings of this study will be reported to a wide range of people who are involved in providing treatment, care and support for children and young people living with HIV. The findings will be used to guide the way young people on HIV treatment are supported in the future

What are the benefits and risks of taking part?

Your child will be part of a study that aims to help young people live well with HIV and to provide them with the information that they need and can understand. . Some young people may find the opportunity to talk about their experiences of growing up with HIV to be a really good thing. Some young people though might find it a difficult subject to talk about. The researcher will take care to ask questions sensitively. It is up to your child what they want to tell us. Also if your child wants there can be someone available from their clinic to talk to if they feel that they want to at any point during the study, including after the interview.

Does my child have to take part?

No, they do not have to take part in the study. Their access to the clinic will not be affected in anyway if you or your child decides that you do not want them to take part. It will not affect any of the services that they currently receive. If your child does decide to take part but later changes their mind this is OK too.

Will my child receive anything for taking part?

Yes, their travel expenses will be covered for the interview. If they are accompanied to the interview then their escort's travel expenses will be covered too. They will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*
Yes, their travel expenses will be covered for the interview. They will receive US$7 per interview or local equivalent. If they are accompanied to the interview then their escort's travel expenses will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before you decide the staff at your clinic can arrange for you to speak to one of the researchers more about it.

I'm happy for my child to take part. Now what?

Once you have signed the consent form and, if your child has given their assent, the researcher will contact you and your child to arrange the first interview.

What happens if you have questions?

If you or your child have any questions you can contact: xxxxxxxxx
If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this!

ODYSSEY QUALITATIVE STUDY:

PARTICIPANT INFORMATION SHEET FOR FOCUS GROUPS 15-19 YEAR OLDS

(Insert version no and date)

We are doing a study to hear from young people (aged 10-19 years) about their experiences of growing up with HIV. We would like you to join our study.
Before you decide if you want to take part please read this information sheet carefully and ask any questions that you may have.

What is the purpose of the study?
This is a study to find out about what it is like for young people growing up with HIV and taking HIV treatment. In particular, we are looking to better understand what it is like to be on HIV treatment, what you discuss within the HIV clinic with healthcare staff and others and what sorts of information you would like to have about growing up with HIV. This will be done by talking with young people, like you, about their experiences. This is because we think that the best way to learn about the experiences of young people is to listen carefully to what they have to say. This type of research is called a qualitative study.

Why is the study being done?
Up until now there hasn't been much research done which asks young people themselves about their experiences of being in trials and on HIV treatment. This is why we are doing the study. By listening to what young people tell us we hope to make some suggestions about how to improve support for young people to take their treatment and in the information that they receive.

Who is doing the study?
This study is being run in two sites in Uganda and Zimbabwe, where the ODYSSEY trial is being conducted. This qualitative study is being done by a small team of researchers from Uganda, Zimbabwe and the United Kingdom. We have done similar research before in these sites and are experienced in talking with young people.

Why are we asking you?
We are asking whether you would like to take part in this study because you are participating in the ODYSSEY trial and are aged between 10-19 years old.

What would I be asked to do?
We would like to talk to you in a group with other young people who are also on HIV treatment and taking part in the ODYSSEY trial. This is called a focus group. We would like you to take part in two focus groups.

In each focus group there will be a maximum of 7 other young people present and the researcher/s. All the young people will be from the same clinic as you. It will last about an hour. We would like to audio record what you say unless you do not want this. You do not

have to talk about things that you do not want to talk about, and you can leave the focus group at any time and without explaining why.

In the first focus group we will talk as a group about young people's experience of taking HIV treatment, being part of the trial and what it is like to complete some of the trial.

In the second focus group we will talk as a group about what we have learnt so far from our research. We are really interested to know what you think about what we have found. We'd also like to talk about whether you think that we have correctly understood your situation and those of other young people like you. Together we will talk about how we should tell other people, such as doctors, the trial teams, and families about what we have learnt and the most effective ways to do this.

What will happen to any information collected about me during this study?
Everyone in the group will be asked to not say anything about what they hear in the focus group, except to the researchers or the study counsellors. All the participants are involved in the trial and attend the same clinic as you.
Any information that you share with us will only be seen by members of the research team. This means that whenever we write or talk about anything you have told us we never use your real name. All information about you will be stored securely.
The only exception to this is if you tell us something that makes us worried about you or another young person's safety, such as physical harm or neglect. If we have to tell someone else, we will talk to you about it first.

How will the research be used?

The findings of this study will be reported to a wide range of people who are involved in providing treatment, care and support for children and young people living with HIV. The findings will be used to guide the way young people on HIV treatment are supported in the future. It will also be used to help people who are conducting other HIV treatment trials with young people.

What are the benefits and risks of taking part?

You will be part of a study that aims to help young people to live well with HIV, maintain long term adherence and to be given the information that they need and can understand to be able to do so. Some young people may find the opportunity to talk about their HIV treatment to be a really good thing. Some young people though might find it difficult to talk about. The researchers have done research with young people and will take care to ask questions sensitively. It is up to you what you want to tell the group. Also if you want, there can be someone available from your clinic to talk to if you feel that you want to at any point during the study, including after the focus group.

Do I have to take part?

No, you do not have to take part in the study. It will not affect any of the services you currently receive. If you do decide to take part but later change your mind this is OK too.

Will I receive anything for taking part?

Yes, your travel expenses will be covered for the focus groups. If you are accompanied to the focus groups then your escort's travel expenses will be covered too. You will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*
Yes, your travel expenses will be covered for the focus groups. You will receive US$7 per focus group or local equivalent. If you are accompanied to the focus group then your escort's travel expenses will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before deciding the staff at your clinic can arrange for you to speak to one of the researchers more about it. We will be very happy to answer any of your questions.

I'm happy to take part. Now what?

Once you have signed the assent or consent form and, if you are under 18 years old your carer has given their consent, the researcher will contact you and your carer to arrange the focus group.

What happens if you have questions?
If you or the person who takes care of you have any questions you can contact: xxxxxxx
If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this! If you do decide to take part your help will be very valuable.

ODYSSEY QUALITATIVE STUDY:

PARTICIPANT INFORMATION SHEET FOR FOCUS GROUPS 10-14 YEAR OLDS

(Insert version no and date)

We are doing a study to hear from young people (aged 10-19 years) about their experiences of growing up with HIV. We would like you to join our study.

Before you decide if you want to take part please read this information sheet carefully. Someone can read it to you if that is easier. It is important that you understand what we are asking you to do and you should feel comfortable to ask any questions that you have, however big or small.

What is the purpose of the study?
This is a study to find out about what it is like for young people when they are growing up with HIV. We are really interested to understand more about what it is like for you and other young people to take your HIV treatment every day. We especially want to understand what you discuss within the HIV clinic with healthcare staff and others and what sorts of information you would like to have about growing up with HIV. We will do this by talking with young people, like you, about what it is like. This is because we think that the best way to learn about this is to listen carefully to what young people have to say.

Why is the study being done?
We don't at the moment know very much about what it is like for young people to take HIV treatment well and what kind of information you think that you need to help you. So we are doing this study so that we can know more about it. This will help us to make suggestions about how to help young people with taking their treatment.

Who is doing the study?
This study is being run in Uganda and Zimbabwe. The researchers working on this study are from Uganda, Zimbabwe as well as the United Kingdom. We have done lots of work like this before.

Why are we asking you?
We are asking whether you would like to take part in this study because you are already talking part in the ODYSSEY trial and are aged between 10-19 years old.

What would I be asked to do?
We would like to talk to you in a group with other young people who are also on HIV treatment and taking part in the ODYSSEY trial. This is called a focus group. We would like you to take part in two focus groups.
In each focus group there will be a maximum of 7 other young people present and the researcher/s. All the young people will be from the same clinic as you. It will last about an hour. We would like to audio record what you say unless you do not want this. You do not have to talk about things that you do not want to talk about, and you can leave the focus group at any time and without explaining why.

In the first focus group we will talk as a group about what it is like to take HIV treatment. We will also talk about how everyone in the group has found being part of the ODYSSEY trial, including filling in some of the trial's questionnaires.

In the second focus group we will talk as a group about what we have learnt so far from our research. We are really interested to know what you think about what we have found. Together we will talk about how we should tell other people, such as doctors, about what we have learnt from our study.

What will happen to any information collected about me during this study?
Everyone in the group will be asked to not say anything about what they hear in the focus group, except to the researchers or the study counsellors. All the participants are involved in the trial and attend the same clinic as you.

Any information that you share with us will only be seen by members of the research team. This means that whenever we write or talk about anything you have told us we never use your real name. We will be very careful to keep all the information about you locked away so that no one else can see it.

The only exception to this is if you tell us something that makes us worried about you or another young person's safety. If we are concerned and think that we should tell someone else, we will talk to you about it first and ask if you would like us to do that.

How will the research be used?

We will tell lots of people who look after children and young people living with HIV about what we have learnt from our study. This will be used to guide the way young people on second-line HIV treatment are supported in the future.

What are the benefits and risks of taking part?

You will be part of a study that aims to help young people live well with HIV and to be given the information that they need and can understand to be able to do so . Some young people may find the opportunity to talk about their experiences of growing up with HIV to be a really good thing. Some young people though might find it a difficult subject to talk about. The researcher will take care to ask questions thoughtfully. It is up to you what you want to tell the group. Also if you want there can be someone available from your clinic to talk to if you feel that you want to at any point during the study, including after the interview.

Do I have to take part?

No, you do not have to take part in the study. If you say no, everything that you receive at the clinic will be just the same as before. If you do decide to take part but later change your mind this is OK too.

Will I receive anything for taking part?

Yes, your travel expenses will be covered for the focus groups. If you are accompanied to the focus groups then the expenses of the person who comes with you will also be covered. You will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*

Yes, your travel expenses will be covered for the focus groups. You will receive US$7 per focus group or local equivalent. If you are accompanied to the focus group then the person who comes with you will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before deciding the staff at your clinic can arrange for you to speak to one of the researchers more about it. We will be very happy to answer any of your questions.

I'm happy to take part. Now what?

Once you have signed the assent or consent form and, if you are under 18 years old your carer has given their consent, the researcher will contact you and your carer to arrange the focus group.

What happens if you have questions?

If you or the person who takes care of you have any questions you can contact: xxxxxx
If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

ODYSSEY QUALITATIVE STUDY:

PARENT/CARER INFORMATION SHEET FOR FOCUS GROUPS

(Insert version no and date)

We are doing a study to hear from young people (aged 10-19 years) about their experiences of growing up with HIV. We would like your child to join our study.
Before you decide if you want your child to take part please read this information sheet carefully and ask any questions you may have.

What is the purpose of the study?
This is a study to find out about what it is like for young people growing up with HIV and taking HIV treatment. In particular, we are looking to better understand what they discuss within the HIV clinic with healthcare staff and others and what sorts of information they would like to have about growing up with HIV. This will be done by talking with young people, like your child, about their experiences. This is because we think that the best way to learn about the experiences of young people is to listen carefully to what they have to say. This type of research is called a qualitative study.

Why is the study being done?
Up until now there hasn't been much research done which asks young people themselves about their experiences of growing up with HIV and the information that they think might help them. This is why we are doing the study. By listening to what young people tell us we hope to make some suggestions about how to improve support for young people.

Who is doing the study?
This study is being run in two sites where the ODYSSEY trial is being conducted. One is at JCRC in Uganda and one is at University of Zimbabwe in Harare, Zimbabwe. This qualitative study is being done by a small team of researchers from Uganda, Zimbabwe and the United Kingdom. We have done similar research before in these sites and are experienced in talking with young people.

Why are we asking your child to take part?
We are asking whether you would like your child to take part in this study because your child is participating in the ODYSSEY trial and are aged between 10-19 years old.

What would my child be asked to do?
We would like to talk to your child in a group with other young people who are also on HIV treatment and taking part in the ODYSSEY trial. This is called a focus group. We would like your child to take part in two focus groups.
In each focus group there will be a maximum of 7 other young people present and the researcher/s. All the young people will be from the same clinic as your child. It will last about an hour. We would like to audio record what your child and the other young people say unless you or your child do not want this. Your child does not have to talk about things that they do not want to talk about, and your child can leave the focus group at any time and without explaining why.

In the first focus group we will talk as a group about young people's experience of taking HIV treatment, being part of the trial and what it is like to complete the some of the trial questionnaires.
In the second focus group we will talk as a group about what we have learnt so far from our research. We are really interested to know what your child thinks about what we have found. Together we will talk about how we should tell other people, such as doctors, the trial teams, and families about what we have learnt and the most effective ways to do this.

What will happen to any information collected about my child during this study?
Everyone in the group will be asked not to say anything about what they hear in the focus group, except to the researchers or the study counsellors. All the participants are involved in the trial and attend the same clinic as your child.

Any information that your child shares with us will only be seen by members of the research team. This means that whenever we write or talk about anything your child has told us we will never use their real name. All information about your child will be stored securely.

The only exception to this is if your child tells us something that makes us worried about them or another young person's safety, such as physical harm or neglect. If we have to tell someone else, we will talk to your child about it first.

How will the research be used?

The findings of this study will be reported to a wide range of people who are involved in providing treatment, care and support for children and young people living with HIV. The findings will be used to guide the way young people on HIV treatment are supported in the future. It will also be used to help people who are conducting other HIV treatment trials with young people.

What are the benefits and risks of taking part?

Your child will be part of a study that aims to help young people maintain long term adherence to second-line treatment. Some young people may find the opportunity to talk about their HIV treatment to be a really good thing. Some young people though might find it difficult to talk about. The researchers have done research with young people and will take care to ask questions sensitively. It is up to your child what they want to tell us. Also if your child wants, there can be someone available from their clinic to talk to if they feel that they want to at any point during the study, including after the focus group.

Does my child have to take part?

No, your child does not have to take part in the study. It will not affect any of the services that they currently receive. If your child does decide to take part but later changes their mind this is OK too.

Will my child receive anything for taking part?

Yes, your child's travel expenses will be covered for the focus groups. If they are accompanied to the focus groups then the expenses of the person who comes with your child will also be covered. They will also receive 10,000 Ugandan shillings or local equivalent. *[Uganda- delete as appropriate]*

Yes, their travel expenses will be covered for the focus groups. They will receive US$7 per focus group or local equivalent. If your child is accompanied to the focus group then the person who comes with them will be covered too. *[Zimbabwe- delete as appropriate]*

Can I have some more information before I decide?

If you would like to find out more before deciding the staff at your clinic can arrange for you to speak to one of the researchers more about it. We will be very happy to answer any of your questions.

I'm happy for my child to take part. Now what?

Once you have signed the assent or consent form and, if you are under 18 years old your carer has given their consent, the researcher will contact you and your carer to arrange the focus group.

What happens if you have questions?

If you or your child have any questions you can contact: xxxxxxxx
If you cannot access a telephone to call, you can ask xxxxxxxx (a person from your clinic/village) to telephone for you so you can ask your question.

Thank you for reading this! If you do decide to take part your help will be very valuable.

INFORMATION SHEETS FOR YOUTH TRIAL BOARD SUBSTUDY

- Information sheets - young people
- Information sheets - parents/ guardian
- Information sheets – YTB facilitators

YOUTH TRIAL BOARD

PARTICIPANT INFORMATION SHEET FOR YOUNG PEOPLE

(Insert version no and date)

What is a clinical trial?

Clinical trials see how well new medication works or whether medication can be given in different ways. They last for a few years and 100s of patients are involved with scientists watching them closely to look at what happens. The aim of most clinical trials is that the findings ('findings' are all the things the scientists see) may lead to better health care.

Lots of children and young people living with HIV are part of clinical trials but, until now, they have had very few opportunities to say how they think a clinical trial is run, explain its findings to other children and young people and how the findings are shown publicly.

What is a Youth Trial Board (YTB)?

We are running a project in partnership with ODYSSEY - a new clinical trial - to set up four YTBs. A YTB will be a group of up to 8 young people living with HIV who come together 3-4 times a year and learn about clinical trials, have a say on how they are run and help produce information for children, young people and the public about what the trial findings are.

The aim of each YTB is:

1) to give a voice to the children and young people involved in the trial,
2) to improve the experience for those children and young people taking part, so they understand what they are taking part in and what the trial finds out.

This is a pilot project, which means no one has tried to do this before. It means that although there will be certain things a YTB must do, we will be working out how they run as we go along and you will have a say in this. We have different countries involved in this pilot, so we can see how YTBs work in different settings.

Helping design YTBs

If you become a member of a YTB, we will keep asking you about what it's like and how you think it could be made better. We will do this at each meeting and at the end of the whole project. We would also like to have an interview with you to chat about what it is like being a YTB member, what works well and what could be done better. We will use the things all the YTB members tell us and what we learn from running YTBs for two years to make a toolkit. This toolkit will tell others about what we have learnt and how to set up their own YTBs.

Before you decide whether you want to be involved, it is important that you understand what we are doing and what being involved will mean. Please read this information sheet carefully and ask any questions you may have.

Thank you!

What are we asking you to do?

Being a YTB member means you need to come to YTB meetings. These meetings will be with up to 7 other young people living with HIV from your country aged 15-19 years old and up to 3 adult facilitators.

We would like to have an interview with you about what it is like being part of a YTB. This interview will be like a conversation and will last for about an hour. It will be a conversation between you and the researcher. There are no wrong or right answers. You do not have to talk about any topics that you do not want to. You can stop the interview at any time, without having to explain why.

We would like to audio record these interviews, if this is OK with you. The interview will take place somewhere that you feel comfortable

What will happen at YTB meetings?

At a YTB meeting you and the other YTB members will:

- Learn about trials and how they work
- Work out ways to ask other children and young people who are on the trial about their experiences
- Learn about how to be an advocate (an advocate is someone that speaks for other people) and then do this at meetings with people who run clinical trials
- Be creative and involved in designing ways to get messages about the trial to the children and young people who are part of it
- Decide what is important and how you are going to tell this to either the people running the trial or to children on the trial
- Help to design how YTBs can work well in the future

Why are we asking you?

We are asking you to think about whether you would like to be involved because you are aged between 15-19 years of age.

Learning from you

If you decide that you would like to take part in a YTB, it is very important that we learn from you and the other YTB members. We will have activities, games and also time to talk in an individual interview, where you will be asked about the best and the worst things about being a member of a YTB. We want to know your ideas and opinions. We call these 'reflections' because you will be telling us about what you feel and think.

Examples of what we would be writing down include what YTB members think works or doesn't work in a YTB and in a clinical trial and what you would like the people running the trial to understand about what it's like to be a young person living with HIV who is taking part in a clinical trial.

You will be asked at the start of being a YTB member to agree for us to use your reflections, we call this 'giving consent'. If you change your mind, you can take your consent away. We will not be angry with you and want to support you to feel happy and comfortable. You are able to stop taking part in the study at any time. You have control over all of this and it's fully your decision.

What will we do with all the information from the YTB meetings and interviews?

We would like to use this information to help us design the YTB model. What all YTB members say in their reflections and interviews will be written down and what you say will help us build a YTB model which can be used in other clinical trials so that young people feel really listened to and are able to change things. These reflections will also be used as part of the guidance we will write on how to set up YTBs in all countries.

Will what I say be confidential?

None of what we see, hear and write down will be linked back to you. Everything will be anonymised, which means it won't have your name so that someone could link it back to you. Anything that does have information that we can link back to you will just be seen by members of the project team. This means that whenever we write or talk about anything you have told us, we never use your real name. All information about you will be stored securely.

What are the benefits and risks of being involved?

You will be part of a project that aims to develop a way to meaningfully involve young people in how trials are run. The overall goal of YTBs is to improve the experiences of children and young people participating in trials and this project is an early step in achieving this goal. There are no risks to you in being involved.

Do I have to take part?

NO, you do not have to take part. If you prefer to not take part, that is absolutely OK. Saying no will also not affect any of the services that you receive. If you decide to take part but later change your mind this is OK too.

YOUTH TRIAL BOARD

PARENT/CARER INFORMATION SHEET

(Insert version no and date)

What is a clinical trial?

Clinical trials see how well new medication works or whether medication can be given in different ways. They can last for a few years and often 100s of patients are involved with scientists watching them closely to look at what happens. The aim of most clinical trials is that the findings ('findings' is all the things the scientists see) may lead to better health care.

Lots of children and young people living with HIV are part of clinical trials but, until now, they have had very few opportunities to say how they think a clinical trial is run, explain its findings to other children and young people and how the findings are shown publicly.

What is a Youth Trial Board (YTB)?

We are running a project in partnership with ODYSSEY - a new clinical trial - to set up four YTBs. A YTB will be a group of up to 8 young people living with HIV who come together 3-4 times a year and learn about clinical trials, have a say on how they are run and help produce information for children, young people and the public about what the trial findings are.

The aim of each YTB is:

1) to give a voice to the children and young people involved in the trial,
2) to improve the experience for those children and young people taking part, so they understand what they are taking part in and what the trial finds out.

This is a pilot project, which means no one has tried to do this before. It means that although there will be certain things a YTB must do, we will be working out how they run as we go along and you will have a say in this. We have different countries involved in this pilot, so we can see how this works in different settings.

Helping design YTBs

If your child becomes a member of a YTB, we will be asking them about what it's like and how they think it could be made better throughout the project. We will do this at each meeting and at the end of the project. We would also like to have an interview with your child to speak with them about what it is like being a YTB member, what works well and what could be improved. We will use the things all the YTB members tell us and what we learn from running YTBs for two years to make a toolkit. This toolkit will tell others about what we have learnt and how to set up their own YTBs.

Before you decide whether you want your child to be involved, it is important that you understand what we are doing and what being involved will mean. Please read this information sheet carefully and ask any questions you may have.

Thank you!

What are we asking your child to do?

Being a YTB member means your child needs to come to YTB meetings. These meetings will be with up to 7 other young people aged 15-19 years old from your country living with HIV and up to 3 adult facilitators.

We would like to have an interview with your child about what it is like for them being part of a YTB. This interview will be like a conversation and will last for about an hour. It will be a conversation between your child and the researcher. There are no wrong or right answers. Your child does not have to talk about any topics that they do not want to. Your child can stop the interview at any time, without having to explain why.

We would like to audio record these interviews, if this is OK with you and your child. The interview will take place somewhere that your child feels comfortable.

What will happen at YTB meetings?

At a YTB meeting your child and the other YTB members will:

- Learn about trials and how they work
- Work out ways to ask other children and young people who are on the trial about their experiences
- Learn about how to be an advocate – so someone that speaks for other people – and then do this at meetings with people who run clinical trials
- Be creative and design ways to get messages about the trial to the children and young people who are part of it
- Decide what is important and how you are going to tell this to either the people running the trial or to children on the trial
- Help to design how YTBs can work well in the future

Why are we asking your child?

We are asking you to think about whether you would like your child to be involved because they are aged between 15-19 years of age.

Learning from your child

If you and your child decide that you would like them to take part, it is very important that we learn from your child and the other YTB members. We will have activities, games and also time to talk in an individual interview, where they will be asked about the best and the worst things about being a member of a YTB. We want to know their ideas and opinions. We call these 'reflections' because they will be telling us about what they feel and think.

Examples of what we would be writing down include what YTB members think works or doesn't work in a YTB and in a clinical trial and what they would like the people running the trial to understand about what it's like to be a young person living with HIV who is taking part in a clinical trial.

Your child will be asked at the start of being a YTB member to agree for us to use their reflections, we call this 'giving consent'. If they change their mind, they can take their consent away. We will not be angry with them and want to support them to feel happy and comfortable. You and your child have control over all of this and it's important to us that you know that.

What will we do with all the information from the YTB meetings?

We would like to use this information to help us design the YTB model. What all YTB members say in their reflections and interviews will be written down and what your child says will help us build a YTB model where young people feel really listened to and are able to change things. These reflections will also be used as part of the guidance we will write on how to set up YTBs in all countries.

Will what my child says be confidential?

None of what we see, hear and write down will be linked back to your child. Everything will be anonymised, which means it won't have their name so that someone could link it back to them. Anything that does have information that we can link back to them will just be seen by members of the project team. This means that whenever we write or talk about anything they have told us, we never use their real name. All information about them will be stored securely.

What are the benefits and risks of being involved?

Your child will be part of a project that aims to develop a way to meaningfully involve young people in how trials are run. The overall goal of YTBs is to improve the experiences of children and young people participating in trials and this project is an early step in achieving this goal. There are no risks to your child in being involved.

Does my child have to take part?

NO, your child does not have to take part. If you prefer for your child not to take part, that is absolutely OK. Saying no will also not affect any of the services that your child receives. If your child decides to take part but later changes their mind this is OK too.

YOUTH TRIAL BOARD

YTB FACILITATOR INFORMATION SHEET

(Insert version no and date)

What is a Youth Trial Board (YTB)?

We are running a project in partnership with ODYSSEY - a new clinical trial - to set up four YTBs. A YTB will be a group of up to 8 young people living with HIV who come together 3-4 times a year and learn about clinical trials, have a say on how they are run and help produce information for children, young people and the public about what the trial findings are.

The aim of each YTB is:

1) to give a voice to the children and young people involved in the trial,
2) to improve the experience for those children and young people taking part, so they understand what they are taking part in and what the trial finds out.

This is a pilot project, which means no one has tried to do this before. It means that although there will be certain things a YTB must do, we will be working out how they run as we go along and you will have a say in this. We have different countries involved in this YTB pilot project, so we can see how this works in different settings.

Helping design YTBs

We are in the process of conducting the pilot of the YTBs in four countries and are looking to understand the experiences of those who have been taking part and/ or running the YTBs. We will be asking YTB participants and facilitators about their experiences of what it has been like being involved and how they think the design and delivery of the YTB project would be improved. We will do this by conducting individual interviews with participants and facilitators to understand their experiences and learn from their ideas and opinions. We will use the information that we learn to improve the YTB model and then to make a YTB toolkit. This toolkit will tell others about what we have learnt and how to set up their own YTBs.

Before you decide whether you want to be involved, it is important that you understand what we are doing and what being involved will mean. Please read this information sheet carefully and ask any questions you may have.

Thank you!

What are we asking you to do?

We would like to have an interview with you about what it is like being part of a YTB as a facilitator. This interview will be like a conversation and will last for about an hour. It will be a conversation between you and the researcher. There are no wrong or right answers. You do not have to talk about any topics that you do not want to. You can stop the interview at any time, without having to explain why.

We would like to audio record these interviews, if this is OK with you. The interview will take place somewhere that you feel comfortable.

Why are we asking you?

We are asking you to think about whether you would like to be involved because you have taken part in the YTB pilot project by being a facilitator. Understanding more about your experience of doing so will be valuable to us in designing the YTB toolkit.

Learning from you

If you decide that you would like them to take part, we would like to talk to you in an individual interview about your experiences of facilitating a YTB, what works well and what could be improved, as well as the training needs of facilitators.

What will we do with all the information?

We would like to use this information from you, the other facilitators and participants to help us design the YTB model and will be used as part of the guidance we will write on how to set up YTBs in all countries.

Will what I say be confidential?

None of what you tell us in your interview will be linked back to you. This means that whenever we write or talk about anything you have told us, we will never use your real name. All information about you will be stored securely.

What are the benefits and risks of being involved?

You are part of project that aims to develop a way to meaningfully involve young people in how trials are run. The overall goal of YTBs is to improve the experiences of children and young people participating in trials and this project is an early step in achieving this goal. We would like to understand how we can learn from the experiences of those involved in the pilot YTBs and how we can improve the YTB model in the future. There are no risks to you in being involved.

Do I have to take part?

NO, you do not have to take part. If you prefer not to take part, that is absolutely OK.

20 APPENDIX II TEMPLATE CONSENT AND ASSENT FORMS

PARENT/CARER – MAIN STUDY CONSENT TO SCREENING

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for the ODYSSEY study.	
I agree to my child being assessed to see whether he/she is eligible to take part in this study.	
I understand this will involve my child being seen by the doctor who will ask questions about my child's health, and my child having some blood taken for testing.	
I agree that the results of these tests and an additional blood sample can be kept by the ODYSSEY team for further tests if my child starts the study. I understand that these results and samples will not be identified by either my or my child's name.	
I understand that if my child cannot participate in the study, the stored blood sample will be discarded and not used for further tests.	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

I have provided the ODYSSEY study information to the potential participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees for his/her child to be screened for the ODYSSEY study.

Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARENT/CARER – MAIN STUDY CONSENT TO RANDOMISATION

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for the ODYSSEY study and I understand what will be required if my child participates in the study.	
The study has been explained to me and all my questions have been answered.	
I understand that my child's participation is voluntary and that I am free to withdraw him or her at any time, without giving any reason, without my medical care or legal rights or my child's medical care or legal rights being affected.	
I agree to inform the study doctor if my child starts any other new medicine during the period of the study.	
I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.	
I agree to allow blood samples to be taken from my child and for my child's samples to be stored for later testing. I understand that these results and samples will not be identified by either my or my child's name and that I may not be given the results of tests performed on stored samples.	
I agree to routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth).	
I agree to UCL collecting information about my child from my child's clinic for this research study. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree for my child to participate in the ODYSSEY study	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

Please turn over the page

I have provided the ODYSSEY study information to the participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees for his/her child to be enrolled into the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

I would/would not *(please circle)* like my child's GP to be notified about participation in this study.

Signature of Parent/Guardian:_____Date:_____

Name of GP:_____

Contact address of GP**:** _____

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT –MAIN STUDY ASSENT TO SCREENING

(To be printed on local-headed paper)

Study number: Anonymous code:

ODYSSEY – A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about this study?	YES ☐ NO ☐
2. Do you understand that your doctor will check how you are and do some tests on your blood to see if you can join the study?	YES ☐ NO ☐
3. Do you agree that **if you start the study** your blood samples (without your name on) can be used during the study and stored for studies which will help us understand more about the virus? (If you don't start the study, we won't use your blood samples)	YES ☐ NO ☐
4. Are you happy to be assessed to see whether you can take part in this study?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, please sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY study information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to be screened for the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARTICIPANT- MAIN STUDY ASSENT TO RANDOMISATION

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about this study?	YES ☐ NO ☐
2. Has somebody explained the study to you?	YES ☐ NO ☐
3. Do you understand what the study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand how the study might help you?	YES ☐ NO ☐
7. Do you understand the risks of taking part?	YES ☐ NO ☐
8. Do you understand it's OK to stop taking part in the study at any time?	YES ☐ NO ☐
9. Do you understand that you cannot choose the group you will be in?	YES ☐ NO ☐
10. Are you happy to take part?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

Please turn over the page

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to be enrolled into the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARTICIPANT – MAIN STUDY CONSENT TO CONTINUED PARTICIPATION FOR YOUNG PEOPLE WHO REACH THE AGE OF CONSENT WHILST IN THE TRIAL

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for the ODYSSEY study and I understand what will be required if I continue to participate in the study.	
The study has been explained to me and my questions have been answered.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.	
I agree to inform the study doctor if I start any other new medicines during the period of the study.	
I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.	
I agree to allow blood samples to be taken and stored for later testing. I understand that these results and samples will not be identified by my name and that I may not be given the results of tests performed on stored samples.	
I agree to routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth).	
I agree to UCL collecting information about me from my clinic for this research study. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree to take part in the ODYSSEY study	

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

Please turn over the page

I have provided the ODYSSEY study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to continue to participate in the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARENT/CARER – RE-CONSENT TO THE ODYSSEY TRIAL

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy.

	Please initial (or mark) box if you agree:
I have read/been read the information sheet (version ____, dated _____) for the ODYSSEY study and I understand what will be required if my child participates in the study.	
The study has been explained to me and all my questions have been answered.	
I understand that my child's participation is voluntary and that I am free to withdraw him or her at any time, without giving any reason, without my medical care or legal rights or my child's medical care or legal rights being affected.	
I agree to inform the study doctor if my child starts any other new medicine during the period of the study.	
I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.	
I agree to allow blood samples to be taken from my child and for my child's samples to be stored for later testing. I understand that these results and samples will not be identified by either my or my child's name and that I may not be given the results of tests performed on stored samples.	
I agree to routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth).	
I agree to UCL collecting information about my child from my child's clinic for this research study. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree for my child to continue to participate in the ODYSSEY study	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

Please turn over the page

I have provided the ODYSSEY study information to the participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees for his/her child to be enrolled into the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

I would/would not *(please circle)* like my child's GP to be notified about participation in this study.

Signature of Parent/Guardian:_____Date:_____

Name of GP:_____

Contact address of GP**:** _____

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT – RE-CONSENT TO THE ODYSSEY TRIAL

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for the ODYSSEY study and I understand what will be required if I participate in the study.	
The study has been explained to me and all my questions have been answered.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
I agree to inform the study doctor if I start any other new medicine during the period of the study.	
I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.	
I agree to allow blood samples to be taken and stored for later testing. I understand that these results and samples will not be identified by my name and that I may not be given the results of tests performed on stored samples.	
I agree to routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth).	
I agree to UCL collecting information about me from my clinic for this research study. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree to continue to participate in the ODYSSEY study	

Participant signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

Please turn over the page

I have provided the ODYSSEY study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to continue participation in the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT- MAIN STUDY RE-ASSENT TO THE ODYSSEY TRIAL

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about this study?	YES ☐ NO ☐
2. Has somebody explained the study to you?	YES ☐ NO ☐
3. Do you understand what the study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand how the study might help you?	YES ☐ NO ☐
7. Do you understand the risks of taking part?	YES ☐ NO ☐
8. Do you understand it's OK to stop taking part in the study at any time?	YES ☐ NO ☐
9. Do you understand that you cannot choose the group you will be in?	YES ☐ NO ☐
10. Are you happy to continue to take part?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

Please turn over the page

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to be enrolled into the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARENT/CARER – CONSENT TO EXTENDED FOLLOW-UP

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for extended follow-up within the ODYSSEY study and I understand what will be required if my child participates.	
The reason for extended follow-up has been explained to me and all my questions have been answered.	
I understand that my child's participation is voluntary and that I am free to withdraw him or her at any time, without giving any reason, without my medical care or legal rights or my child's medical care or legal rights being affected.	
I agree to inform the study doctor if my child starts any other new medicine during the extended follow-up period.	
I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.	
I agree to UCL collecting information on routine blood results and clinical information on my child from my child's clinic for the extended follow-up period. This data may be used by UCL and other authorised research collaborators to conduct the trial	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree for my child to participate in the extended follow-up period for ODYSSEY study	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

Please turn over the page

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY extended follow-up information to the participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits and willingly agrees for his/her child to participate in the extended follow-up period for the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARTICIPANT – CONSENT TO EXTENDED FOLLOW-UP

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for extended follow-up within the ODYSSEY study and I understand what will be required if I participate.	
The reason for extended follow-up has been explained to me and all my questions have been answered.	
I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
I agree to inform the study doctor if I start any other new medicine during the extended follow-up period.	
I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.	
I agree to UCL collecting information on my routine blood results and clinical information from my clinic for the extended follow-up period. This data may be used by UCL and other authorised research collaborators to conduct the trial.	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree to participate in the extended follow-up period for ODYSSEY study	

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

Please turn over the page

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY extended follow-up information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits and willingly agrees to participate in the extended follow-up period for the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARTICIPANT – ASSENT TO EXTENDED FOLLOW-UP

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY**: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.**

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about extended follow-up for this study?	YES ☐ NO ☐
2. Has somebody explained extended follow-up for this study to you?	YES ☐ NO ☐
3. Do you understand what follow-up for the study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand how extended follow-up might help you?	YES ☐ NO ☐
7. Do you understand the risks of taking part?	YES ☐ NO ☐
8. Do you understand that it's OK to stop taking part in extended follow-up at any time?	YES ☐ NO ☐
9. Are you happy to take part?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

Please turn over the page

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to be enrolled into the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARENT/CARER – CONSENT TO STORAGE OF BLOOD SAMPLES FOR FUTURE TESTING

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please initial (or mark) box if you agree:

I agree to allow blood samples to be taken from my child and for my child's samples to be stored for later testing. I understand that these results and samples will not be identified by either my or my child's name and that I may not be given the results of tests performed on stored samples.	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

I have provided the ODYSSEY study information to the participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, risks and benefits of blood sample storage and willingly agrees for his/her child to have their blood samples stored for future testing.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT - CONSENT TO STORAGE OF BLOOD SAMPLES FOR FUTURE TESTING

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please initial (or mark) box if you agree:

I agree to allow blood samples to be taken and stored for later testing. I understand that these results and samples will not be identified by my name and that I may not be given the results of tests performed on stored samples.	

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

I have provided the ODYSSEY study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, risks and benefits of blood sample storage and willingly agrees to have their blood samples stored for future testing.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT – ASSENT TO STORAGE OF BLOOD SAMPLES FOR FUTURE TESTING

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Do you understand that we would like to keep some of your blood samples to test in the future?	YES ☐ NO ☐
2. Do you understand that we will not put your name on the samples so that other people will not know that they belong to you?	YES ☐ NO ☐
3. Do you understand that you may not be given the results from these tests?	YES ☐ NO ☐
4. Are you happy for us to keep your blood samples to test in the future?	YES ☐ NO ☐

If any answers are **'no'**, **don't sign your name**.

If you are happy for us to store your blood samples to test in the future, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of blood sample storage and willingly agrees to have their blood samples stored for future testing.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: **one signed original to be kept in ODYSSEY trial file by the researcher**
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARENT/CARER – MAIN STUDY & WB PK 1 CONSENT TO SCREENING (3 TO <14KG)

(To be printed on local-headed paper)
(Insert version no and date)

Study number:
Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) about the ODYSSEY study and the PK (blood levels) study.	
I agree to my child being assessed to see whether he/she is eligible to take part in this study.	
I understand this will involve my child being seen by the doctor who will ask questions about my child's health, and my child having some blood taken for testing.	
I agree that the results of these tests and an additional blood sample can be kept by the ODYSSEY team for further tests if my child starts the study. I understand that these results and samples will not be identified by either my or my child's name.	
I understand that if my child cannot participate in the study, the stored blood sample will be discarded and not used for further tests.	
I agree to my child taking part in the PK (blood levels) study if they enter ODYSSEY and are allocated dolutegravir.	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

I have provided the ODYSSEY study information to the potential participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees for his/her child to be screened for the ODYSSEY study.

Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in odyssey trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARENT/CARER – MAIN STUDY & WB PK 1 CONSENT TO RANDOMISATION (3 TO <14KG)

(To be printed on local-headed paper)
(Insert version no and date)

Study number:
Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line antiretroviral therapy.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) about the ODYSSEY study and the PK (blood levels) study and I understand what will be required if my child participates in the study.	
The study has been explained to me and all my questions have been answered.	
I understand that my child's participation is voluntary and that I am free to withdraw him or her at any time, without giving any reason, without my medical care or legal rights or my child's medical care or legal rights being affected.	
I agree to inform the study doctor if my child starts any other new medicine during the period of the study.	
I understand that clinical information may be reviewed by properly authorised individuals as part of the study and that such information will be treated as strictly confidential.	
I agree to allow blood samples to be taken from my child and for my child's samples to be stored for later testing. I understand that these results and samples will not be identified by either my or my child's name and that I may not be given the results of tests performed on stored samples.	
I agree to routine blood results and clinical information being included anonymously in continued follow-up after the study has ended (identified only by study number and date of birth).	
I agree to UCL collecting information about me from my clinic for this research study. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree for my child to participate in the ODYSSEY study.	
I agree to my child taking part in the PK (blood levels) study if they are allocated dolutegravir.	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

I have provided the ODYSSEY study information to the participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees for his/her child to be enrolled into the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

I would/would not *(please circle)* like my child's GP to be notified about participation in this study.
[Country specific, delete if not applicable]

Signature of Parent/Guardian:_____Date:_____

Name of GP:_____

Contact address of GP**:** _____

IMPORTANT: one signed original to be kept in odyssey trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT – MAIN STUDY & WB PK 1 ASSENT TO SCREENING (3 TO <14KG)

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY – A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about this study and the PK (blood levels) study?	YES ☐ NO ☐
2. Do you understand that your doctor will check how you are and do some tests on your blood to see if you can join the study?	YES ☐ NO ☐
3. Do you agree that **if you start the study** your blood samples (without your name on) can be used during the study and stored for studies which will help us understand more about the virus? (If you don't start the study, we won't use your blood samples)	YES ☐ NO ☐
4. Are you happy to be assessed to see whether you can take part in this study?	YES ☐ NO ☐
5. Do you agree to taking part in the PK (blood levels) study?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY study information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to be screened for the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in odyssey trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARTICIPANT- MAIN STUDY & WB PK 1 ASSENT TO RANDOMISATION (3 TO <14KG)

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about this study and the PK (blood levels) study?	YES ☐ NO ☐
2. Has somebody explained the study to you?	YES ☐ NO ☐
3. Do you understand what the study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand how the study might help you?	YES ☐ NO ☐
7. Do you understand the risks of taking part?	YES ☐ NO ☐
8. Do you understand it's OK to stop taking part in the study at any time?	YES ☐ NO ☐
9. Do you understand that you cannot choose the group you will be in?	YES ☐ NO ☐
10. Are you happy to take part?	YES ☐ NO ☐
11. Do you agree to taking part in the PK (blood levels) study?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to be enrolled into the ODYSSEY study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARENT/CARER - CONSENT TO PHARMACOKINETIC (WB PK 1) STUDY (3 TO <25KG)

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for the ODYSSEY weight band PK 1 (blood levels) study and I understand what will be required if my child participates in the study.	
The weight band PK 1 study has been explained to me and my questions have been answered.	
I understand that my child's participation in this study is voluntary and that I am free to withdraw him or her at any time, without giving any reason, without my medical care or legal rights or my child's medical care or legal rights being affected.	
I agree for small quantities of blood to be stored with anonymised labelling so that further work can be done to help understand more about HIV treatment. *[Country specific, delete if not applicable]*	
I agree to UCL collecting information about me from my clinic for this research study. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree for my child to participate in the ODYSSEY weight band PK 1 (blood levels) study if they are eligible.	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

I have provided the ODYSSEY WB PK 1 study information to the participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees for his/her child to participate in the ODYSSEY WB PK 1 study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: **one signed original to be kept in ODYSSEY trial file by the researcher**
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT - ASSENT TO PHARMACOKINETIC (WB PK 1) SUBSTUDY (3 TO <25KG)

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about the blood levels study?	YES ☐ NO ☐
2. Has somebody explained this study to you?	YES ☐ NO ☐
3. Do you understand what this study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand how this study might help you?	YES ☐ NO ☐
7. Do you understand the disadvantages of taking part?	YES ☐ NO ☐
8. Do you understand it's OK to stop taking part in the study at any time?	YES ☐ NO ☐
9. Do you understand that if you take part in the blood levels study you will need to come to the clinic for a whole day (over a 24 hour period) to check the level of medicine in your blood and maybe sleep there?	YES ☐ NO ☐
10. Are you happy to take part?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY WB PK 1 study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the ODYSSEY WB PK 1 study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARENT/CARER - CONSENT TO PHARMACOKINETIC (WB PK 2) STUDY (≥25KG)

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for the ODYSSEY weight band PK 2 (blood level)s study and I understand what will be required if my child participates in the study.	
The weight band PK study has been explained to me and my questions have been answered.	
I understand that my child's participation in this study is voluntary and that I am free to withdraw him or her at any time, without giving any reason, without my medical care or legal rights or my child's medical care or legal rights being affected.	
I agree for small quantities of blood to be stored with anonymised labelling so that further work can be done to help understand more about HIV treatment. *[Country specific, delete if not applicable]*	
I agree to study data including my child's study number and age being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree for my child to participate in the ODYSSEY weight band PK 2 (blood levels) study if they are eligible.	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

I have provided the ODYSSEY WB PK 2 study information to the participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees for his/her child to participate in the ODYSSEY WB PK 2 study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT - ASSENT TO PHARMACOKINETIC (WB PK 2) STUDY (≥25KG)

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about the blood levels study?	YES ☐ NO ☐
2. Has somebody explained this study to you?	YES ☐ NO ☐
3. Do you understand what this study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand how this study might help you?	YES ☐ NO ☐
7. Do you understand the disadvantages of taking part?	YES ☐ NO ☐
8. Do you understand it's OK to stop taking part in the study at any time?	YES ☐ NO ☐
9. Do you understand that if you do take part in the PK (blood levels) study you will need to come to the clinic for a whole day to check the level of medicine in your blood and maybe sleep there?	YES ☐ NO ☐
10. Do you understand that if you do take part in the PK (blood levels) study your dose of medicine will be changed after the first blood sampling day?	YES ☐ NO ☐
11. Do you understand that if you do take part in the PK (blood levels) study you will need to come back to the clinic for a second full day to check the level of medicine in your blood and maybe sleep there?	YES ☐ NO ☐
12. Are you happy to take part?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY WB PK 2 study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the ODYSSEY WB PK 2 study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

PARENT/CARER - CONSENT TO PHARMACOKINETIC (TB PK) STUDY

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please initial (or mark) box if you agree:

I have read/been read the information sheet (version ____, dated _____) for the ODYSSEY TB PK (blood levels) study and I understand what will be required if my child participates in the study.	
The TB PK study has been explained to me and my questions have been answered.	
I understand that my child's participation in this study is voluntary and that I am free to withdraw him or her at any time, without giving any reason, without my medical care or legal rights or my child's medical care or legal rights being affected.	
I agree for small quantities of blood to be stored with anonymised labelling so that further work can be done to help understand more about HIV and TB effective treatment. *[Country specific, delete if not applicable]*	
I agree to UCL collecting information about me from my clinic for this research study. This data may be used by UCL and other authorised research collaborators to conduct the trial and associated sub-studies.	
I agree to anonymised study data being transferred to ViiV Healthcare, and to drug agencies in other countries.	
I agree for my child to participate in the ODYSSEY TB PK (blood levels) study	

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint above)	Print name	Date

I have provided the ODYSSEY TB PK study information to the participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees for his/her child to participate in the ODYSSEY TB PK study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: **one signed original to be kept in ODYSSEY trial file by the researcher**
one signed copy to be given to the parent/carer
one signed copy to be kept in the clinic file

PARTICIPANT - ASSENT TO PHARMACOKINETIC (TB PK) STUDY

(To be printed on local-headed paper)
(Insert version no and date)

Study number: Anonymous code:

ODYSSEY: A randomised trial of dolutegravir (DTG)-based antiretroviral therapy vs. standard of care (SOC) in children with HIV infection starting first-line or switching to second-line ART.

Please tick yes or no to the questions below

1. Have you read (or had read to you) the information about the blood levels study?	YES ☐ NO ☐
2. Has somebody explained this study to you?	YES ☐ NO ☐
3. Do you understand what this study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand how this study might help you?	YES ☐ NO ☐
7. Do you understand the disadvantages of taking part?	YES ☐ NO ☐
8. Do you understand it's OK to stop taking part in the study at any time?	YES ☐ NO ☐
9. Do you understand that you will need to come to the clinic for a whole day to check the level of medicine in your blood?	YES ☐ NO ☐
10. Do you understand that you will need to come back to the clinic for a second full day to check the level of drugs in your blood and maybe sleep there?	YES ☐ NO ☐
11. Are you happy to take part?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the ODYSSEY TB PK study information to the participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the ODYSSEY TB PK study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

CONSENT AND ASSENT FORMS FOR QUALITATIVE SUBSTUDY

Consent/ assent forms for in-depth interviews - IDIs (10-18 year olds)

- Assent form- IDIs- 10-17 years olds
- Consent form- IDIs- 18 year olds
- Consent form- IDIs- parents/ carers
- Consent form- IDIs- caregivers

Consent/ assent forms for in-depth interviews (DTG) - IDIs (10-19 year olds)

- Assent form- IDIs- 10-17 years olds (DTG)
- Consent form- IDIs- 18-19 year olds (DTG)
- Consent form- IDIs- parents/ carers (DTG)

Consent / assent forms for focus group discussions - FGDs (10-19 year olds)

- Assent form- FGDs- 10-17 years olds
- Consent form- FGDs- 18-19 year olds
- Consent form- FGDs- parents/ carers

ODYSSEY QUALITATIVE STUDY:

ASSENT FORM FOR IN-DEPTH INTERVIEWS 10-17 YEAR OLDS

(To be printed on local-headed paper)
(Insert version no and date)
Please tick yes or no to answer the questions below.

1. Have you read (or had read to you) the information about this study?	YES ☐ NO ☐
2. Has somebody explained the study to you?	YES ☐ NO ☐
3. Do you understand what the study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand it's OK to stop taking part at any time?	YES ☐ NO ☐
7. Do you understand that you don't have to answer any questions that you do not want to?	YES ☐ NO ☐
8. Is it OK if we audio record our discussions?	YES ☐ NO ☐
9. Do you understand that we will speak with you on two separate occasions?	YES ☐ NO ☐
10. Are you happy to take part?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: **one signed original to be kept in ODYSSEY trial file by the researcher**
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

ODYSSEY QUALITATIVE STUDY:

CONSENT FORM FOR IN-DEPTH INTERVIEWS YOUNG PEOPLE (18 YEARS OLD)

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to take part in this study.

I have read and understood the information sheet on the study, version X	YES ☐ NO ☐
I have been given the opportunity to ask questions and I am satisfied with the answers that you have given me.	YES ☐ NO ☐
I agree to my contact details being given to the study team so that they can contact me to arrange the interview and about other study arrangement matters.	YES ☐ NO ☐
I understand that the researcher will interview me on two separate occasions. This will involve them talking to them for about an hour each time about my experience of being on second-line HIV treatment.	YES ☐ NO ☐
I agree to this interview being audio-recorded.	YES ☐ NO ☐
I know that I do not have to talk about things that I do not want to talk about. I can stop talking to the researchers at any time and without giving a reason for this.	YES ☐ NO ☐
I understand that everything that I talk to the researchers about is confidential. However if the researchers are told that myself or another child is at serious risk of harm, they may have to pass this information on to someone else.	YES ☐ NO ☐
I agree that anonymised direct quotes from the interview may be used in the public reporting of this study.	YES ☐ NO ☐

My questions have been answered by ……

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

ODYSSEY QUALITATIVE STUDY:

CONSENT FORM FOR IN-DEPTH INTERVIEWS PARENT/CARERS

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to my child taking part in this study.

I have read and understood the information sheet on the study, version X	YES ☐ NO ☐
I have been given the opportunity to ask questions and I am satisfied with the answers that you have given me.	YES ☐ NO ☐
I agree to my contact details being given to the study team so that they can contact me to arrange the interview and about other study arrangement matters.	YES ☐ NO ☐
I understand that the researcher will interview my child on two separate occasions. This will involve them talking with my child for about an hour about my child's experience of being on second-line treatment.	YES ☐ NO ☐
I agree to this interview being audio-recorded.	YES ☐ NO ☐
I know that my child does not have to talk about things that he/she does not want to talk about. My child can stop talking to the researchers at any time and without giving a reason for this.	YES ☐ NO ☐
I understand that everything that my child talks to the researchers about is confidential. However if the researchers are told that a child is at serious risk of harm, they may have to pass this information on to someone else.	YES ☐ NO ☐
I agree that anonymised direct quotes from the interview may be used in the public reporting of this study.	YES ☐ NO ☐

My questions have been answered by ……

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

ODYSSEY QUALITATIVE STUDY:

CONSENT FORM FOR IN-DEPTH INTERVIEWS WITH CAREGIVERS

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to taking part in this study.

I have read and understood the information sheet on the study, version X	YES ☐ NO ☐
I have been given the opportunity to ask questions and I am satisfied with the answers that you have given me.	YES ☐ NO ☐
I agree to my contact details being given to the study team so that they can contact me to arrange the interview and about other study arrangement matters.	YES ☐ NO ☐
I understand that the researcher will conduct an interview with me. This will involve us talking for about an hour about what it is like caring for my child and my child's experience of growing up with HIV.	YES ☐ NO ☐
I agree to this interview being audio-recorded.	YES ☐ NO ☐
I know that I do not have to talk about things that I not want to talk about. I can stop talking to the researchers at any time and without giving a reason for this.	YES ☐ NO ☐
I understand that everything that I talk to the researchers about is confidential. However if I tell the researchers that a child is at serious risk of harm, they may have to pass this information on to someone else.	YES ☐ NO ☐
I agree that anonymised direct quotes from the interview may be used in the public reporting of this study.	YES ☐ NO ☐

My questions have been answered by ……

Caregiver's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

ODYSSEY QUALITATIVE STUDY:

ASSENT FORM FOR IN-DEPTH INTERVIEWS 10-17 YEAR OLDS (DTG)

(To be printed on local-headed paper)
(Insert version no and date)
Please tick yes or no to answer the questions below.

1. Have you read (or had read to you) the information about this study?	YES ☐ NO ☐
2. Has somebody explained the study to you?	YES ☐ NO ☐
3. Do you understand what the study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand it's OK to stop taking part at any time?	YES ☐ NO ☐
7. Do you understand that you don't have to answer any questions that you do not want to?	YES ☐ NO ☐
8. Is it OK if we audio record our discussions?	YES ☐ NO ☐
9. Are you happy to take part?	YES ☐ NO ☐

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

ODYSSEY QUALITATIVE STUDY:

CONSENT FORM FOR IN-DEPTH INTERVIEWS YOUNG PEOPLE (18-19 YEARS OLD) (DTG)

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to take part in this study.

I have read and understood the information sheet on the study, version X	YES ☐ NO ☐
I have been given the opportunity to ask questions and I am satisfied with the answers that you have given me.	YES ☐ NO ☐
I agree to my contact details being given to the study team so that they can contact me to arrange the interview and about other study arrangement matters.	YES ☐ NO ☐
I understand that the researcher will interview me that will last for about an hour about my experience of growing up with HIV and being on HIV treatment.	YES ☐ NO ☐
I agree to this interview being audio-recorded.	YES ☐ NO ☐
I know that I do not have to talk about things that I do not want to talk about. I can stop talking to the researchers at any time and without giving a reason for this.	YES ☐ NO ☐
I understand that everything that I talk to the researchers about is confidential. However if the researchers are told that myself or another child is at serious risk of harm, they may have to pass this information on to someone else.	YES ☐ NO ☐
I agree that anonymised direct quotes from the interview may be used in the public reporting of this study.	YES ☐ NO ☐

My questions have been answered by ……

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

ODYSSEY QUALITATIVE STUDY:

CONSENT FORM FOR IN-DEPTH INTERVIEWS PARENT/CARERS (DTG)

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to my child taking part in this study.

I have read and understood the information sheet on the study, version X	YES ☐ NO ☐
I have been given the opportunity to ask questions and I am satisfied with the answers that you have given me.	YES ☐ NO ☐
I agree to my contact details being given to the study team so that they can contact me to arrange the interview and about other study arrangement matters.	YES ☐ NO ☐
I understand that the researcher will interview my child for about an hour about my child's experience of growing up with HIV and being on HIV treatment.	YES ☐ NO ☐
I agree to this interview being audio-recorded.	YES ☐ NO ☐
I know that my child does not have to talk about things that he/she does not want to talk about. My child can stop talking to the researchers at any time and without giving a reason for this.	YES ☐ NO ☐
I understand that everything that my child talks to the researchers about is confidential. However if the researchers are told that a child is at serious risk of harm, they may have to pass this information on to someone else.	YES ☐ NO ☐
I agree that anonymised direct quotes from the interview may be used in the public reporting of this study.	YES ☐ NO ☐

My questions have been answered by ……

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

ODYSSEY QUALITATIVE STUDY:

ASSENT FORM FOR FOCUS GROUP DISCUSSIONS (10-17 YEAR OLDS)

(To be printed on local-headed paper)
(Insert version no and date)
Please tick yes or no to answer the questions below.

1. Have you read (or had read to you) the information about this study?	YES ☐ NO ☐
2. Has somebody explained the study to you?	YES ☐ NO ☐
3. Do you understand what the study is about?	YES ☐ NO ☐
4. Have you asked all the questions you want?	YES ☐ NO ☐
5. Have your questions been answered in a way you understand?	YES ☐ NO ☐
6. Do you understand it's OK to stop taking part at any time?	YES ☐ NO ☐
7. Do you understand that you don't have to answer any questions that you do not want to?	YES ☐ NO ☐
8. Do you understand that there will be two focus groups that we would like you to take part in?	YES ☐ NO ☐
9. Do you understand that you should not tell anyone what you hear about other people in the focus groups, but that you can talk about it with the researchers and clinic counsellors?	YES ☐ NO ☐
10. Is it OK if we audio record our discussions?	YES ☐ NO ☐
11. Are you happy to take part?	YES ☐ NO ☐

If you **do** want to take part, you can sign your name below.

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

Thank you for your help!

ODYSSEY QUALITATIVE STUDY:

CONSENT FORM FOR FOCUS GROUP DISCUSSIONS (YOUNG PEOPLE OVER 18-19 YEARS)

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to taking part in this study.

I have read and understood the information sheet on the ODYSSEY qualitative study, version……..	YES ☐ NO ☐
I have been given the opportunity to ask questions and I am satisfied with the answers that you have given me.	YES ☐ NO ☐
I agree to my contact details being given to the qualitative study team and understand that they will contact me.	YES ☐ NO ☐
I understand that I am being asked to participate in two focus groups. For each focus group this will involve the researcher talking with me and up to seven other young people for about an hour about their experiences of being on second-line HIV treatment.	YES ☐ NO ☐
I agree to the focus groups being audio-recorded.	YES ☐ NO ☐
I know that I do not have to talk about things that I do not want to talk about. I understand that I can stop talking to the researchers at any time and without giving a reason for this.	YES ☐ NO ☐
I understand that everything that I to the group about is confidential. I understand that I and the other participants will agree to not talk about what anyone else says in the focus groups, except for with the researchers and counsellors.	YES ☐ NO ☐
I agree that anonymised direct quotes from the focus groups may be used.	YES ☐ NO ☐

My questions have been answered by ……

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.

Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

ODYSSEY QUALITATIVE STUDY:

CONSENT FORM FOR FOCUS GROUP DISCUSSIONS (PARENT/CARERS)

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to my child taking part in this study.

I have read and understood the information sheet on the ODYSSEY qualitative study, version……..	YES ☐ NO ☐
I have been given the opportunity to ask questions and I am satisfied with the answers that you have given me.	YES ☐ NO ☐
I agree to my contact details being given to the qualitative study team and understand that they will contact me should my child be selected to take part in the study.	YES ☐ NO ☐
I understand that my child will participate in two focus groups. For each focus group this will involve them talking with my child and up to seven other young people for about an hour about their experiences of being on second-line HIV treatment.	YES ☐ NO ☐
I agree to the focus groups being audio-recorded.	YES ☐ NO ☐
I know that my child does not have to talk about things that he/she does not want to talk about. My child can stop talking to the researchers at any time and without giving a reason for this.	YES ☐ NO ☐
I understand that everything that my child talks to the researchers about is confidential and that my child and other participants will agree to not talking about what anyone else says in the focus group, except for with the researchers and counsellors.	YES ☐ NO ☐
I understand that if the researchers are told that a child is at serious risk of harm, they may have to pass this information on to someone else.	YES ☐ NO ☐
I agree that anonymised direct quotes from the focus group may be used.	YES ☐ NO ☐

My questions have been answered by ……

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Qualitative study information to the potential participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Qualitative study.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

CONSENT FORMS AND ASSENT FORMS FOR YOUTH TRIAL BOARD PROJECT

Consent/ assent forms for in-depth interviews - IDIs (10-18 year olds)

- Assent form - 10-17 years olds
- Consent form - 18 year olds
- Consent form - parents/ carers
- Consent form – YTB facilitators

YOUTH TRIAL BOARD PROJECT

ASSENT FORM FOR YOUTH TRIAL BOARD PROJECT FOR YOUNG PEOPLE

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to taking part in this project.

I have read and understood the information sheet on the Youth Trial Board project, version……..	YES ☐ NO ☐
I have been given the chance to ask questions and I am happy with the answers that you have given me.	YES ☐ NO ☐
I understand that being a Youth Trial Board member means that what we say and discuss in our meetings over the course of the project may be observed and notes taken.	YES ☐ NO ☐
I understand that I am being asked to take part in an individual interview about my experiences participating in the Youth Trials Board project.	YES ☐ NO ☐
I understand that everything that is said in the meetings is confidential and that the notes will be anonymised.	YES ☐ NO ☐
I understand that at any time I can withdraw my consent for the observations about what I say in the meetings and the interview to be used.	YES ☐ NO ☐
I agree that anonymised direct quotes from the meetings and interview can be used.	YES ☐ NO ☐

My questions have been answered by ……

If any answers are **'no'** or you don't want to take part, **don't sign your name**.
If you **do** want to take part, you can sign your name below.

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the project to you needs to sign too:

I have provided the Youth Trial Board project information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Youth Trial Board project.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

YOUTH TRIAL BOARD PROJECT

CONSENT FORM FOR YOUTH TRIAL BOARD PROJECT FOR YOUNG ADULT PARTICIPANTS

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to taking part in this project.

I have read and understood the information sheet on the Youth Trial Board project, version……..	YES ☐ NO ☐
I have been given the chance to ask questions and I am happy with the answers that you have given me.	YES ☐ NO ☐
I understand that being a Youth Trial Board member means that what we say and discuss in our meetings over the course of the project may be observed and notes taken.	YES ☐ NO ☐
I understand that I am taking part in an individual interview about my experiences participating in the Youth Trials Board project.	YES ☐ NO ☐
I understand that everything that is said in the meetings and interview is confidential and that the notes will be anonymised.	YES ☐ NO ☐
I understand that at any time I can withdraw my consent for the observations about what I say in the meetings and the interview to be used.	YES ☐ NO ☐
I agree that anonymised direct quotes from the meetings and interview can be used.	YES ☐ NO ☐

My questions have been answered by ……

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Youth Trial Board project information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Youth Trial Board project.

Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

YOUTH TRIAL BOARD PROJECT

CONSENT FORM FOR YOUTH TRIAL BOARD PROJECT FOR PARENTS/ GUARDIANS

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to taking part in this project.

I have read and understood the information sheet on the Youth Trial Board project, version……..	YES ☐ NO ☐
I have been given the chance to ask questions and I am happy with the answers that you have given me.	YES ☐ NO ☐
I understand that my child being a Youth Trial Board member means that what they say and discuss in the meetings over the course of the project may be observed and notes taken.	YES ☐ NO ☐
I understand that my child will take part in an individual interview about their experiences participating in the Youth Trials Board project.	YES ☐ NO ☐
I understand that everything that is said in the meetings and interview is confidential and that the notes will be anonymised.	YES ☐ NO ☐
I agree that anonymised direct quotes from the meetings and interview can be used.	YES ☐ NO ☐

My questions have been answered by ……

Parent/carer's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Youth Trial Board project information to the potential participant's parent/legal guardian in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in the Youth Trial Board project.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

YOUTH TRIAL BOARD PROJECT

CONSENT FORM FOR YOUTH TRIAL BOARD PROJECT FOR FACILITATORS

(To be printed on local-headed paper)
(Insert version no and date)

I _____ agree to taking part in this project.

I have read and understood the information sheet on the Youth Trial Board project, version……..	YES ☐ NO ☐
I have been given the chance to ask questions and I am happy with the answers that you have given me.	YES ☐ NO ☐
I understand that I am taking part in an individual interview about my experiences participating in the Youth Trials Board project.	YES ☐ NO ☐
I understand that everything that is said in the interview is confidential and that the notes will be anonymised.	YES ☐ NO ☐
I understand that at any time I can withdraw my consent for what I say in the interview to be used.	YES ☐ NO ☐
I agree that anonymised direct quotes from interview can be used.	YES ☐ NO ☐

My questions have been answered by ……

Participant's signature (or thumbprint)	Print name	Date
Witness' signature (if thumbprint used above)	Print name	Date

The person who explained the study to you needs to sign too:

I have provided the Youth Trial Board project information to the potential participant in full and answered all his/her questions. To the best of my knowledge, he/she understands the purpose, interventions, risks and benefits of this study and willingly agrees to participate in an interview about the the Youth Trial Board project.		
Signature of person conducting the informed consent process	Print name	Date

IMPORTANT: one signed original to be kept in ODYSSEY trial file by the researcher
one signed copy to be given to the participant
one signed copy to be kept in the clinic file

21 APPENDIX III TEMPLATE GP LETTER

(To be printed on local headed paper).
(Insert version no and date)

Dear Dr _____

The parents of_____and him/herself, have agreed to participate in the ODYSSEY study. This is a randomised multicentre international trial co-ordinated by PENTA, which is funded by the European Commission (see www.PENTA-ID.org).

ODYSSEY aims to compare the efficacy and toxicity of antiretroviral regimens containing two NRTIs and the new integrase inhibitor dolutegravir versus standard combination regimens containing two/three NRTIs and either an NNRTI, a protease inhibitor or a first generation integrase inhibitor, raltegravir. Adherence to and acceptability of the different regimens will also be compared.

The trial will enrol 700 children under 18 years of age from clinical centres in Europe, Africa, Asia, North and South America and will include 2 groups of children: those initiating antiretroviral therapy and those switching to a second-line regimen. All children will be followed until the last patient recruited has completed 96 weeks of follow-up.

Your patient has been randomised to:
☐ dolutegravir containing regimen
☐ standard combination therapy.

I would be very grateful if you could inform me of any concomitant medication that you prescribe to this child during the study.

I enclose a summary of the trial and a copy of the Patient Information Sheet. If you would like a copy of the full protocol or have any comments or problem, please contact:

Dr _____

Enc.
Trial Summary
Patient Information Sheet

22 APPENDIX IV TEMPLATE ADHERENCE QUESTIONNAIRES

Data entered by: ____ on __ __/__ __ __/20__

ODYSSEY FORM 31 - Adherence questionnaire Parent/Carer

Trial Number | | | | | | | Anonymous Code | | | | Form31_V0.10_9th January 2017

Date of Birth D D M M M Y Y Y Y Date of Form D D M M M 2 0 Y Y

Visit (Tick): Screening (ODYSSEY B only)☐ 4☐ 24☐ 36☐ 48☐ 60☐ 72☐ 84☐ 96☐ Unscheduled visit ☐

Other scheduled visit ☐ (Write week number) | | |

TO BE COMPLETED BY THE CLINICAL TEAM

Completed by Carer alone? Yes ☐ No ☐ *If No who else was involved?* .....

TO BE COMPLETED BY THE PARENT/CARER

1. What is your relationship to the child? Parent/Carer ☐ Other ☐ *If Other, specify:* .....

2. Who gives antiretroviral medicines to your child? *Tick all that apply*

a. She / He takes them on their own ☐ b. Parent/Carer ☐ c. Other ☐

If a child takes their own medications, please also complete the young person's adherence questionnaire

We know that is difficult taking medicines every day. Most people miss doses from time to time and it is rare that people take medication perfectly. We are interested in finding out what it is like for you and your child.

3. Has your child missed any doses in the last week? Yes ☐ No ☐ I don't know ☐

4. Has your child missed any doses in the last month? *(excluding the last week)* Yes ☐ No ☐ I don't know ☐

5. There are many reasons why people do not like to take their medicines. Did your child miss their medicines for any of these reasons? *Tick all that apply*

☐ No doses were missed *(Go to Q6)*

☐ The medicine had run out

☐ I or my child forgot

☐ The timing of medicine is difficult

☐ My child did not have any food to take the medicines with

☐ The daily routine was different from normal *(e.g. holidays, sleepovers etc.)*

☐ I was not always with the child to give them their medicines

☐ I did not want other people to know my child is taking medicine

☐ My child dislikes the taste of the medicines

☐ My child was unwell or was vomiting

☐ My child refused to take medicine

☐ I think the medicines are harmful

☐ I have doubts about giving medicines due to my beliefs

☐ I was too depressed or unwell

☐ I was fed up or tired of giving medicine

6. How would you rate your child's adherence (taking antiretroviral medication every day as prescribed) since the last visit? *Please tick the statement you think is most true to you:*

Excellent ☐ Very good ☐ Fair ☐ Not that good ☐ Poor ☐

7. Thank you for taking the time to fill out this form. Please add any comments you have:

.....

Data entered by: ____ on __ __ / __ __ / 2 0 __

ODYSSEY FORM 32 - Adherence questionnaire Young Person

Trial Number | | | | | | | Anonymous Code | | | | Form32_V0.8_9th January 2017

Date of Birth | D | D | M | M | Y | Y | Y | Y | Date of Form | D | D | M | M | M | 2 | 0 | Y | Y |

Visit (Tick): Screening (ODYSSEY B only)☐ 4☐ 24☐ 36☐ 48☐ 60☐ 72☐ 84☐ 96☐ Unscheduled visit ☐

Other scheduled visit ☐ (Write week number) | | | |

TO BE COMPLETED BY THE CLINICAL TEAM

1. Completed by Young Person alone? Yes ☐ No ☐ *If No who else was involved?*.....

TO BE COMPLETED BY THE YOUNG PERSON

2. Who gives you your medicines? *Tick all that apply*

a. I take them myself ☐ b. Parent/Carer ☐ c. Other ☐

We know that is can be difficult taking medicines every day. Most people miss doses from time to time and it is rare that all medication is taken perfectly. We are interested in finding out what it is like for you.

3. Have you missed any doses in the last week? Yes ☐ No ☐

4. Have you missed any doses in the last month? *(excluding the last week)* Yes ☐ No ☐

5. There are many reasons why people do not like to take their medicines. Have you missed your medicines for any of these reasons? *(tick all that apply)*

☐ **I didn't miss any** *(Go to Q6)*

☐ I had run out of medicine

☐ I forgot

☐ The timing of medicine is difficult

☐ I did not have any food to take my medicines with

☐ My routine was different from normal *(e.g. holidays, sleepovers etc.)*

☐ My parent/carer was not always around to give me my medicines

☐ I did not want other people to know I was taking medicine

☐ I don't like the taste of the medicines

☐ I was unwell or was vomiting

☐ I had low mood or was feeling too sad

☐ I refused to take medicine

☐ I was fed up or tired of taking medicine

☐ I think the medicines are harmful

☐ I have doubts about taking medicines due to my beliefs

6. How would you rate your adherence (taking antiretroviral medication every day as prescribed) since the last visit? *Please tick the statement you think is most true to you:*

Excellent ☐ Very good ☐ Fair ☐ Not that good ☐ Poor ☐

7. Thank you for taking the time to fill out this form. Please add any comments you have:

.....

.....

23 APPENDIX V TEMPLATE ACCEPTABILITY QUESTIONNAIRES

Data entered on CACTUS by: _____ on __ __/ __ __ __/ 2 0 __

FORM 33 - Acceptability, Mood and Sleep Questionnaire — Parent/Carer

Trial Number | Anonymous Code | Form 33_ V0.16_21st December 2016

Date of Birth (D D M M M Y Y Y Y) | Date of Form (D D M M M 2 0 Y Y) | (write week number)

Visit (Tick): 4☐ 12☐ 24☐ 48☐ 72☐ 96☐ 120☐ 144☐ 168☐ 192☐ Other scheduled visit ☐

INSTRUCTIONS TO THE CLINICAL TEAM: Pre-complete the header and assist the parents/carers with the completion of the drug names if required. Complete the corresponding ART codes. *(Refer to the MOP for list of ART codes).*
Assist with the completion of the rest of the form as required.

TO BE COMPLETED BY THE PARENT/CARER

1. What is your relationship to the child? Parent/Carer ☐ Other ☐ *If Other, specify:* .....

2. How often does your child take their antiretroviral medicines? Once a day ☐ Twice a day ☐

3. Are any of the following a problem for your child?

a. Taking antiretroviral medicines in the morning?	Yes ☐	No ☐	None taken in the morning ☐
b. Taking antiretroviral medicines in the evening?	Yes ☐	No ☐	None taken in the evening ☐
c. Taking antiretroviral medicines at weekends?	Yes ☐	No ☐	
d. The number of tablets?	Yes ☐	No ☐	No tablets are taken ☐
e. The amount of liquid?	Yes ☐	No ☐	No liquids are taken ☐

4. Does your child take all their antiretroviral medicines at once? Yes ☐ No ☐ *If Yes, complete Q5 and proceed to Q7. If No, go to Q6*

5. If your child takes all their antiretroviral medicines at once, complete this section	**YES**	**NO**	**Not applicable,** this medicine is a liquid
A. Does your child have any problems with the **size** of the tablet(s)?	☐	☐	☐
B. Does your child have any problems **swallowing** their medicines?	☐	☐	
C. Does your child have any problems with the **taste** of the medicines?	☐	☐	
→ ***Now go to Q7 "Mood and Sleep within the last month"***			

6. If your child takes their antiretroviral medicines one after another, complete this section: *Please write your medicines if you know their names, or describe how they look. Eg. Yellow pill.*	**YES**	**NO**	**Not applicable,** this medicine is a liquid
Medicine 1: *Medicine's name, colour or what it looks like* ..... ☐☐☐ *The nurse or doctor fills these boxes*			
A. Does your child have any problems with the **size** of the tablet?	☐	☐	☐
B. Does your child have any problems **swallowing** the medicine?	☐	☐	
C. Does your child have any problems with the **taste** of the medicine?	☐	☐	
→*If your child takes two or more antiretroviral medicines please complete this section:* **Medicine 2:** *Medicine's name, colour or what it looks like* ..... ☐☐☐ *The nurse or doctor fills these boxes*			
A. Does your child have any problems with the **size** of the tablet?	☐	☐	☐
B. Does your child have any problems **swallowing** the medicine?	☐	☐	
C. Does your child have any problems with the **taste** of the medicine?	☐	☐	
→*If your child takes three or more antiretroviral medicines please complete this section:* **Medicine 3:** *Medicine's name, colour or what it looks like* ..... ☐☐☐ *The nurse or doctor fills these boxes*			
A. Does your child have any problems with the **size** of the tablet?	☐	☐	☐
B. Does your child have any problems **swallowing** the medicine?	☐	☐	
C. Does your child have any problems with the **taste** of the medicine?	☐	☐	

→ ***If your child takes a fourth antiretroviral medicine, please record on the next page.*** **Page 1 of 2**

FORM 33 - Acceptability, Mood and Sleep Questionnaire Parent/Carer

Trial Number | Anonymous Code | Date of Visit D D M M M 2 0 Y Y

→*If your child takes four medicines please complete this section:*
Medicine 4: *Medicine's name, colour or what it looks like* .....

The nurse or doctor fills these boxes

A. Does your child have any problems with the **size** of the tablet?	☐	☐	☐
B. Does your child have any problems **swallowing** the medicine?	☐	☐	
C. Does your child have any problems with the **taste** of the medicine?	☐	☐	

MOOD AND SLEEP WITHIN THE LAST MONTH

7. In the last month has your child experienced any of the following? *Tick all that apply*

Dizziness or room spinning ☐	Low mood or feeling sad often ☐	Other 1: ☐ (Give details).....
Problems concentrating ☐	Hurting or harming him/herself ☐ *(e.g. taking an overdose, cutting)*	Other 2: ☐ (Give details).....
Feeling worried often ☐	Thinking life is not worth living ☐	Other 3: ☐ (Give details).....
Feeling angry or aggressive often ☐	Expressing thoughts about ending life (suicidal thoughts) ☐	None of the above ☐

8. In the last month, what time did your child usually go to bed at night? *(24h)* h h m m

9. In the last month, how long did your child usually take to fall asleep each night? *Tick one answer only*

Less than 15 minutes ☐ 15 minutes to half an hour ☐ Half an hour to an hour ☐ More than an hour ☐ I don't know ☐

10. In the last month, approximately how many hours of sleep did your child get each night? *(Write the number of hours)* ☐

		Never	Infrequently *(e.g. once or twice a month)*	Occasionally *(e.g. once or twice a week)*	Frequently *(e.g. 3 or more times a week)*	Don't know
11.	**In the last month, how often did your child wake during the night?** *Tick one only*	☐	☐	☐	☐	☐
12.	**In the last month, how often did your child experience nightmares?** *Tick one only*	☐	☐	☐	☐	☐
13.	**In the last month, how often did your child experience vivid dreams? (not nightmares)** *Tick one only*	☐	☐	☐	☐	☐
14.	**In the last month, how often has your child had trouble staying awake at school or during everyday activities?** *Tick one only*	☐	☐	☐	☐	☐

15. In the last month how would you rate your child's sleep quality overall? *Tick one answer only*


Very Good ☐


Good ☐


Fair ☐


Not that good ☐


Very bad ☐

FOR ODYSSEY B ONLY

16. How does your child find taking their antiretroviral medicine now compared to before starting ODYSSEY (when your child was taking first-line treatment)?

A lot easier ☐ A little easier ☐ No difference ☐ A little more difficult ☐ A lot more difficult ☐

THANK YOU FOR TAKING THE TIME TO FILL OUT THIS FORM **Page 2 of 2**

FORM 34 - Acceptability, Mood and Sleep Questionnaire — Young Person

Data entered on CACTUS by: _____ on __ __/__ __ __/20__

Form 34_ V0.9_06 January 2017

Trial Number

Anonymous Code

Date of Birth (D D M M Y Y Y Y)

Date of Form (D D M M M) 2 0 (Y Y)

(write week number)

Visit (Tick): 4☐ 12☐ 24☐ 48☐ 72☐ 96☐ 120☐ 144☐ 168☐ 192☐ Other scheduled visit ☐

INSTRUCTIONS TO THE CLINICAL TEAM: Pre-complete the header and assist the young person with the completion of the drug names if required. Complete the corresponding ART codes. *(Refer to the MOP for list of ART codes).*
Assist with the completion of the rest of the form as required.

TO BE COMPLETED BY THE YOUNG PERSON

1. How often do you take your antiretroviral medicines? Once a day ☐ Twice a day ☐

2. Are any of the following a problem for you?

a. Taking antiretroviral medicines in the morning?	Yes ☐	No ☐	I don't take them in the morning ☐
b. Taking antiretroviral medicines in the evening?	Yes ☐	No ☐	I don't take them in the evening ☐
c. Taking antiretroviral medicines at weekends?	Yes ☐	No ☐	
d. The number of tablets?	Yes ☐	No ☐	I don't take tablets ☐
e. The amount of liquid?	Yes ☐	No ☐	I don't take liquids ☐

3. Do you take all your medicines at once? Yes ☐ No ☐ *If Yes, complete Q4, then proceed to Q6. If No, go to Q5.*

4. If you take all your medicines at once, complete this section	**YES**	**NO**	**Not applicable** Medicines are liquid
A. Do you have any problems with the **size** of the tablet(s)?	☐	☐	☐
B. Do you have any problems **swallowing** their medicines?	☐	☐	
C. Do you have any problems with the **taste** of the medicines?	☐	☐	
→ ***Now go to Q6 "Mood and Sleep within the last month"***			

5. If you take your medicines one after another, complete this section *Please write your medicines if you know their names, or describe how they look. Eg. Yellow pill.*	**YES**	**NO**	**Not applicable** This medicine is a liquid
Medicine 1: *Medicine's name, colour or what it looks like* ..... ☐☐☐ *The nurse or doctor fills these boxes*			
A. Do you have any problems with the **size** of the tablet?	☐	☐	☐
B. Do you have any problems **swallowing** the medicine?	☐	☐	
C. Do you have any problems with the **taste** of the medicine?	☐	☐	
If you take two or more antiretroviral medicines please complete this section: **Medicine 2:** *Medicine's name, colour or what it looks like* ..... ☐☐☐ *The nurse or doctor fills these boxes*			
A. Do you have any problems with the **size** of the tablet?	☐	☐	☐
B. Do you have any problems **swallowing** the medicine?	☐	☐	
C. Do you have any problems with the **taste** of the medicine?	☐	☐	
If you take three or more antiretroviral medicines please complete this section: **Medicine 3:** *Medicine's name, colour or what it looks like* ..... ☐☐☐ *The nurse or doctor fills these boxes*			
A. Do you have any problems with the **size** of the tablet?	☐	☐	☐
B. Do you have any problems **swallowing** the medicine?	☐	☐	
C. Do you have any problems with the **taste** of the medicine?	☐	☐	

→ ***If you take a fourth antiretroviral medicine, please record on the next page.***

FORM 34 - Acceptability, Mood and Sleep Questionnaire — Young Person

Trial Number | Anonymous Code | Date of Visit (D D M M M 2 0 Y Y)

→*If you take four medicines please complete this section:*
Medicine 4: *Medicine's name, colour or what it looks like* .....

The nurse or doctor fills these boxes

A. Do you have any problems with the **size** of the tablet?	☐	☐	☐
B. Do you have any problems **swallowing** the medicine?	☐	☐	
C. Do you have any problems with the **taste** of the medicine?	☐	☐	

SLEEP AND MOOD WITHIN THE LAST MONTH

6. In the last month have you experienced any of the following? *Tick all that apply*

Dizziness or room spinning ☐	Low mood or feeling sad often ☐	Other 1: ☐ (Give details).....
Problems concentrating ☐	Hurting/harming myself *(e.g. taking an overdose, cutting)* ☐	Other 2: ☐ (Give details).....
Feeling worried often ☐	Thinking life is not worth living ☐	Other 3: ☐ (Give details).....
Feeling angry or aggressive often ☐	Thinking about ending life (suicidal thoughts) ☐	None of the above ☐

7. In the last month, what time did you usually go to bed at night? *(24h)* (h h : m m)

8. In the last month, how long did you usually take to fall asleep each night? *Tick one answer only*

Less than 15 minutes ☐ 15 minutes to half an hour ☐ Half an hour to an hour ☐ More than an hour ☐ I don't know ☐

9. In the last month, approximately how many hours of sleep did you get each night? *Write the number of hours* ☐

		Never	Infrequently *(e.g. once or twice a month)*	Occasionally *(e.g. once or twice a week)*	Frequently *(e.g. 3 or more times a week)*	Don't know
10.	**In the last month, how often did you wake during the night?** *Tick one only*	☐	☐	☐	☐	☐
11.	**In the last month, how often did you experience nightmares?** *Tick one only*	☐	☐	☐	☐	☐
12.	**In the last month, how often did you experience vivid dreams (not nightmares)?** *Tick one only*	☐	☐	☐	☐	☐
13.	**In the last month, how often have you had trouble staying awake at school or during everyday activities?** *Tick one only*	☐	☐	☐	☐	☐

14. In the last month how would you rate your sleep quality overall? *Tick one answer only*


Very Good ☐


Good ☐


Fair ☐


Not that good ☐


Very bad ☐

FOR ODYSSEY B ONLY

15. How do you find taking your antiretroviral medicine now compared to before starting ODYSSEY (when you were taking first-line treatment)? *Tick one answer only*

A lot easier ☐ A little easier ☐ No difference ☐ A little more difficult ☐ A lot more difficult ☐

THANK YOU FOR TAKING THE TIME TO FILL OUT THIS FORM

Page 2 of 2

24 APPENDIX VI ADAPTED WHO CLINICAL STAGING OF HIV/AIDS FOR PATIENTS WITH CONFIRMED HIV INFECTION

The table below summarising WHO clinical staging for children and adolescents (1); Diagnostic criteria for these conditions, are described in Appendix VII

Children (<15 years of age)	**Adolescents (≥15 years of age)**
Clinical Stage 1	**Clinical Stage 1**
• Asymptomatic • Persistent generalized lymphadenopathy	• Asymptomatic • Persistent generalized lymphadenopathy
Clinical stage 2	**Clinical stage 2**
• Unexplained persistent hepatosplenomegaly • Papular pruritic eruptions • Fungal nail infection • Angular cheilitis • Lineal gingival erythema • Extensive wart virus infection • Extensive molluscum contagiosum • Recurrent oral ulcerations • Unexplained persistent parotid enlargement • Herpes zoster • Recurrent or chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis or tonsillitis)	• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media and pharyngitis) • Herpes zoster • Angular cheilitis • Recurrent oral ulceration • Papular pruritic eruptions • Seborrhoeic dermatitis • Fungal nail infections
Clinical Stage 3 (*= severe WHO clinical stage 3 for the ODYSSEY trial)	
• Unexplained moderate malnutrition or wasting not adequately responding to standard therapy* • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5°C intermittent or constant, for longer than one month) • Persistent oral candidiasis (after first 6–8 weeks of life)* • Oral hairy leukoplakia • Acute necrotizing ulcerative gingivitis or periodontitis • Lymph node tuberculosis	• Unexplained severe weight loss (>10% of presumed or measured body weight)* • Unexplained chronic diarrhoea for longer than one month • Unexplained persistent fever (above 37.6°C intermittent or constant, for longer than one month) • Persistent oral candidiasis* • Oral hairy leukoplakia • Pulmonary tuberculosis (current) • Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia)

• Pulmonary tuberculosis • Severe recurrent bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis* • Chronic HIV-associated lung disease including bronchiectasis* • Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre)and or chronic thrombocytopaenia (<50 × 10^9 per litre)	• Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis • Unexplained anaemia (<8 g/dl), neutropaenia (<0.5 × 10^9 per litre) or chronic thrombocytopaenia (<50 × 10^9 per litre)
Clinical Stage 4	
• Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy • Pneumocystis pneumonia • Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia) • Chronic herpes simplex infection (orolabial or cutaneous of more than one month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than one month • Central nervous system toxoplasmosis (after one month of life) • Extrapulmonary cryptococcosis (including meningitis) • HIV encephalopathy • Disseminated endemic mycosis (coccidiomycosis or histoplasmosis) • Disseminated non-tuberculous mycobacterial infection • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis • Cerebral or B-cell non-Hodgkin lymphoma • Progressive multifocal leukoencephalopathy • Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy	• HIV wasting syndrome • Pneumocystis pneumonia • Recurrent severe bacterial pneumonia • Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration or visceral at any site) • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Extrapulmonary tuberculosis • Kaposi's sarcoma • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Extrapulmonary cryptococcosis including meningitis • Disseminated non-tuberculous mycobacterial infection • Progressive multifocal leukoencephalopathy • Chronic cryptosporidiosis (with diarrhoea) • Chronic isosporiasis • Disseminated mycosis (coccidiomycosis or histoplasmosis) • Recurrent non-typhoidal Salmonella bacteraemia • Lymphoma (cerebral or B-cell non-Hodgkin) or other solid HIV-associated tumours • Invasive cervical carcinoma • Atypical disseminated leishmaniasis • Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy

References:

1. World Health Organization. WHO case definitions of HIV for surveillance, and revised clinical staging and immunological classification of HIV related disease in adults and children. Geneva: World Health Organization; 2007.

25 APPENDIX VII ADAPTED DIAGNOSTIC CRITERIA FOR WHO CLINICAL STAGING EVENTS IN CHILDREN YOUNGER THAN 15 YEARS

The table is reproduced from WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children (1). Definitions for moderate (grade 3) and severe (grade 4) malnutrition are modified using definitions from WHO (1) and CDC (2,3).

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
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

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE 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 or weight-for-height up to −2 standard deviations from the mean OR clear deviation from a previous growth trajectory or documented crossing of percentile lines, 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 OR or documented crossing of percentile lines, 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 (>37.5°C intermittent or constant for longer than one month)	Reports of fever or night sweat 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 malaria areas.	Confirmed by documented fever of >37.50 ◦C 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.
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.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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 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 Stage 4		
Unexplained severe wasting, stunting or severe malnutrition not adequately	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	Documented weight for height or weight for age of more than –3 standard deviations from the mean

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
responding to standard therapy*	oedema of both feet, and/or weight-for-height of –3 standard deviations from the mean or downward crossing of at least two weight percentile lines.	or documented downward crossing of at least two complete weight percentile lines 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.
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;

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
		- 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.
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.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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

* Modified definitions for moderate (grade 3) and severe (grade 4) malnutrition from WHO and CDC clinical stage classifications (1,2,3)

References:

1. World Health Organization. WHO case definitions of HIV for surveillance, and revised clinical staging and immunological classification of HIV related disease in adults and children. Geneva: World Health Organization; 2007.
2. Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR. 1994;43(RR-12):1-10.
3. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 1992;41(RR-17):1-19.

26 APPENDIX VIII CRITERIA FOR WHO CLINICAL STAGING EVENTS FOR YOUNG PEOPLE 15 YEARS AND OLDER

Criteria for WHO clinical staging events (1).

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	Fungal culture of the nail or nail plate material.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
	the nail from the nail bed) of the fingernails (white discoloration – especially involving proximal part of 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).

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
Acute necrotizing ulcerative gingivitis or 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.
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 vasculitis, haemorrhage and necrosis.	Compatible histology or cytomegalovirus demonstrated in cerebrospinal fluid by culture or DNA (by polymerase chain reaction).

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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 tumours, neuroimaging techniques.
Invasive cervical carcinoma	No presumptive clinical diagnosis.	Histology or cytology.

CLINICAL EVENT	CLINICAL DIAGNOSIS	DEFINITIVE DIAGNOSIS
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.

References:

1. World Health Organization. WHO case definitions of HIV for surveillance, and revised clinical staging and immunological classification of HIV related disease in adults and children. Geneva: World Health Organization; 2007.

27 APPENDIX IX ADAPTED DAIDS TOXICITY GRADINGS

The toxicity grading table is adapted from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014]. Available from: http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf (1). The changes from the previous version of the DAIDS Table are highlighted in yellow.

Neutrophil grading for children aged >7 days, are based on WHO 2010 guidelines (2) recognising the lower normal levels in African populations. These are highlighted in grey.

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)
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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	Thinning detectable by study participant (or by caregiver for young children and disabled adults)	Thinning or patchy hair loss detectable by health care provider	Complete hair loss	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
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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Anorexia	Loss of appetite without decreased oral intake	Loss of appetite associated with decreased oral intake without significant weight loss	Loss of appetite associated with significant weight loss	Life-threatening consequences OR Aggressive intervention indicated (e.g., tube feeding, total parenteral nutrition)
Ascites	No symptoms	Symptoms AND Intervention indicated (e.g., diuretics, therapeutic paracentesis)	Symptoms recur or persist despite intervention	Life-threatening consequences
Bloating or Distension *Report only one*	Symptoms causing no or minimal interference with usual social & functional activities	Symptoms causing greater than minimal interference with usual social & functional activities	Symptoms causing inability to perform usual social & functional activities	NA
Cholecystitis	NA	Symptoms AND Medical intervention indicated	Radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences (e.g., sepsis, perforation)
Constipation	NA	Persistent constipation requiring regular use of dietary modifications, laxatives, or enemas	Obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction)
Diarrhoea *≥ 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)
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)

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
NEUROLOGICAL				
Acute CNS Ischaemia	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
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
Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Neurosensory Alteration (includes paresthesia and painful neuropathy) *Specify type, if applicable*	Minimal paresthesia causing no or minimal interference with usual social & functional activities OR No symptoms with sensory alteration on examination	Sensory alteration or paresthesia causing greater than minimal interference with usual social & functional activities	Sensory alteration or paresthesia causing inability to perform usual social & functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Seizures ***New Onset Seizure*** *≥ 18 years of age*	NA	NA	1 to 3 seizures	Prolonged and repetitive seizures (e.g., status epilepticus) OR Difficult to control (e.g., refractory 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				
Fetal Death or Stillbirth (report using mother's participant ID) *Report only one*	NA	NA	Fetal loss occurring at ≥ 20 weeks gestation	NA
Preterm Delivery[7] (report using mother's participant ID)	Delivery at 34 to < 37 weeks gestational age	Delivery at 28 to < 34 weeks gestational age	Delivery at 24 to < 28 weeks gestational age	Delivery at < 24 weeks gestational age
Spontaneous Abortion or Miscarriage[8] (report using mother's participant ID) *Report only one*	Chemical pregnancy	Uncomplicated spontaneous abortion or miscarriage	Complicated spontaneous abortion or miscarriage	NA
PSCYCHIATRIC and SLEEP PROBLEMS				
Insomnia	Mild difficulty falling asleep, staying asleep, or waking up early	Moderate difficulty falling asleep, staying asleep, or waking up early	Severe difficulty falling asleep, staying asleep, or waking up early	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

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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Uveitis	No symptoms AND Detectable on examination	Anterior uveitis with symptoms OR Medicamylasal 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
Cytokine Release Syndrome[9]	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[10] (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[11]	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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Underweight[12] *> 5 to 19 years of age*	NA	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	NA	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	NA	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
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
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[13] *Report only one*				
> 15 years of age	2.5 to < 5 cm in diameter OR 6.25 to < 25 cm2 surface area AND Symptoms causing no or minimal interference with usual social & functional activities	≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities	≥ 10 cm in diameter OR ≥ 100 cm2 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)

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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
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[14], High*** *> 28 days of age*	NA	NA	> ULN	> 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 in DAIDS 2014. Total Bilirubin for Term and Preterm Neonates	See Appendix A in DAIDS 2014. Total Bilirubin for Term and Preterm Neonates	See Appendix A in DAIDS 2014. Total Bilirubin for Term and Preterm Neonates	See Appendix A in DAIDS 2014. Total Bilirubin for Term and Preterm Neonates

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
Calcium, High (mg/dL; *mmol/L*) *≥ 7 days of age*	10.6 to < 11.5 *2.65* to < *2.88*	11.5 to < 12.5 *2.88* to < *3.13*	12.5 to < 13.5 *3.13* to < *3.38*	≥ 13.5 *≥ 3.38*
< 7 days of age	11.5 to < 12.4 *2.88* to < *3.10*	12.4 to < 12.9 *3.10* to < *3.23*	12.9 to < 13.5 *3.23* to < *3.38*	≥ 13.5 ≥ *3.38*
Calcium (Ionized), High (mg/dL; *mmol/L*)	> ULN to < 6.0 *> ULN to < 1.5*	6.0 to < 6.4 *1.5 to < 1.6*	6.4 to < 7.2 *1.6 to < 1.8*	≥ 7.2 *≥ 1.8*
Calcium, Low (mg/dL; *mmol/L*) *≥ 7 days of age*	7.8 to < 8.4 *1.95* to < *2.10*	7.0 to < 7.8 *1.75* to < *1.95*	6.1 to < 7.0 *1.53* to < *1.75*	< 6.1 *< 1.53*
< 7 days of age	6.5 to < 7.5 *1.63* to < *1.88*	6.0 to < 6.5 *1.50* to < *1.63*	5.50 to < 6.0 *1.38* to < *1.50*	< 5.50 *< 1.38*
Calcium (Ionized), Low (mg/dL; *mmol/L*)	< LLN to 4.0 *< LLN to 1.0*	3.6 to < 4.0 *0.9 to < 1.0*	3.2 to < 3.6 *0.8 to < 0.9*	< 3.2 *< 0.8*
Cardiac Troponin I, High	NA	NA	NA	Levels consistent with myocardial infarction or unstable angina as defined by the local laboratory
Creatine Kinase, High	3 to < 6 x ULN	6 to < 10 x ULN	10 to < 20 x ULN	≥ 20 x ULN
Creatinine, High	1.1 to 1.3 x ULN	> 1.3 to 1.8 x ULN OR Increase of > 0.3 mg/dL above baseline	> 1.8 to < 3.5 x ULN OR Increase of 1.5 to < 2.0 x above baseline	≥ 3.5 x ULN OR Increase of ≥ 2.0 x above baseline
Creatinine Clearance[15] or eGFR, Low *Report only one*	NA	< 90 to 60 ml/min or ml/min/1.73 m2 OR 10 to < 30% decrease from baseline	< 60 to 30 ml/min or ml/min/1.73 m2 OR ≥ 30 to < 50% decrease from baseline	< 30 ml/min or ml/min/1.73 m2 OR ≥ 50% decrease from 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

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
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	130 to < 160	160 to < 190	≥ 190	NA
≥ 18 years of age	*3.37 to < 4.12*	*4.12 to < 4.90*	*≥ 4.90*	
> 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[16], Low (mEq/L; *mmol/L*)	1.2 to < 1.4 *0.60 to < 0.70*	0.9 to < 1.2 *0.45 to < 0.60*	0.6 to < 0.9 *0.30 to < 0.45*	< 0.6 *< 0.30*
Phosphate, Low (mg/dL; *mmol/L*)				
> 14 years of age	2.0 to < LLN *0.81 to < LLN*	1.4 to < 2.0 *0.65 to < 0.81*	1.0 to < 1.4 *0.32 to < 0.65*	< 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 < 135*	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/mm3; x*10^{9}cells/L*)	300 to < 400	200 to < 300	100 to < 200	< 100
> 5 years of age (not HIV infected)	*300 to < 400*	*200 to < 300*	*100 to < 200*	*< 100*
Absolute Lymphocyte Count, Low (cell/mm3; x*10^{9}cells/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[17] (cells/mm3;x*10^{9}cells/L*)				
> 7 days of age	750 –< 1,000 *0.75 –<1.0*	500 – 749 *0.5 –0.749*	250 – 499 *0.25 –0.499*	< 250 *< 0.250*
2 to 7 days of age	1,250 to 1,500 *1.250 to 1.500*	1,000 to 1,249 *1.000 to 1.249*	750 to 999 *0.750 to 0.999*	< 750 *< 0.750*

PARAMETER	GRADE 1 MILD	GRADE 2 MODERATE	GRADE 3 SEVERE	GRADE 4 POTENTIALLY LIFE-THREATENING
≤ 1 day of age	4,000 to 5,000 *4.000 to 5.000*	3,000 to 3,999 *3.000 to 3.999*	1,500 to 2,999 *1.500 to 2.999*	< 1,500 *< 1.500*
Fibrinogen, Decreased (mg/dL; *g/L*)	100 < 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, Low (g/dL; *mmol/L*)[18]				
≥ 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/mm3; *cells/L*)	100,000 to < 124,999 *100.000 x 109 to < 124.999 x 109*	50,000 to < 100,000 *50.000 x 109 to < 100.000 x 109*	25,000 to < 50,000 *25.000 x 109 to < 50.000 x 109*	< 25,000 *< 25.000 x 109*
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/mm3;x10^9*cells/L*)				
> 7 days of age	2,000 to 2,499 *2.000 to 2.499*	1,500 to 1,999 *1.500 x to 1.999*	1,000 to 1,499 *1.000 to 1.499*	< 1,000 *< 1.000*
≤ 7 days of age	5,500 to 6,999 *5.500 to 6.999*	4,000 to 5,499 *4.000 to 5.499*	2,500 to 3,999 *2.500 to 3.999*	< 2,500 *< 2.500*
URINALYSIS				
Glycosuria (random collection tested by dipstick)	Trace to 1+ or ≤ 250 mg	2+ or > 250 to ≤ 500 mg	> 2+ or > 500 mg	NA

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

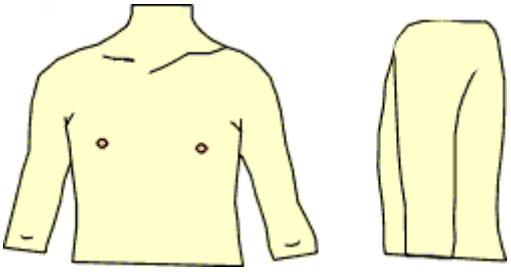
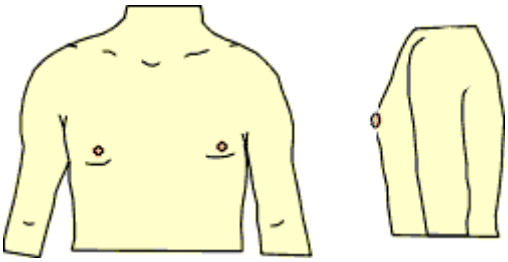
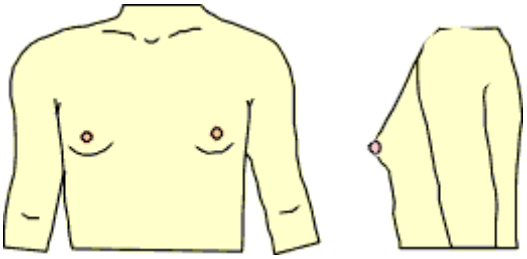
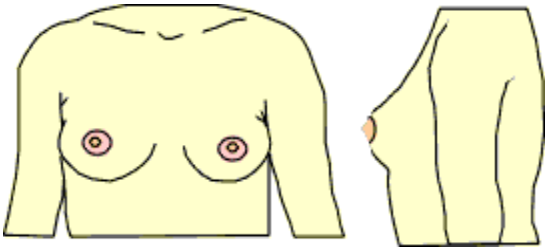
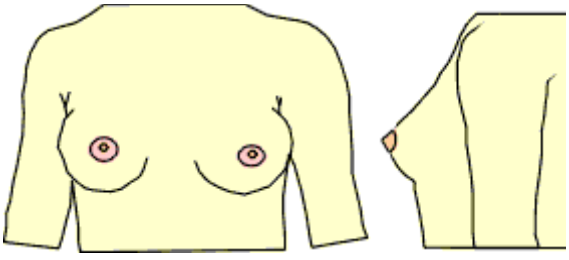
1 Blood pressure norms for children < 18 years of age can be found in: Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. Pediatrics 2011;128;S213; originally published online November 14, 2011; DOI: 10.1542/peds.2009-2107C.
2 As per Bazett's formula.
3 For pruritus associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
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 delivery of a live-born neonate occurring at ≥ 20 to < 37 weeks gestational age.
8 Definition: A clinically recognized pregnancy occurring at < 20 weeks gestational age.
9 Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and/or shortness of breath.
10 For pain associated with injections or infusions, see the *Site Reactions to Injections and Infusions* section (page 23).
11 Definition: A disorder characterized by fever, arthralgia, myalgia, skin eruptions, lymphadenopathy, marked discomfort, and/or dyspnea.
12 WHO reference tables may be accesed 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.
14 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.
15 Use the applicable formula (i.e., Cockroft-Gault in mL/min or Schwatrz in mL/min/1.73m2).
16 To convert a magnesium value from mg/dL to mmol/L, laboratories should multiply by 0.4114.
17 Neutrophil grading, are based on WHO 2010 guidelines(2) recognising the lower normal levels in African populations.
18 The conversion factor used to convert g/dL to mmol/L is 0.6206 and is the most commonly used conversion factor. 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 the appropriate conversion factor for the particular laboratory.
19 Severity grading for total bilirubin in neonates is complex because of rapidly changing total bilirubin normal ranges in the first week of life followed by the benign phenomenon of breast milk jaundice after the first week of life. Severity grading in this appendix corresponds approximately to cut-offs for indications for phototherapy at grade 3 and for exchange transfusion at grade 4.

References:

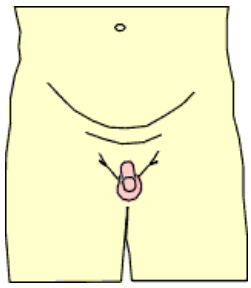
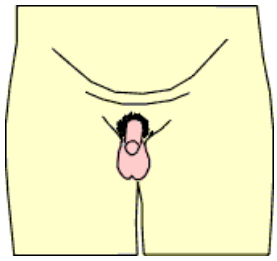
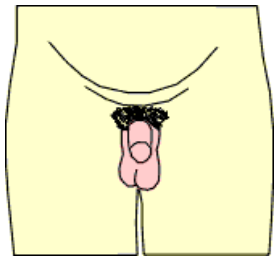
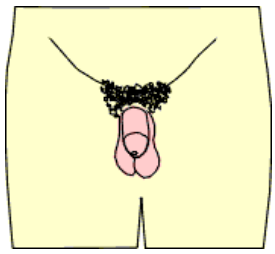
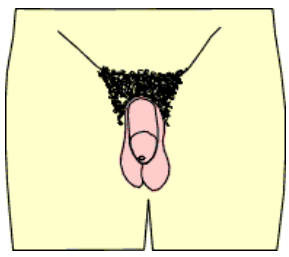
1. Division of AIDS National Institute of Allergy and Infectious Diseases National Institutes of Health US Department of Health and Human Services. Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events 2014 [updated Version 2.0 November 2014]. Available from: http://rcc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8.
2. WHO. Antiretroviral therapy for HIV infection in infants and children: Towards universal access. Recommendations for a public health approach: 2010 revision. In: WHO, editor. 2010.

28 APPENDIX X TANNER SCALES

The Five Stages of Female Breast and Pubic Hair Development should be staged separately (1, 2).

Stage		Female Breast	Pubic Hair
1		Breasts during childhood. The breasts are flat and show no signs of development.	None
2		Breast bud stage. Milk ducts and fat tissue forms a small mound.	Sparse, lightly pigmented, straight, medial border of labia.
3		Breasts continue to grow. Breasts become rounder and fuller.	Darker, beginning to curl, increased amount.
4		Nipple and areola form separate small mound. Not all girls go through this stage. Some skip stage 4 and go directly to stage 5.	Coarse, curly, abundant but amount less than in adult.
5		Breast growth enters final stage. Adult breast is full and round shaped.	Adult feminine triangle, spread to medial surface of thighs

The Five Stages of Male Genitalia and Pubic Hair Development should be staged separately

Stage		Male Genitalia	Pubic Hair
1		Penis and testicles of a child. Testicles between 1 and 3 milliliters in volume.	No pubichair.
2		First signs for penis and testicle growth, Testicles become larger. Testicles between 4 and 6 millilitres in volume.	Pubic hair beginning to grow: appears sparse and downy straight.
3		Penis continues to grow getting wider and longer. Testicles continue to grow larger. Testicles between 7 and 16 millilitres in volume.	Pubic hair appears curlier and coarser with increased pigmentation.
4		Penis continues to grow getting wider and longer. Testicles continue to grow larger. Penis gland or head is more developed. Testicles between 12 and 24 milliliters in volume. Testicles are about 1 1/2 inches long.	Pubic hair becomes adult type, but less.
5		Penis growth enters final stage. Average erect penis length 6 1/4 inches. 90% are 5 - 7 inches. Glans penis or head is fully developed. Testicles 16 - 27 millilitres in volume. Testicles are about 1-3/4 inches.	Pubic hair is thick spreading to medial thighs.

References:

1. Marshall WA, Tanner JM. Variations in pattern of pubertal changes in girls. Archives of disease in childhood. 1969;44(235):291-303.
2. Marshall WA, Tanner JM. Variations in the pattern of pubertal changes in boys. Archives of disease in childhood. 1970;45(239):13-23.

29 APPENDIX XI SAFE LIMITS OF BLOOD SAMPLE VOLUMES IN CHILDREN

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

Allowable blood draw limits for children (1,2):

- For healthy children:
  - 3% total blood volume 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 7: Maximum allowable total blood draw volumes*

Wt, kg	TBV, ml	Blood draw volume in 24 hours, ml		Total volume in 30 days, ml	
		Unwell (2.5% TBV)	**Healthy (3% TBV)**	Unwell (5% TBV)	**Healthy (10% TBV)**
3	240	6	**7**	12	**24**
4	320	8	**10**	16	**32**
5	400	10	**12**	20	**40**
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).

References:

1. Howie S. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ 2011;89:46–53

Jack R. Maximum allowable total blood draw volumes. Children's Hospital and Regional Medical Center Laboratory, Seattle, WA. August 2001. https://www.ucdmc.ucdavis.edu/clinicaltrials/StudyTools/Documents/Blood_Draws_Maximum_Allowable.doc

30 APPENDIX XII IMMUNOLOGY/VIROLOGY SUBSTUDY

INTRODUCTION AND RATIONALE

This proposal is based upon two main observations from using integrase inhibitors in clinical studies. The first stems from the STARTMRK study (1, 2). It showed that in adults there was a progressive increase in CD4 counts in the raltegravir arm. The reasons were unclear and it has been postulated that it could be a negative effect of the efavirenz arm rather than a positive impact of raltegravir. However in the recently completed REALITY study of over 1800 patients, raltegravir significantly increased the CD4 count after 48 weeks, even though raltegravir had only been taken for the first 12 weeks of treatment (3). In further analyses by MRC CTU (not published yet), the largest effect was in children under 17 with declining impact with increasing age and no impact in adults older than 40 years of age. This is strongly supportive of an impact of raltegravir on thymic output. Whether this is related to a more rapid decline in viral load, the viral reservoir or a direct impact on CD4 cell dynamics is unclear, and forms the basis for this proposed study. Other studies also show that integrase inhibitors lead to greater increases in CD4 count than comparator regimes (1-5). The reasons for this are unclear but may be due to an increase in naïve CD4 cells (6).

If correct, this finding could have important implications for treating HIV infected children and adults, as it may imply that integrase inhibitors can lead to an increase in thymic output.

T-cells produced in the thymus from bone marrow derived precursor cells establish the peripheral naïve T-cell pool during the first year of life. The export of T-cells from the thymus (thymic output) then gradually declines from its peak at 1 year of age to much lower levels by early adulthood. In humans, increased peripheral T-cell division with age is relied upon to maintain the naïve T-cell pool. The relative contribution of these two mechanisms therefore changes with age. Our recent work has demonstrated the importance of maintaining thymic output in children with HIV infection to optimise CD4 reconstitution and we have just completed analysis in the cohort from Children with HIV Early antiretroviral trial (CHER) (7), which shows that thymic output is the main determinant of CD4 cell reconstitution in HIV infected infants (Payne H et al. Personal communication). Though the mechanism is unknown, it is clear therefore that the finding of increased naïve CD4 cells in response to integrase inhibitors may be due to increased naïve cell proliferation and/or increased thymic output.

Until recently, thymic output has been commonly estimated from T-cell receptor excision circles (TRECS) and/or markers such as CD31 expressed on recent thymic emigrants. Because concentrations of TREC and markers of recent thymic emigrants are confounded by peripheral T-cell division they cannot in themselves be used as quantitative estimates of thymic output. We have established methods using measurements of TRECs and cell division using the marker Ki67 in the total naïve CD4 T-cell population and a recently described mathematical model to obtain explicit measures of thymic output in HIV infected patients (8). We have adapted this methodology for use in frozen cells and propose to apply it to stored samples collected from the proposed study quantify T-cell dynamics and assess if DTG leads to increased thymic output.

DTG may also be operating to increase CD4 cells through its effects on immune activation, possibly as a result of ongoing low level viral replication. HIV establishes latency early after primary infection and the resting CD4+ T cells constitute the main pool of cells responsible for persistence (9). Homeostatic cell proliferation mechanisms as well as stochastic phenomena of cell activation by different stimuli have been proposed as models of persistence in the presence of suppressive cART (9). However it was recently shown that persistence is rather an active process driven by the virus aiming at its own survival (10). Many of the cells in this pool undergo clonal expansion and strong selection of cells with HIV integration sites in specific genes as these seem to offer a survival advantage through expansion of infected clones (11). Eliminating the viral reservoir is the main challenge of the functional cure agenda (12) and therapeutic strategies should incorporate qualitative and quantitative assessments of this compartment. Integrase Strand Transfer Inhibitors (INSTIs) exhibit virological features that suggest that these compounds are advantageous for reducing the viral reservoir in patients that initiate treatment, as well as those commencing second-line therapy (13).

In view of the absence of resistance even when given as monotherapy (14), dolutegravir appears particularly appealing for use in children, and the Odyssey trial offers a unique opportunity to assess its impact in both groups of patients. There have been conflicting reports on the effect of raltegravir on intensification of cART suggesting that there might be a temporary effect on 2LTR circles (15) probably reflecting the absence of consensus on the role of ongoing low level viral replication as a mechanism of replenishment of the reservoir (16). The aim of the virological component of this substudy is to assess the dynamic impact of dolutegravir on the viral reservoir and its impact on clonal expansion selection of infected cells when compared to SOC for treatment naïve and treatment experienced patients.

Recent data (14, 17, 18) on the use of dolutegravir in highly experienced patients as well as its use as part of dual therapy present us with a potential new paradigm in HIV treatment. Odyssey is therefore expected to a) inform policies and treatment strategies in paediatric HIV b) advance our knowledge of the viral reservoir and c) add invaluable clinical utility/validity data to the use of emerging virological and immunological markers for estimating the size of the viral reservoir (19). It is therefore critical to ensure storage of adequate, good quality samples (cells and plasma) in order to maximise the potential future benefit maintaining commitment to the trial participants.

This sub-study could provide the data that shows that integrase inhibitors can lead to a greater increase in thymic output and/or a decrease in CD4 cell death than other regimes. It could demonstrate the use of this class of ARVs is particularly advantageous for children and would strongly support the use of integrase inhibitors in HIV infected children.

OBJECTIVE

The objective of the substudy is to assess the impact of DTG on the mechanisms of CD4 reconstitution, immune activation and HIV reservoir and replication.

METHODS

Blood samples for plasma will be collected at each study visit according to the trial assessment schedule of the main ODYSSEY trial and separated into plasma prior to storage. PBMCs will be collected at enrolment, and at 12, 48 and 96 weeks for sites participating in the immunology/virology substudy.

Immunology assays: T-cell subsets of PBMCs (CD3, CD4 and CD45RA) and activation markers (CD38 and HLA-DR) will be stained by surface labelling. PBMCs will then be fixed and permeabilized and stained for the intranuclear marker Ki67 and levels determined by flow cytometry. CD4+/CD45RA+ T-cells will be isolated by negative immunoselection using magnetic beads. Genomic DNA will be extracted using QIAamp DNA minikits (QIAGEN) and Real-time quantitative PCR (qPCR) will be carried out to determine the number of TRECs per cell.

The method for estimating thymic output has been described (8). An explicit expression for thymic export in terms of total naïve cell numbers, naïve cell TREC content and Ki67 expression is given as:

$$\theta(t) = \left(\frac{y(t)\tau(t)}{\Delta} + \frac{d\tau(t)}{dt} \right) \frac{N(t)}{c - \tau(t)}$$

Thymic Export (cells day-1) =

where c is a constant representing the average TREC content of thymocytes entering the peripheral naïve population, y(t) is the fraction of naïve CD4+ T-cells expressing Ki67, Δ is the duration of Ki67 expression, τ is the TREC concentration in the peripheral naïve CD4+ T-cell population and N(t) is the total size of the naïve CD4+ T-cell pool. Calculations to estimate total body CD4+/CD45RA+ T-cell numbers N(t) will be performed as previously described using estimates on the linear relationship between blood volume and body weight to estimate total body T-cell numbers.

The impact of treatment on thymic output will be analysed using Non-Linear Mixed Effect modelling to ascertain the impact of DTG on thymic output. The requirements for these models are to have repeated measurements of multiple individuals over time. In addition to determining fixed effects (average of a measure within a population) this method has the ability to estimate how an individual differs from the average (random effects). Perhaps most importantly it can be used to assess how factors such as treatment determine individual responses. Such an approach has been used successfully for predicting long term CD4 counts in HIV infected children following ART (20).

We have recently completed studies in children and adults examining the impact of immune activation in response to different ART regimes (21). We will study a range of markers in plasma and cell samples that will be stored from baseline and at multiple time points after randomization, and then frozen at -80oc or in liquid nitrogen respectively. Samples from Uganda will be stored locally and later transferred to the Institute of Child Health, UCL. Samples from Zimbabwe and South African sites will be stored locally and then transferred to the African Health Research Institute (AHRI) Laboratories for analyses. We will analyse soluble markers (including known markers of immune activation such as IL1ra, IL6, TNFalpha, IL10, TF, D-dimers and other markers that we have shown to be sensitive to HIV infection) using Meso Scale Discovery assays (MesoScale Discovery, Gaithersburg, MD, US) or by ELISA (22). Immunophentyping will be performed as previously described to measure CD45RA and CD45RO

subpopulations of CD4 and CD8 cells as well as CD31, CD38, HLA-DR and Ki67 (21). All of these assays have been established by us and are in regular use within our laboratories (At ICH and AHRI).

Viral assays: For the reservoir assays we have developed a quantitative Total HIV-1 DNA and RNA by digital droplet PCR as well as an ultrasensitive quantitative RNA assay (22), and whole genome sequencing methodologies by next-generation sequencing (NGS) (23-24). A modified approach based on an already published method will be used for estimating 2LTR-circles and integrated HIV DNA (25). For the ODYSSEY substudy NGS of the integrase gene will be used as NGS allows increased sensitivity in minor variant detection (26). Clonality of infection will be assessed by integration sites analysis (11). A case-control approach with a limited number of matched patients in SOC vs DTG will be used to detect low-level replication/seeding of the reservoirs and the replication pathway (viral replication or T-cell division); if viral replication predominates DTG has a potential beneficial effect in reducing reservoirs.

The results could have important implications for treating HIV infected children and adults, as higher long term CD4 counts and smaller viral reservoirs are being extensively studied in their association with better long-term health.

Number of patients: Based on CHER data we estimated that 350 children (175 per arm) would provide 80% power (2-sided α =0.05) to detect a treatment difference of 0.18 $\log_{10}$ cells in thymic output at 96 weeks, adjusting for baseline output. We will describe changes in thymic output, immune activation biomarkers and viral reservoirs and replication.

STATISTICAL ANALYSIS PLAN

The primary outcome, thymic output at week 96, will be analysed using analysis of covariance to compare the mean log10 output between the two treatment arms, adjusting for baseline output and stratification factors. Secondary outcomes will be analysed by the same approach.

References:

1. DeJesus E, Rockstroh JK, Lennox JL, Saag MS, Lazzarin A, Zhao J, et al. Efficacy of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: week-192 overall and subgroup analyses from STARTMRK. HIV clinical trials. 2012;13(4):228-32.
2. Rockstroh JK, Lennox JL, Dejesus E, Saag MS, Lazzarin A, Wan H, et al. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. Clin Infect Dis. 2011;53(8):807-16.
3. REALITY Trial Team, editor 12-week raltegravir-intensified quadruple therapy versus triple first-line ART reduces viral load more rapidly but does not reduce mortality in severely immunosuppressed African HIV-infected adults and older children: the REALITY trial. AIDS July 2016; Durban, South Africa.
4. Gotuzzo E, Markowitz M, Ratanasuwan W, Smith G, Prada G, Morales-Ramirez JO, et al. Sustained efficacy and safety of raltegravir after 5 years of combination antiretroviral therapy as initial treatment of HIV-1 infection: final results of a randomized, controlled, phase II study (Protocol 004). J Acquir Immune Defic Syndr. 2012;61(1):73-7.
5. Negredo E, Massanella M, Puertas MC, Buzon MJ, Puig J, Perez-Alvarez N, et al. Early but limited effects of raltegravir intensification on CD4 T cell reconstitution in HIV-infected patients with an immunodiscordant response to antiretroviral therapy. J Antimicrob Chemother. 2013;68(10):2358-62.

6. Garrido C, Rallon N, Soriano V, Lopez M, Zahonero N, de Mendoza C, et al. Mechanisms involved in CD4 cell gains in HIV-infected patients switched to raltegravir. AIDS. 2012;26(5):551-7.
7. Cotton MF, Violari A, Otwombe K, Panchia R, Dobbels E, Rabie H, et al. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. Lancet. 2013;382(9904):1555-63.
8. Sandgaard KS, Lewis J, Adams S, Klein N, Callard R. Antiretroviral therapy increases thymic output in children with HIV. AIDS. 2014;28(2):209-14.
9. Chomont N, El-Far M, Ancuta P, Trautmann L, Procopio FA, Yassine-Diab B, et al. HIV reservoir size and persistence are driven by T cell survival and homeostatic proliferation. Nat Med. 2009;15(8):893-900.
10. Rouzine IM, Weinberger AD, Weinberger LS. An evolutionary role for HIV latency in enhancing viral transmission. Cell. 2015;160(5):1002-12.
11. Maldarelli F, Wu X, Su L, Simonetti FR, Shao W, Hill S, et al. HIV latency. Specific HIV integration sites are linked to clonal expansion and persistence of infected cells. Science. 2014;345(6193):179-83.
12. Siliciano RF, Greene WC. HIV latency. Cold Spring Harb Perspect Med. 2011;1(1):a007096.
13. Mesplede T, Wainberg MA. Resistance against Integrase Strand Transfer Inhibitors and Relevance to HIV Persistence. Viruses. 2015;7(7):3703-18.
14. Rojas J BJ, Lonca M, Torres B, Parera M, Gonzalez A, Mallolas J, Tricas A, Moreno L, Garcia F, Gatell JM, Martinez E, editor Dolutegravir monotherapy in HIV-infected patients with sustained viral suppression: a 24-week pilot study. 15th European AIDS Conference; October 2015; Barcelona.
15. Hatano H, Strain MC, Scherzer R, Bacchetti P, Wentworth D, Hoh R, et al. Increase in 2-long terminal repeat circles and decrease in D-dimer after raltegravir intensification in patients with treated HIV infection: a randomized, placebo-controlled trial. J Infect Dis. 2013;208(9):1436-42.
16. Kearney MF, Spindler J, Shao W, Yu S, Anderson EM, O'Shea A, et al. Lack of detectable HIV-1 molecular evolution during suppressive antiretroviral therapy. PLoS Pathog. 2014;10(3):e1004010.
17. Gubavu C, Prazuck T, Niang M, Buret J, Mille C, Guinard J, et al. Dolutegravir-based monotherapy or dual therapy maintains a high proportion of viral suppression even in highly experienced HIV-1-infected patients. J Antimicrob Chemother. 2016;71(4):1046-50.
18. Katlama C SC, Blanc C, Denis A, Caby F, Schneider L, Valantin MA, Tubiana R, Kirstetter M, Valdenassi E, Peytavin G, Calvez V, Marcelin AG, editor Dolutegravir monotherapy in HIV-infected patients with suppressed HIV viremia. 15th European AIDS Conference; 2015 October 21-24, 2015; Barcelona.
19. Bruner KM, Hosmane NN, Siliciano RF. Towards an HIV-1 cure: measuring the latent reservoir. Trends Microbiol. 2015;23(4):192-203.
20. Lewis J, Walker AS, Castro H, De Rossi A, Gibb DM, Giaquinto C, et al. Age and CD4 count at initiation of antiretroviral therapy in HIV-infected children: effects on long-term T-cell reconstitution. J Infect Dis. 2012;205(4):548-56.
21. Klein N, Sefe D, Mosconi I, Zanchetta M, Castro H, Jacobsen M, et al. The immunological and virological consequences of planned treatment interruptions in children with HIV infection. PloS one. 2013;8(10):e76582.
22. The BREATHER (PENTA 16) Trial Group. Weekends-off efavirenz-based antiretroviral therapy in HIV-infected children, adolescents, and young adults (BREATHER): a randomised, open-label, non-inferiority, phase 2/3 trial. Lancet HIV. 2016;3(9):e421-30.
23. Gall A, Ferns B, Morris C, Watson S, Cotten M, Robinson M, et al. Universal amplification, next-generation sequencing, and assembly of HIV-1 genomes. J Clin Microbiol. 2012;50(12):3838-44.
24. Hunt M, Gall A, Ong SH, Brener J, Ferns B, Goulder P, et al. IVA: accurate de novo assembly of RNA virus genomes. Bioinformatics. 2015;31(14):2374-6.
25. Vandergeeten C, Fromentin R, Merlini E, Lawani MB, DaFonseca S, Bakeman W, et al. Cross-clade ultrasensitive PCR-based assays to measure HIV persistence in large-cohort studies. J Virol. 2014;88(21):12385-96.

26. Fonager J, Larsson JT, Hussing C, Engsig FN, Nielsen C, Fischer TK. Identification of minority resistance mutations in the HIV-1 integrase coding region using next generation sequencing. J Clin Virol. 2015;73:95-100.

31 APPENDIX XIII WEIGHT BAND PHARMACOKINETIC SUBSTUDIES (WB-PK) 1 & 2

WB-PK1: Pharmacokinetics of dolutegravir in children weighing 3 to <25kg

WB-PK2: A crossover pharmacokinetics substudy of dolutegravir in children weighing 25 to <40kg with switch to DTG 50mg QD

INTRODUCTION AND RATIONALE

Dolutegravir (DTG) is recommended as an alternative to EFV 600mg third drug (to be combined with 2 NRTIs) for first-line ART in adults and adolescents in the WHO 2016 guidelines. Once DTG becomes widely available from generic companies, the regimen is expected to be quickly adopted by most countries, for first-line and second-line therapy (1,2). To make DTG-based regimens available for children data on dosing according to WHO weight bands using formulations produced by generic companies are required. DTG is currently licensed in the EU for children weighing ≥15kg and in the US for children weighing ≥30kg based on the results of the ongoing dose-finding study, IMPAACT P1093 (3).

While IMPAACT P1093 is ongoing, ODYSSEY provides an opportunity to complement their results by studying the dosing in children according to WHO weight bands, and in children weighing ≥25kg, to align DTG dose with ABC/3TC fixed dose combination (FDC). The adult FDC of DTG/ABC/3TC (Triumeq, 50/600/300mg) is licensed by EMA for adults and adolescents weighing ≥40kg, whereas adult ABC/3TC (600/300mg) is licensed by FDA/EMA for children weighing ≥25kg.

The plan for these DTG pharmacokinetic (PK) substudies are endorsed by the WHO Paediatric Antiretrovirals Working Group (PAWG), which includes representatives from WHO, FDA and EMA as well as the ODYSSEY and P1093 teams. The dosing and safety data from these substudies will enable the use of formulations that are planned for manufacturing by generic companies.

Children in weight band PK substudies will be dosed with the DTG 5mg dispersible tablets (DT) or DTG 25mg, 50mg film-coated tablets. The film-coated pediatric-strength 25mg tablet and 50mg tablets are known to have comparable bioavailability. The DTG 5mg dispersible tablets have higher bioavailability than the film coated tablets, with the (dose-normalized) AUC(0-inf) estimated to be 1.6- to 1.8-fold higher than that of the 50mg tablets (4,5).

Children weighing 3 to <25kg

The P1093 team is studying DT, which readily disperse in 2-5 mL of water or can be taken direct to mouth. The P1093 team conducts intensive PK analyses in 10 children and sparse PK in 12 children in age-groups of 4 weeks to 6 months, 6 months to 2 years and 2 to 6 years using 5mg DT.

In discussion with the P1093 team during the WHO PAWG meetings, it was agreed that ODYSSEY will provide complementary PK data for corresponding WHO weight bands.

AIM OF WB-PK1 AND WB-PK2 SUBSTUDIES

To assess the pharmacokinetics, safety and tolerability of DTG in children 3-<40kg using simplified formulations and WHO weight band-aligned dosing.

OBJECTIVES

1) To provide PK data, for children in the first three WHO weight bands (Lower WB-PK1, ongoing)
2) To provide PK data with DTG film-coated 25mg tablets in children 14-<25kg (WB-PK1, part I, completed)
3) To provide PK data in children 14-<20kg on DTG administered as dispersible tablets and in children 20-<25kg on DTG administered as dispersible tablets or film-coated 50mg tablets QD (WB_PK1 part II, completed)
4) To provide PK data with DTG 50mg in children 25-<40kg (WB-PK2, completed)
5) To provide safety data for new dosing

METHODS

Study Design:

Children from ODYSSEY A or B will be enrolled into PK substudies across 7 weight bands with the aim to have 8 children per weight band with evaluable PK data on the investigated dose.

WB-PK1 substudy: Children randomised to DTG in weight bands 3-<6kg, 6-<10kg, 10-<14kg, 14-<20kg and 20-<25kg will have a 24h PK curve after at least one week of dolutegravir treatment. WB-PK1 part I investigated DTG PK exposures in children 14-<20kg and 20-<25kg on once daily DTG 25mg FCT (the study is completed). Lower WB-PK (ongoing) and WB-PK1 part II (completed) investigate DTG PK parameters in children 3-<25kg using dispersible DTG formulations, and in children 20-<25kg using DTG 50mg FCT.

WB-crossover-PK2 substudy: Children weighing 25-<40kg taking DTG according to the previous version of the protocol (25mg for 25-<30kg and 35mg in 30-<40kg) have two 24h PK curves performed: the first curve at least one week after taking their pre-switch dose and the second curve at least one week after the switch to a 50mg tablet (the study is completed).

The plasma concentrations for DTG are assayed at the department of Pharmacy of the Radboud University Medical Center in Nijmegen, the Netherlands. The samples are shipped to the Netherlands in batches. A quick turnaround data analysis of PK parameters enables review of PK and short-term safety results by ODYSSEY and ViiV experts and the IDMC.

Inclusion criteria:

Children should meet the inclusion criteria for the main trial (ODYSSEY A or ODYSSEY B) AND be randomised to DTG, AND meet the following additional inclusion criteria for the WB-PK substudies:

- Weight 3-<25kg for WB-PK1 substudies
  - Weight 3-<14kg for Lower WB-PK1 substudy (ongoing)
  - Weight 14-<25kg for WB-PK1 part I substudy and part II substudy (completed)
- Weight 25-<40kg for WB-PK2 substudy (completed)
- Parents/carers and children, where applicable, give informed written consent

Exclusion criteria:

In addition to the exclusion criteria for the main trial:

- Children who suffer from illnesses that could influence drug pharmacokinetics, i.e. severe diarrhoea, vomiting, renal disease or liver disease

- Children treated with concomitant medications known to have interactions with dolutegravir
- Children with current acute severe malnutrition

Number of Patients: We aim to enroll at least 8 children per weight band with evaluable PK curves on the investigated doses. If we see large differences within a weight band for a dose/formulation we will consider recruiting additional children in the relevant weight-band. Further PK study with different DTG doses may be required if the main PK parameters ($AUC_{0\text{-}24h,}$ C_{trough} or C_{max}) are substantially different compared to adults on DTG 50mg QD.

Clinical Sites: The PK substudies are undertaken at clinical sites in Uganda (JCRC Kampala, JCRC Mbarara and Baylor), South Africa (PHRU Soweto, PHRU Klerksdorp and Durban International Clinical Research Site) and Zimbabwe (UZCRC Harare).

Clinical Procedures: Eligible children for the PK substudies are admitted to the PK unit in the morning after an overnight fast. Medication adherence during the last 3 days prior to the PK day is ascertained ensuring that none of the doses were missed. PK blood samples are taken via an i.v. cannula. For each 24 h curve, blood samples are taken at t=0 (prior to DTG dose), and at t= 1, 2, 3, 4, 6 and 24h after the dose. Standardised meals are served during the PK day at pre-specified time points. Total blood volume for PK samples during a 24-hour PK day is approximately 6-20 ml for all children across 7 different weight bands between 3kg and ≤40kg and is within the limits of maximum allowable total blood draw volumes over 24 hours for children (see Appendix XI). The details are outlined in the MOP.

Safety Assessments: Children in the PK substudies are reviewed at 2, 4 and 12 weeks after starting on DTG or changing to the higher dose. Where scheduled visits for the main protocol do not coincide children should attend for additional visits. The safety assessments at these visits include: clinical assessment, collection of bloods to assess haematology and biochemistry safety parameters and acceptability and sleep questionnaires. Additional safety blood tests or investigations may be performed if clinically indicated to investigate symptoms or monitor emergent laboratory test abnormalities. Adverse events (as at standard follow-up visits) should be reported on the case report form. Adverse events (clinical and laboratory) should be graded using the 2014 Division of AIDS toxicity grading tables (see Appendix IX). Notable events (pregnancy, liver toxicity meeting DTG stopping criteria, ABC hypersensitivity reactions and possible suicidality-related adverse events), grade 3 and 4 clinical and laboratory events, and all events resulting in change of ART, should be reported on the main trial Event Form, including relationship with DTG or other antiretrovirals. Serious adverse events, defined according to ICH GCP, and notable events (pregnancy, liver toxicity meeting DTG stopping criteria, ABC hypersensitivity reactions and possible suicidality-related adverse events) should be reported to the CTU within 24 hours of the sites being aware.

Design Overview and Dose Rationale: WB-PK 1 substudy investigates PK of DTG in children 3-<25kg. It has four components:

- Lower WB-PK: PK of DTG in children in the three lower WHO weight bands 3-<6kg, 6-<10kg and 10-<14kg using DTG dispersible tablets QD
- WB-PK1 part I: PK of DTG in children 14-<20kg and 20-<25kg using DTG film-coated tablets at 25mg QD

- WB-PK1 part II: PK of DTG administered as dispersible tablets in children 14-<20kg and 20-<25kg QD or film-coated 50mg tablets QD in children 20-<25kg

The doses in these substudies provide a range from 0.8 to 3.6mg/kg/day (tables 8a – 8c). DTG doses up to 2mg/kg were shown to be safe in adults (see below). Infants ≥6 months old at the lower end of the first two weight bands on dispersible tablets and children in the 14-<20kg and 20-<25kg weight bands on DTG 50mg FCT receive DTG dose of >2mg/kg but for a limited time as they gain weight rapidly.

WB-PK1 part I investigated DTG 25mg film-coated tablet in children 14-<25kg. This substudy is completed. The results showed that DTG 25mg QD given as FCT to children 14-<20kg and 20-<25kg (table 8a) produced lower DTG C_{trough} and $AUC_{0\text{-}24h}$ compared to fasted adults on DTG 50mg QD (6).

Table 8a: Dolutegravir dosing in WB-PK1 part I substudy (completed)

WHO Wt bands, kg	Administered DTG once daily (formulations and daily dose, mg)		DTG dose, mg/kg
	5mg dispersible tablet	25mg tablet	
14-<20		1 (25mg)	1.25-1.8
20-<25		1 (25mg)	1.0-1.25

WB-PK1 part II substudy (table 8b) investigate higher doses for the 14-<20kg and 20-<25kg to match the PK parameters in adults. The preliminary results showed that both DTG 30mg DT and 50mg FCT in children 20-<25kg produced GM C_{trough} comparable to values in adults on DTG 50mg QD and GM $AUC_{0\text{-}24h}$ in between reference values in adults on DTG 50mg QD and BID doses. GM C_{max} on both doses exceeded adult GM reference values on DTG 50mg QD and BID. Ongoing safety monitoring is reassuring. The results will be presented at CROI 2019 (late-breaker abstract accepted [44]).
Lower WB-PK1 substudy assesses the doses for the three lowest weight bands (3-<14kg) using dispersible tablets based on preliminary results of P1093 (table 8b). The study is ongoing.

Table 8b: Dolutegravir dosing in Lower WB-PK1 and WB-PK1 part II substudies

WHO Wt bands, kg	Administered DTG once daily (formulations and daily dose, mg)		DTG dose, mg/kg
	5mg dispersible tablet	50mg tablet	
3-<6ψ	1 (5mg) / 2 (10mg)*		0.8-1.7 / 1.7-3.3
6-<10	3 (15mg)*		1.5-2.5
10-<14	4 (20mg)*		1.4-2.0
14-<20	5 (25mg)		1.25-1.8
20-<25	6 (30mg)§	1 (50mg)§	1.2-2.5

ψ. Infants <6 months of age will receive DTG 5mg QD while infants ≥6 months of age will receive DTG 10mg QD, both as dispersible tablets.
*Dose may be modified based on data from the ongoing P1093 study and the data from this study.
§ Children 20-<25kg will receive either DTG 30mg QD (six 5mg dispersible tablets) or DTG 50mg QD (one 50mg film-coated tablet) depending on site. Participants at UZCRC (Zimbabwe), Baylor (Uganda) and PHRU sites in Soweto and Matlosana (South Africa) will receive dispersible DTG 30mg whilst those at JCRC sites in Lubowa and Mbarara (Uganda) and Durban International Clinical Research Centre (South Africa) will receive film-coated DTG 50mg.

Based on population PK modelling and the available results from P1093 and the ODYSSEY WB-PK1 substudies, the proposed DTG doses are predicted to result in GM C_{trough} values that exceed antiviral target concentrations across all weight bands. The predicted GM C_{trough} and AUC_{0-24h} exposures for children are expected to be in between values observed in adults receiving 50mg QD and BID used in the SPRING-1 and VIKING studies respectively (7-9). However, given the greater PK variability in children, wide confidence intervals are expected and paediatric exposures on the upper limit of the confidence interval are expected to exceed those observed in adults. In the 3-<6kg weight band we aim to provide some PK data on the 10mg DT which could align with future FDCs. Following discussions with ViiV we will initially use a lower dose in the youngest children (<6 months) where exposures may be highest. Depending on the results further PK substudies evaluating different DTG doses and formulations may be required to achieve optimal and pragmatic dosing in children.

Children weighing 25 to <40kg

For children aged 6-<12 years, initially two doses aligning with P1093 were taken forward for use in ODYSSEY (protocol version 2.0): 25mg for children 25-<30kg, and 35mg for children 30-<40kg. However, issues with this dosing pose some challenges for wide implementation of DTG-based regimens for children ≥25kg:

- For a WHO weight band 25-<35kg, two different doses of 25mg and 35mg are used which is impractical for implementation in countries using WHO weight bands.
- Generic companies produce scored 50mg tablets and 5 mg tablets, therefore the dose of 35mg can only be made with separate 5mg tablets (7 tablets) or with half of one 50mg tablet plus two 5mg tablets. Both options will be inconvenient for families and difficult for programs.
- In addition the ABC/3TC fixed dose formulation is licensed at the adult dose (600/300mg QD) in children ≥25kg, while the ABC/3TC/DTG co-formulated combination (Triumeq) is licensed in children ≥40kg. To align paediatric and adult treatment regimens it would be useful if Triumeq could be given to children ≥25kg. This would mean that children in this weight band receive a DTG dose of 1.25-2 mg/kg/day which is similar to the daily dose currently recommended in treatment-experienced adults i.e. 50mg BID (100mg/day). Adult studies reported that QD and BID administration had similar tolerability and toxicity (7, 10-13).

The weight band crossover PK2 substudy (WB-PK2) was set up to investigate PK of DTG in children weighing 25-<40kg on the currently used doses (25mg for 25-<30kg, and 35mg for 30-<40kg) and after a switch to DTG 50mg. The initial doses provided a range from 0.8 to 1.17mg/kg/day; after the switch the dose ranged from 1.25 to 2mg/kg/day. The cross-over study design took advantage of the fact that ODYSSEY was already open in the 25-<40kg weight band and allowed within-participant comparisons of PK parameters between licensed doses and new proposed doses of DTG.

The results presented at the 10th International Workshop on HIV Pediatrics in Amsterdam, showed that the new dose of DTG 50mg QD provided DTG C_{trough} and AUC exposures comparable to fasted adults on DTG 50mg QD and C_{max} has not exceeded C_{max} in adults on DTG 50mg BID (14). The dose was seen to be safe and acceptable for children within the 25-<40kg weight bands. Following this, children in the main trial weighing 25-<40kg were switched to DTG 50mg QD as per previous version of the protocol.

Sparse PK sampling will be done in a subset of children on stored plasma samples collected in the main trial to correlate with long term tolerability data (See Trial Assessment Schedule). Retrospective data on viral loads will enable PK/PD analyses.

STATISTICAL ANALYSIS PLAN

Review of tolerability and toxicity data: The PK results and clinical and laboratory events will be reviewed by ODYSSEY and ViiV experts and the IDMC.

- Drug levels (particularly C_{max}) are anticipated to be higher than BID adult drug levels and levels in children treated with lower doses. It is therefore important to monitor tolerability and toxicity, particularly in the first month on treatment. Adverse events and treatment discontinuations will be described in detail and summarised using descriptive statistics. Comparisons will be made with data from P1093, ODYSSEY data (outside of the substudies) and adult studies (Table 9) using descriptive statistics with attention to weight and time on treatment.
- All available clinical and laboratory safety data and PK data will be reviewed by the IDMC who, if there are concerns in any of the weight bands, may recommend to the TSC to extend follow up of children in specified weight bands enrolled to the PK substudies or to recruit additional children in the weight band before decisions for dosing in the main trial are made. The IDMC will continue reviewing safety data during the duration of the randomised phase of the trial.

Table 9: Pharmacokinetic parameters for dolutegravir in literature

Studies	$AUC_{0\text{-}tau}$ (h*mg/L)	$AUC_{0\text{-}24}$ (h*mg/L)	C_{max} (mg/L	T_{max} (h)	$T_{1/2}$ (h)	C_{trough}/ C_{12h}/C_{24h} (mg/L)	C_0 (mg/L)	Reference
Adults DTG 50 mg QD (fasted, DTG monotherapy, n=10)		43.4 (20)	3.34 (16)	2.00 (0.97-4.0)	12.0 (22)	0.83 (26)		Min 2011 (12)
Adults DTG 50 mg QD (SPRING-1, n=15)	48.1 (40)		3.40 (27)			1.20 (62)		Van Lunzen 2013 (10)
Adults DTG BID 50 mg (VIKING-3, n=180)		93.4 (50)	5.41 (40)	2.00 (0-7.87)		2.72 (70)	3.20 (69)	VIKING (ING112961) (8)
Healthy adults DTG 50 mg BID (fasted, n=12)	46.3 (55)	92.7 (55)	5.55 (49)		9.5 (48)	2.41 (77)		Dooley 2013(13)
12-<18 year olds DTG 50 mg QD (n=10)		43.1 (46)	3.48 (38)	3.00 (1.0-6.0)	11.9 (43)	0.90 (59)		Viani et al, 2015 (15)
6-<12 year olds, DTG 25mg in 20-<30kg (n=4), DTG 35mg in 30-<40kg (n=2) and DTG 25-50mg QD in >40kg(n=5)		50.5 (63)				0.92 (89)		Viani et al, 2014 (16)
2-<6 year olds DTG ~0.8mg/kg DTG QD (granules) (n=10)		44.4 (36)				0.51 (68)		Ruel 2017 (17)

Table entries are geometric mean (CV%) and for T_{max} median (range)

Analysis of PK data: Pharmacokinetic parameters ($AUC_{0\text{-}24}$, Vd, CL, $t_{1/2}$) will be calculated using WinNonlin/Phoenix (Pharsight Corporation, CA, USA). C_{max}, T_{max} and C_{min} will be determined from observed concentration time data. Geometric Mean and 95% confidence intervals will be estimated for pharmacokinetic parameters of DTG (except for T_{max}). Descriptive statistics for the plasma concentrations of DTG will be evaluated.

In WB-PK2, current DTG dose (25mg or 35 mg) and 50mg DTG will be compared in all children with two evaluable PK curves. Within-patient ratios of $AUC_{0\text{-}24}$, C_{max} and C_{min} for current dose versus 50mg DTG will be calculated. Overall GMRs (geometric mean ratios) for current dose versus 50mg 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.

SUBSEQUENT DOSING IN THE MAIN TRIAL

Based on available PK and safety data from P1093 and the ODYSSEY WB-PK substudies, doses in the main ODYSSEY trial for children 3-<14kg are being reviewed and, if necessary, modified (with further

PK and safety data if required) leading to a decision on the appropriate DTG dose for children in these weight bands. (Appendix XIX).

References:

1. Third Conference on Antiretroviral Drug Optimization (CADO III). Johannesburg, SA, Nov 29-Dec 1, 2017
2. WHO. Paediatric Antiretroviral Drug Optimization (PADO) Meeting 3. 6-7 December 2016. WHO. Available from: http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado3/en/index7.html.
3. NCT01302847. Safety of and immune response to dolutegravir in HIV-1 infected infants, children, and adolescents (IMPAACT P1093) [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT01302847.
4. Patel P, Song I, Borland J, et al. Relative bioavailability of a paediatric granule formulation of the HIV integrase inhibitor dolutegravir in healthy adult subjects. Antivir Ther. 2014;19(3):229-33.
5. Buchanan AM, Holton M, Conn I, Davies M, Choukour M, Wynne BR. Relative Bioavailability of a Dolutegravir Dispersible Tablet and the Effects of Low- and High-Mineral-Content Water on the Tablet in Healthy Adults. Clin Pharmacol Drug Dev. 2017 Nov;6(6):577-583.
6. Bollen PDJ, Turkova A, Mujuru H, Musiime V, Amuge P, Lugemwa A, Colbers A, J Spyer MJ, Lensen S, Moore CL, Hakim J, Kity C, Bbuye D, Atwine L, Giaquinto C, Ford D, Gibb DM, Burger DM, and the ODYSSEY trial team. Steady-state pharmacokinetics and early safety data in HIV-infected African children weighing 14 to <25kg on film-coated dolutegravir 25mg tablets in the ODYSSEY trial. 10th International Workshop on HIV Pediatrics, Amsterdam, the Netherlands, 20-21 July 2018, abstract 22
7. Eron JJ, Clotet B, Durant J, et al. Safety and efficacy of dolutegravir in treatment-experienced subjects with raltegravir-resistant HIV type 1 infection: 24-week results of the VIKING Study. J Infect Dis. 2013 Mar 1;207(5):740-8.
8. Castagna A, Maggiolo F, Penco G, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. J Infect Dis. 2014 Aug 1;210(3):354-62.
9. Akil B, Blick G, Hagins DP, et al. Dolutegravir versus placebo in subjects harbouring HIV-1 with integrase inhibitor resistance associated substitutions: 48-week results from VIKING-4, a randomized study. Antivir Ther. 2015;20(3):343-8.
10. van Lunzen J, Maggiolo F, Arribas JR, Rakhmanova A, Yeni P, Young B, et al. Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial. The Lancet infectious diseases. 2012;12(2):111-8.
11. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013 Nov;13(11):927-35.
12. Min S, Sloan L, DeJesus E, Hawkins T, McCurdy L, Song I, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of dolutegravir as 10-day monotherapy in HIV-1-infected adults. AIDS. 2011;25(14):1737-45.
13. Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013;62(1):21-7.
14. Turkova A, Bollen PDJ, Kaudha E, Chidziva E, Lugemwa A, Kekitiinwa A, Parker A, Shakeshaft C, Montero S, Colbers A, Nanduudu A, Mujuru H, Makumbi S, Amuge P, Rojo P, Ford D, Burger DM, Gibb DM, and the ODYSSEY trial team. Steady-state pharmacokinetics and early safety

data in HIV-infected African children weighing ≥25kg after switching to 50mg film-coated dolutegravir tablets in the ODYSSEY trial. 10th International Workshop on HIV Pediatrics, Amsterdam, the Netherlands, 20-21 July 2018, abstract 03

15. Viani RM, Alvero C, Fenton T, Acosta EP, Hazra R, Townley E, et al. Safety, Pharmacokinetics and Efficacy of Dolutegravir in Treatment-experienced HIV-1 Infected Adolescents: Forty-eight-week Results from IMPAACT P1093. The Pediatric infectious disease journal. 2015;34(11):1207-13.
16. Viani R. IMPAACT 1093: Safety Pharmacokinetics and Efficacy of Dolutegravir in Treatment Experienced HIV + Children. P901. CROI 2014
17. Ruel T. Dolutegravir pharmacokinetics, safety and efficacy in HIV+ children 2 to < 6 years old. P806. CROI 2017.

32 APPENDIX XIV PHARMACOKINETIC SUBSTUDY IN PARTICIPANTS RECEIVING RIFAMPICIN AS PART OF ANTI-TB TREATMENT OR TB PREVENTION THERAPY WHILE ON DTG:

TB-PK substudy: pharmacokinetics of dolutegravir co-administered with rifampicin

INTRODUCTION AND RATIONALE

Rifampicin significantly lowers dolutegravir 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 dolutegravir. It has been shown in HIV-infected and uninfected adults receiving rifampicin that increasing dolutegravir dose to 50mg BID results in a similar exposure compared with dolutegravir 50mg QD without rifampicin (1,2). A recent study showed DTG was effective and well-tolerated in HIV/TB co-infected adults receiving rifampicin-based TB treatment (2). Furthermore, in adults with resistant HIV, who received dolutegravir 50mg BID without rifampicin, there was no added toxicity (3). Based on the above, we expect that the exposure to dolutegravir in children with their daily dose doubled (per protocol dose given BID) while on rifampicin will be comparable to QD dosing without rifampicin and with no additional safety problems. The dolutegravir dose will need to remain BID 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

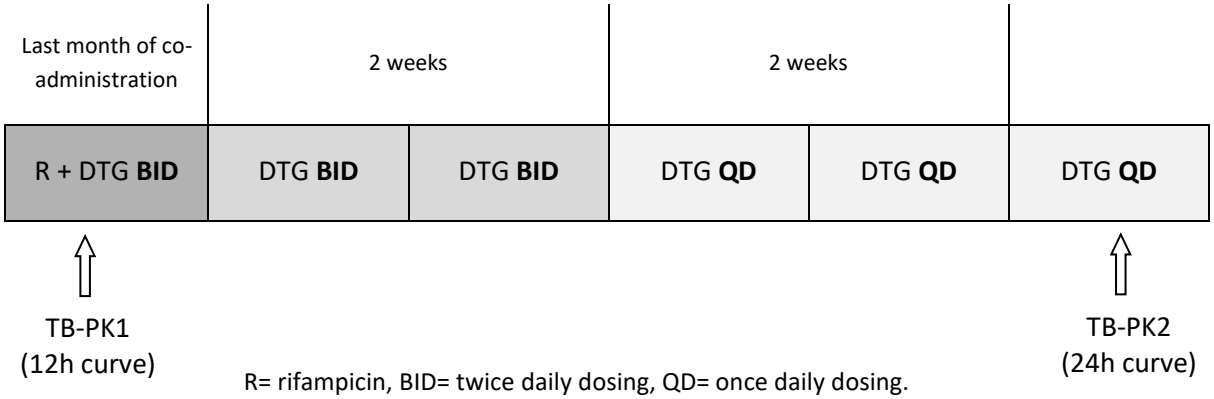
To estimate the impact of rifampicin on dolutegravir plasma concentrations in children.

METHODS

Study Design:

The PK substudy is set up in a crossover design in order to estimate the impact of rifampicin on the plasma pharmacokinetics of dolutegravir within a child. A first 12h PK curve of dolutegravir 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 TB treatment completion, dolutegravir BID dosing will be continued for another 2 weeks and then reduced to QD. At least 2 weeks after resuming QD dosing of dolutegravir a 'steady-state' for dolutegravir will be reached and a second PK-curve (TB-PK2) will be recorded in the same child (Figure 1).

Figure 1. Dolutegravir dosing and timing of TB- PK1 and TB-PK2



The plasma concentrations for dolutegravir and rifampicin will be assayed at the department of Clinical Pharmacy of the Radboud University Medical Center in Nijmegen, The Netherlands.

Inclusion criteria:
Children should meet the inclusion criteria for the main trial (ODYSSEY A or ODYSSEY B) AND:

- Receive DTG as part of their ART
- Receive rifampicin as part of anti-TB treatment or TB prevention therapy
- Parents/carers and children, where applicable, give informed written consent

Exclusion Criteria:
In addition to the exclusion criteria for the main trial:

- Illnesses that could influence drug pharmacokinetics, i.e. severe diarrhoea, vomiting, renal disease or liver disease
- Concomitant medications known to have interactions with dolutegravir
- Acute severe malnutrition at the time of PK days

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

Number of Patients: 12 children (6 children aged ≥ 6 to <12 years old and 6 children aged 12 to <18 years old) will be included in this PK substudy in order to achieve 10 evaluable subjects. The sample size calculation is outlined elsewhere (1). This number may need to be increased if intersubject variability of dolutegravir PK parameters in children appears to be larger than the 33% reported in non HIV-infected adults or if less than 2 children per WHO weight band have evaluable PK data. In addition, younger children <6 years on DTG-based ART who are diagnosed with TB or TB infection and treated with rifampicin-containing regimen will be recruited, however small numbers are expected at the PK sites.

Clinical Sites: The PK substudies will be undertaken at clinical sites in Uganda, South Africa, and Zimbabwe

Clinical Procedures: Eligible children for the PK substudies will be admitted to the PK unit in the morning after an overnight fast. Medication adherence during the last 3 days prior to the PK day will be confirmed ensuring that none of the doses were missed. Dolutegravir and rifampicin will be given at the same time. PK blood samples will be taken via an i.v. cannula. Dolutegravir concentrations will be measured at t=0 (prior to the dose), and at t= 1, 2, 3, 4, 6, 12 or 24h (after the dose). Rifampicin concentrations will be measured at t=0, 2, 4, and 6h for children weighing ≥6kg. For children weighing 3-<6kg only one rifampicin PK sample at t=2hr will be taken, the time points for DTG samples remain the same. Standardized meals will be served during the PK day at pre-specified time points. Total blood volume drawn for each PK curve will be between 6 to 25 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 XI). The procedure details will be outlined in the MOP.

Safety Assessments: As per the main trial protocol. The clinical examination 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 per the main Trial Assessment Schedule. Additional safety blood tests or investigations may be performed as guided by clinical decision to investigate symptoms or monitor emergent laboratory test abnormalities as clinically indicated. Adverse events will be reported on the case report form. Adverse events (clinical and laboratory) will be graded using the 2014 Division of AIDS toxicity grading tables (see Appendix IX). Grade 3 and 4 clinical and laboratory events, and all events resulting in change of ART, will be reported on the main trial CRFs and relationship with medications, the child is taking at the time, will be evaluated. Serious adverse events, defined according to ICH GCP, and notable events (pregnancy, liver toxicity meeting DTG stopping criteria, ABC hypersensitivity reactions and possible suicidality-related adverse events) will be reported to the CTU within 24 hours of the sites being aware.

STATISTICAL ANALYSIS PLAN

Pharmacokinetic parameters ($AUC_{0\text{-}tau}$, $AUC_{0\text{-}24}$, Vd, CL, $t_{1/2}$) will be calculated using WinNonlin/Phoenix (Pharsight Corporation, CA, USA). 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 dolutegravir at TB PK1 and TB PK2and rifampicin at TB PK1. The results will be compared to the published adult data (1).

BID DTG (with RIF) and QD DTG will be compared in all children with two evaluable PK curves. Within-patient ratios of $AUC_{0\text{-}24}$, C_{max} and C_{min} for BID DTG (with RIF) versus QD DTG will be calculated. Overall GMRs (geometric mean ratios) for BID DTG versus QD 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.

Descriptive statistics (mean (SD) and median (IQR) for the plasma concentrations of DTG and RIF will also be evaluated.

References:

1. Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013;62(1):21-7.
2. Dooley K, Kaplan R, Mwelase T, Grinsztejn B, Ticona E, Lacerda M, et al. Safety and efficacy of dolutegravir-based ART in TB/HIV co-infected adults at week 48. 22nd International AIDS Conference, Amsterdam, the Netherlands, 23-27 July 2018, abstract TUAB0206.
3. Castagna A, Maggiolo F, Penco G, Wright D, Mills A, Grossberg R, et al. Dolutegravir in antiretroviral-experienced patients with raltegravir- and/or elvitegravir-resistant HIV-1: 24-week results of the phase III VIKING-3 study. J Infect Dis. 2014;210(3):354-62.

33 APPENDIX XV QUALITATIVE SUBSTUDY

Optimising adherence to HIV treatment

RATIONALE

It is known that adherence to chronic illness treatment drops off in adolescence and unfortunately HIV is no exception (1). Consequently, a primary reason that a young person may need to be moved onto second-line treatment is because they have failed first line treatment due to adherence problems. Our previous research has shown that adherence problems in this population are predominately caused by social and relational challenges and rarely due to a lack of knowledge about the need to take ART (2, 3).

Three key issues are associated with initiation of the second-line ART in young people. Firstly, the increased risk of mortality due to therapeutic and virological failure. Secondly, the socially complex reasons behind problematic ART adherence in HIV paediatric populations in general (2-6). Thirdly, the awareness that second-line ART has long been used as a deterrent, or threat, to enforce adherence to first line treatment in young people which may not be helpful (5). Children and young people reported being told by clinic staff and their carers about how much harder second-line treatment would be to take, for example because of the pill burden, size of pills and side effects, and that they have no further therapeutic alternative(2). Hence, whilst existing challenges to adherence are unlikely to have resolved for those young people moving on to second-line treatment, they might also be dealing with potentially more challenging second-line regimens and the awareness that these are, effectively, their 'last option'.

The intervention arms of ODYSSEY involve participants being put onto dolutegravir. There has been a recent WHO alert raising concerns about the possible risks of taking dolutegravir during pregnancy for increased chances giving birth to a baby with spinal bifida. The trial sites are conducting specialised counselling to advise participants in the intervention arm about this recent alert about Doluegravir. This will involve clinic staff explaining the nature of the risks and counselling female participants who may be sexually active to take contraception.

AIMS

1. To explore how moving onto second-line treatment affects young people's treatment engagement and identify how best to support them to maintain optimal treatment adherence.
2. To explore young people and their caregivers' understanding of the dolutegravir (DTG) alert and their sexual and reproductive health (SRH) needs within the context of the ODYSSEY trial.

OBJECTIVES

1. To understand the experiences of young people moving onto second-line ART, including the acceptability and effects of an altered pill burden and other treatment changes where applicable.
2. To explore their capacity and engagement in adhering to their second-line treatment and whether and how this changes over time, including whether this differs across both arms in ODYSSEY B.

3. To conduct anonymised, comparative analysis with trial data on self-reported adherence in order to triangulate results and contribute to improving questionnaire measurements for data collected in the trial.
4. To consider what narratives circulate around second-line treatment and what effect this has on young people's perceptions of their health and well-being in the present and the future.
5. To identify what support is needed and can be put in place to strengthen young people's ability to maintain optimal adherence to second-line treatment.
6. To assess trial participants' understandings of the DTG alert and explore the impact of related discussions on their understanding of the trial and SRH.
7. To describe the attitudes of caregivers to supporting the needs of adolescents living with HIV, in particular in relation to trial participation, adherence as well as sexual and reproductive health information.

METHODS

This is a 36 month qualitative study conducted in two trial sites, at JCRC in Uganda and at the University of Zimbabwe, Harare in Zimbabwe, employing longitudinal qualitative methods.
In each site we will conduct:
1) 2 in-depth individual interviews – at approximately 3 and 12 months after initiation onto second-line treatment
2) a series of focus group discussions with trial participants at different stages of the trial
3) consultations with a Youth Trial Board currently being set up in participating countries (through a separately ViiV-funded project) to develop our dissemination materials.
4) in-depth interviews with trial participants to explore the influence of discussions around the DTG alert.
5) in-depth interviews with caregivers of trial participants

Inclusion criteria for in-depth interviews and focus group with young people:

- Participants enrolled in ODYSSEY trial
- Age 10-19 years
- Participants have known about their HIV status for a minimum of six months before participating in the qualitative study

Inclusion criteria for in-depth interviews with caregivers:

- Caregiver of young person enrolled in the ODYSSEY trial and qualitative study
- The young person has given consent for their caregiver to be approached to participate.

Number of Patients: Up to 60 participants will be included in the study in total. A sample size of 60 participants is appropriate to explore specific qualitative questions in the two sites identified for the qualitative substudy. We will adopt a purposive sampling approach to identify and recruit up to 30 participants in each site. Participants will be invited from both the intervention and standard of care arms across the ODYSSEY trial. We will obtain separate assents/consents (together with caregiver consents for participants aged under 18 years old) for this research. There is a patient information sheet, informed consent form and assent form for the in-depth interviews and a separate set of

information and consent/assent forms for the focus groups. Additional consent will be collected for the third round of interviews.

Number of Caregivers: In addition, up to 30 caregivers (15/site) will be recruited to participate in individual in-depth interviews to explore their experience of supporting a young person living with HIV, as well as their attitudes to trial participation and SRH informational needs of young people living with HIV. Young people already participating in the qualitative study will be asked if they are comfortable with their caregivers being invited to participate in the qualitative study. A purposive sampling approach will be adopted to identify potential caregivers to be included within the trial, reflecting key sampling dimensions of interest. Subject to the young person's agreement, their caregivers will then be invited to participate.

Data collection:
Individual interviews:
Baseline interviews will be conducted approximately three months from starting second-line therapy; participants will be interviewed individually. This interview will be organised within the early stages of their initiation into the trial and will particularly explore their expectations and early experiences of second-line treatment and their reported adherence behaviour.
The second individual interview will be conducted with the same participants, approximately nine months after the first interview, to explore how they are adapting to and managing their second-line treatment.

A third round of interviews (maximum of 20 per site) will be conducted with a purposively selected sample to explore the influence of DTG-alert related conversations on their understanding, experiences of and attitudes towards trial participation, the DTG risk and more broadly sexual and reproductive health. Participants taking part in these DTG-related interviews will be selected from within the existing qualitative sample (this will be done as third interview) and others from within the trial population (their first interview). The sample will be selected to ensure maximum representativeness of the trial population. Key sampling characteristics will be gender (both male and female will be involved); age; and trial arm.

A maximum of 15 caregiver interviews per site will be conducted to better understand the attitudes towards and experiences in supporting the needs of adolescents living with HIV, in particular in relation to trial participation and treatment adherence. In these interviews we will also ask caregivers about their experiences of supporting adolescents growing up with HIV and their opinions towards the provision of sexual and reproductive health information to adolescents living with HIV.

***Focus group discussions*:**
Two sets of focus group discussions will be held with groups of young people and will include subsamples of those who have participated in the interview phases and trial participants not yet involved in the qualitative substudy. The group compositions will be decided by the research team who will take into account local considerations around gender, age and whether young people are known to each other.
The first set of focus groups will be held at approximately months 14-18 from trial start, to explore the participant's perspectives on the acceptability and sleep questionnaires completed at the beginning of the trial. There will be 5-8 participants in each focus group and we plan to hold up to 3 focus groups

in each site. The results of these discussions will be fed back to the trial team and clinicians and may inform the design of data collection tools for the remaining duration of the trial, and for future use in trials with paediatric HIV populations.

A final set of focus groups will be held up to approximately 3-6 months after the completion of the final interviews. During these focus groups, we will feedback and discuss our preliminary findings with the young people as well as discuss their experience of DTG related discussions and their attitudes towards their SRH informational needs. This will serve not only as an opportunity to refine and validate our findings from the data collected so far, but also to discuss and plan how we disseminate our findings both to key stakeholders and young people themselves.

Subject to feasibility and timing we will seek the collaboration of the linked ODYSSEY Youth Trial Board in the design, development and dissemination of any youth-targeted materials.

DATA ANALYSIS

All the data will be audio recorded, transcribed verbatim and translated. These transcripts will be checked by the local researchers and the PI/co-investigators, who will discuss each interview with the research team, checking for completeness and emerging themes to be explored in later interviews. Data will be stored securely on the MRC/UVRI/JCRC servers in Uganda and on the CeSHHAR servers in Zimbabwe.

Data analysis will be conducted by the local researchers in collaboration with the PI and co-investigators. A thematic coding framework, informed by the study objectives will be developed after the first interview by the study team, so that emerging findings can inform the thematic coding framework. This framework will be used for coding the study data, with constant comparison across the team to ensure consistency in coding.

The qualitative data, both from the in-depth interviews and the focus group discussions, will be subject to a thematic analysis with coding undertaken accompanied by the iterative development of analytical memos. This will involve comprehensive analysis of the data by case to examine how reported adherence behaviour may change over time and to account for these reported changes. Once the interviews and focus group data have been analysed separately, a comparative analyses of both will be conducted to maximise the benefit of using mixed qualitative methods. The team have considerable experience of collecting and analysing dyad data (from the young person and related caregiver). These dyad data will be analysed together to explore important relational concerns and experience. However, these data will only be presented in dyad form if it can be done in such a way that does not enable deductive disclosure.

In addition, a comparative analysis of the qualitative data and the quantitative adherence data to compare how young people describe their adherence in the qualitative study and how they report it within the trial will be performed, and where appropriate anonymised cases will be examined in more detail.

References:

1. Nachega JB, Hislop M, Nguyen H, Dowdy DW, Chaisson RE, Regensberg L, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. J Acquir Immune Defic Syndr. 2009;51(1):65-71.

2. Kawuma R, Bernays S, Siu G, Rhodes T, Seeley J. 'Children will always be children': exploring perceptions and experiences of HIV-positive children who may not take their treatment and why they may not tell. African journal of AIDS research : AJAR. 2014;13(2):189-95.
3. Bernays S, Paparini S, Gibb D, Seeley J. When information does not suffice: young people living with HIV and communication about ART adherence in the clinic. Vulnerable Child Youth Stud. 2016;11(1):60-8.
4. Bernays S, Jarrett P, Kranzer K, Ferrand RA. Children growing up with HIV infection: the responsibility of success. Lancet. 2014;383(9925):1355-7.
5. Bernays S, Seeley J, Rhodes T, Mupambireyi Z. What am I 'living' with? Growing up with HIV in Uganda and Zimbabwe. Sociology of health & illness. 2015;37(2):270-83.
6. Mupambireyi Z, Bernays S, Bwakura-Dangarembizi M, Cowan FM. "I don't feel shy because I will be among others who are just like me...": The role of support groups for children perinatally infected with HIV in Zimbabwe. Child Youth Serv Rev. 2014;45:106-13.

34 APPENDIX XVI YOUTH TRIAL BOARD PROJECT

A multi-country model of user involvement to engage adolescents living with HIV in the development and delivery of paediatric clinical trials

RATIONALE

Patient participation and involvement in clinical trials and studies has been shown to improve the patient's experience and ensure a better quality of trial or study (1, 2). The inclusion of children and adolescents in these trials needs a higher level of support than their adult counterparts and although this presents particular challenges there is a significant need for effective research to be done with this key group (3, 4). However, children and adolescents growing up with HIV are a group whose voices are often not heard (5). This is due to a number of factors, such as not informing the child about their HIV diagnosis, stigma and fear. Coupled with the continuing challenges in including young people in clinical research in general, this group are commonly not involved in research in a meaningful way. Current provision tends to rely on one young person's inclusion on a trial committee and is often inadequate to ensure young people are genuinely represented. More proactive models of engagement are urgently needed to improve user involvement.

AIM

The aim of this project is to develop a simple low-cost model of meaningful engagement and participation of adolescent patient representatives in paediatric clinical trials and research studies.

OBJECTIVES

1. To conduct a literature review of the available evidence about existing participation models for young people in clinical research to inform the design.
2. To work with young people living with HIV and key stakeholders to design and pilot a user engagement model (participation model) for including young people in development, delivery and dissemination of the ODYSSEY trial.
3. To include practical communication strategies between trialists and young people throughout the process.
4. To ensure the relevance and applicability of the participation model in low and high income settings.
5. Once piloted, to integrate the model into future adolescent trial to ensure its ongoing application and refinement and to secure its sustainability.
6. To identify how this model can be adapted to be used in other clinical trials and research outside of HIV to maximise its generalisability.

METHODS

A model of meaningful engagement and participation of children living with HIV in the development and delivery of a paediatric clinical trial, using ODYSSEY trial as an example, will be developed and piloted in 4 countries participating in ODYSSEY: the UK, South Africa, Uganda and Zimbabwe for 2 years. Those children involved will be living with HIV, aged between 15-19. They will be recruited through a set criteria to ensure they represent the country demographic of children living with HIV (gender, ethnicity, social circumstances).

Stage 1: Developing the model

A literature review will be conducted to identify and review the published and grey English language literature on involving young people in clinical trials. Once this review has been completed, a consultation phase with partners in the four sites (based in South Africa, UK, Uganda and Zimbabwe)

and other key individuals (young people living with HIV and experts with knowledge and experience in this field) who are able to advise us on our approach will be performed.

Stage 2: Piloting the model, including ongoing reflection (2 years)

The model will involve establishment of a Youth Trial boards (YTB), groups of up to 8 young people in four countries; the UK, Uganda, South Africa and Zimbabwe. Consent will be obtained from legal guardians and assent/consent depending on their age from the participants prior to any involvement in this project. Following this, each YTB will meet in-country a number of times a year for the duration of the YTB project. Opportunities to link YTB groups together through face to face or virtual meetings will be pursued. The groups will be facilitated by individuals skilled in working with young people and in research, with local NGO involvement in some sites. Each YTB will receive training to ensure understanding of clinical trials, understand their role and support their participation. The in-country staff will work closely with researchers from PENTA and London School of Hygiene and Tropical Medicine, to ensure that there is effective communication between the sites and across the project team. This will also ensure that there is similarity in the roll out of the pilot model across the sites and that information is shared. Participant observations of the group meetings will be arranged in order to see ways to improve the model and to ensure that we are consistently capturing the ideas and opinions of the young people involved. Once the YTBs are established in each country consent will be sought to conduct individual interviews with YTB member and facilitators to understand their experiences of taking part in a YTB and to gather their ideas about what they have enjoyed, works well and how the YTB model could be improved further. This will inform the guidance that we produce alongside the model.

Stage 3: Beyond ODYSSEY trial

Once the YTB groups have an understanding of how ODYSSEY and clinical trials work in general, they will then be involved at the development stage of a new clinical trial. When the model is finalised, it can be used by other investigators inside and outside paediatric HIV trials and studies.

Inclusion criteria: Young people aged 15-19 years who are fully aware of their positive HIV status.

Number of Patients: At least 32 young people across the four sites. These young people will be purposively selected by each in-country team to broadly represent the characteristics of the clinic/ population group.

Project Timeline: 40 months

Anticipated Enrolment Rate: From Spring 2017

Output: A patient participation model in clinical trials for adolescents will be designed and piloted. At the end of the project this model will then be adopted and applied to new clinical trials as opportunities arise.

DATA ANALYSIS

Throughout the project, YTB meetings will be observed and participant observation and field notes will be taken. This will form the basis for our reflections on the process of developing and shaping the model. Individual in-depth interviews will be audio recorded and summarised. These data will be analysed using a thematic analysis approach with the supervision of LSHTM researchers.

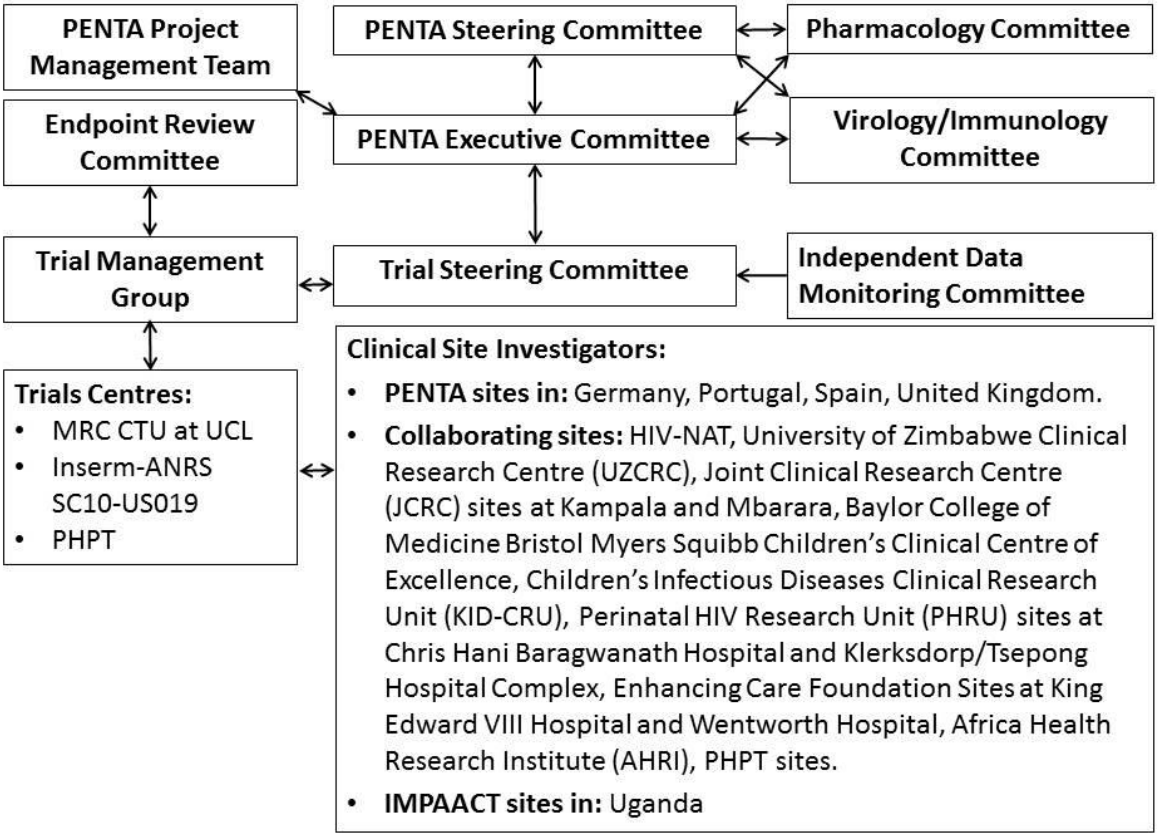
References:

1. Moorcraft, S. Y., Marriott, C., Peckitt, C. , Cunnighman, D., Chau, I., Starling, N., Watkins, D., & Rao, S. Patients' willingness to participate in clinical trials and their views on aspects of cancer research: results of a prospective patient survey. *Trials.* 2016; 17: 17.
2. Institute of Medicine (US) Committee on Cancer Clinical Trials and the NCI Cooperative Group Program; Nass SJ, Moses HL, Mendelsohn J, editors. *A National Cancer Clinical Trials System*

for the 21st Century: Reinvigorating the NCI Cooperative Group Program. Washington (DC): National Academies Press (US); 2010. 4, Physician and Patient Participation in Cancer Clinical Trials. Available from: https://www.ncbi.nlm.nih.gov/books/NBK220370/

3. Moore L, and Kirk S. 'A Literature Review of Children's and Young People's Participation in Decisions Relating to Health Care'. *Journal of Clinical Nursing* 19, no. 15/16 (August 2010): 2215–25.
4. Cherrill, J., Hudson, H., Cocking, C., Unsworty, V., Franck, L., Fakis, A., McIntyre, J. & Choonara, I. Clinical trials: the viewpoint of children with a chronic illness compared with healthy children. *Archives of Disease in Childhood* 2010; 95:229-232
5. Clacherty, G. & Donald, D. Child participation in research: reflections on ethical challenges in the southern African context. *African Journal Of AIDS Research* 2007; 6: 147-156.

35 APPENDIX XVII ODYSSEY STRUCTURE



36 APPENDIX XVIII FOLATE AND VITAMIN B12 SUBSTUDY

Folate and vitamin B12 status among children and adolescents in the ODYSSEY trial

INTRODUCTION AND RATIONALE

Recent concerns have been raised about the use of dolutegravir (DTG) in pregnant women. In a preliminary unscheduled analysis of an ongoing NIH-funded birth surveillance study in Botswana, an increased risk of neural tube defects (NTDs) among infants of women who became pregnant while taking DTG-based regimens has been reported (1-3). It is well known that maternal folate and/or vitamin B12 deficiency increases the risk of NTDs however it is unknown whether DTG may affect folate or B12 levels.

ODYSSEY provides an opportunity to compare folate and B12 levels in participants on DTG versus non DTG regimens to determine if there is an association between DTG and folate status.

Folate and vitamin B12 play a critical role in DNA and RNA synthesis. Folate-requiring reactions include the reactions involved in amino acid metabolism, purine and pyrimidine synthesis, and the formation of the primary methylating agent, *S*-adenosylmethionine (4). The key folate metabolite is tetrahydrofolate (THF). Folate coenzymes are compartmentalized between the cytosol and the mitochondria and they cannot be transported between compartments (4). Folate one-carbon (1C) metabolism serves to activate and transfer 1C units for biosynthetic processes. As 1C-loaded folates are known not to transfer across intracellular membranes, the 1C-carrying metabolite THF must be generated in both the mitochondria and cytosol. Formate, a small 1C metabolite produced in the mitochondria, enters the cytosol and provides 70% of the cell's 1C units. Both pyrimidines and purines (DNA building blocks) require folate 1C metabolism for their synthesis. Similarly, DNA methylation, which is involved in gene expression regulation, is folate 1C-dependent.

Cobalamin (vitamin B12) serves as a coenzyme in the methionine synthase reaction required for the conversion of 5-methyltetrahydrofolate (5-methyl-THF) to THF, an active folate form participating in folate-dependent enzymatic reactions. In its absence, folate is "trapped" as 5-methyl-THF, therefore, vitamin B12 deficiency reduces the regeneration of THF required for DNA synthesis, which may result in a secondary folate deficiency and impair cell division (5).

DNA synthesis impairment due to folate and/or vitamin B12 deficiency leads to arrest of the red blood cell division at the G2 growth stage, continuation of cell growth and increased mean cell volume (MCV) (macrocytosis). The red cell MCV, therefore, could be an indicator of folate or B12 deficiency.

Different medications (e.g. methotrexate, trimethoprim, phenytoin, antimalarials, antacids) may cause or contribute to folate and/or B12 deficiency by various mechanisms, including decreased absorption (due to reduction of gastric acid or competion for the receptors on intestinal mucosal cells), effect on enzymes involved in folate metabolism or inhibition of cellular utilisation of folate. Since NT development requires both rapid cell proliferation and gene expression regulation, then 1C metabolism is crucial for this embryonic event, and could represent the cellular process that becomes disturbed by DTG, leading to NTDs.

Folate status can be measured using plasma (or serum) and red blood cell (RBC) folate levels. The plasma or serum folate level is an informative biomarker of short-term folate status. It reflects a recent folate intake and is sensitive to dietary changes or action of folate-decreasing medications. RBC folate level tend to reflect long-term folate status and estimates the folate stores over the last 3-4 months (5).

ODYSSEY provides an opportunity to compare folate levels in participants on DTG versus non DTG regimens to determine if there is a potential association between DTG and folate /B12 status.

AIM

To compare folate and B12 levels among children and adolescents randomized to a DTG containing ART regimen versus those on SOC ART regimen

OBJECTIVES

1. To compare red cell folate level at 96 weeks or later in participants randomized to DTG versus participants randomized to SOC (Primary objective)
2. To compare change in plasma folate level from baseline to week 4 in participants randomized to DTG versus participants randomized to SOC
3. To compare change in MCV levels from baseline to weeks 48 and 96 in participants randomized to DTG versus participants randomized to SOC
4. To compare vitamin B12 serum level at 96 weeks or later in participants randomized to DTG versus participants randomized to SOC

METHODS

Folate and B12 will be assayed in children enrolled in ODYSSEY at sites in Uganda who were aged ≥6 years at enrolment (if required the substudy may also extended to other sites).

Red cell folate and B12 will be assayed in prospectively collected samples using the same blood draw as for other scheduled blood tests in the trial at 96 weeks or later (for patients who have passed their 96 week visit the samples will be collected at their first visit after the substudy opens). Where assays cannot be done in real time, the blood samples will be stored for subsequent testing. Plasma folate levels will be assayed at baseline and at 4 weeks after commencing ART using plasma samples that are routinely stored as part of the main ODYSSEY protocol.

Testing plasma folate levels before and after ART initiation will allow us to evaluate the impact of treatment on folate levels within an individual.

Blood samples and assays

EDTA whole blood samples and serum are routinely collected in the ODYSSEY study and plasma samples are stored. MCV is captured as part of the haematology assays at screening, week 0, 24 and then every 24 weeks, and these data are available to analyse the differences in MCV between the arms. The plasma and whole blood folate levels will be performed on

the cobas e 411 instrument (Roche diagnostics, Manheim). The Elecsys Folate assay will be used for the determination of folate in plasma, and the Folate RBC Hemolyzing Reagent will be used in conjunction with the Elecsys Folate RBC assay for the determination of folate in erythrocytes. Plasma B12 levels will be performed on the cobas e 411 instrument (Roche diagnostics, Manheim). The Elecsys Vitamin B12 II electrochemiluminescence immunoassay will be used for the determination of B12 in plasma.

Substantial variation between folate assays used in different laboratories exists, therefore testing will be centralised.

SAMPLE SIZE AND STATISTICAL ANALYSIS PLAN

The sample size is based on objectives 1 and 2. Since plasma folate levels and red blood cell folate levels in children in Africa are unknown we have assumed that a difference of half a standard deviation or more between groups may be clinically relevant.

1. Comparison of red blood cell folate level at week 96 (or later): To detect a difference of half a standard deviation in folate levels between DTG and SOC arms, with 80% power at the 5% level of significance, a sample size of 124 children is required (62 in each treatment arm).
2. Comparison of plasma folate levels at week 4: To detect a difference of half a standard deviation in folate levels between DTG and SOC arms, adjusting for baseline levels, using one pre-treatment and one post-treatment measure (assuming correlation between pre- and post-treatment levels of 0.3, with 80% power at the 5% level of significance, a sample size of 116 children is required (58 in each treatment arm).

Increasing the sample size to 140 children (70 in each arm) will allow for 10% of samples being potentially unanalysable for any reason.

Mean red blood cell folate levels and B12 at week 96 (or later) will be compared between the two randomised groups in an intention-to-treat analysis. In an as treated analysis we will look at the difference between groups depending on the ART received at the time of the sample.

Mean plasma folate levels at 4 weeks will be compared between the two randomised groups with adjustment for values at randomisation by analysis of covariance (ANCOVA).

Mean MCV levels at 48 and 96 weeks will be compared between the two randomised groups with adjustment for values at randomisation by ANCOVA. In as treated analysis we will also look at the difference between groups depending on the ART received at the time of the sample

References:

1. Zash R, Holmes L, Makhema J, Diseko M, Jacobson DL, Mayondi G, Mmalane M, Mofenson L, Gaolathe T, Petlo C, Essex M, Lockman S and Shapiro RL. Surveillance for neural tube defects following antiretroviral exposure from conception, the Tsepamo study (Botswana). AIDS 2018. Amsterdam, the Netherlands, 23–27 July 2018. Symposia session TUSY15**.** http://programme.aids2018.org/Programme/Session/1589
2. World Health Organization. Statement on DTG. May 18, 2018; Geneva.

3. FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq). May 18, 2018.
4. Bailey LB, Gregory JF 3rd. Folate Metabolism and requirements. J Nutr 1999; 129: 779-82. Available: https://doi.org/10.1093/jn/129.4.779
5. Bailey LB, Hausman DB. Folate status in women of reproductive age as basis of neural tube defect risk assessment. Ann N Y Acad Sci 2018;1414(1):82-95.

37 APPENDIX XIX DOLUTEGRAVIR DOSING IN THE ODYSSEY TRIAL ACROSS DIFFERENT PROTOCOL VERSIONS

	ODYSSEY v2.0*	ODYSSEY v3.0		ODYSSEY v4.0		ODYSSEY v5.0 onwards	
	Main trial participants	Main trial participants	WB PK substudy participants	Main trial participants	WB PK substudy participants	Main trial participants	WB PK substudy participants
3-<6kg	-	-		-	5mg or 10mg DTψ	-	5mg or 10mg DTψ
6-<10kg	-	-		-	15mg DT	-	15mg DT
10-<14kg	-	-		-	20mg DT	-	20mg DT
14-<15kg	-	-	25mg	25mg→25mg DT§	25mg DT	25mg DT	N/A
15-<20kg	20mg*	20mg					
20-<25kg	25mg	25mg	25mg	25mg→30mg DT or 50mg¥	30mg DT or 50mg†	50mgπ	N/A
25-<30kg	25mg	25mg→50mg**	50mg	25mg→50mg**	NA	50mg	NA
30-<35kg	35mg	35mg→50mg**	50mg	35mg→50mg**	NA	50mg	NA
35-<40kg	35mg	35mg→50mg**	50mg	35mg→50mg**	NA	50mg	NA
≥40kg	50mg	50mg	NA	50mg	NA	50mg	NA

ψ Infants <6 months of age receive DTG 5mg QD while infants ≥6 months of age receive DTG 10mg QD, both as dispersible tablets.

* In May 2017 the EMA licensed the use of 20mg DTG in children 15 - <20kg and ≥6years, following this, children were able to be recruited in this weight and age-band.

** From 1st of April 2018, after ethics notification, sites following protocol version 3.0 and above were recommended to increase the DTG dose of children 25 - <40kg to 50mg FCT QD at their next scheduled study visit based on the results of the WB-PK2. WB-PK2 participants remained on DTG 50mg with ongoing follow-up. Non-PK participants recruited after implementation were initiated on the 50mg film-coated DTG dose.

† Both doses are examined in WB-PK1 part II substudy in this weight-band.

§ Children 15 - <20kg previously receiving DTG 20mg QD were changed to DTG film-coated 25mg tablets upon the approval of protocol v4.0. Subsequently all children 14-<20kg changed to DTG 25mg QD dispersible tablets following the review of WB-PK1 part I results and approval by the relevant ethical and regulatory authorities.

¥ Children 20 - <25kg previously receiving DTG 25mg QD as one 25mg film-coated tablet changed to either DTG 30mg QD dispersible tablets or DTG 50mg QD (film-coated tablet) depending on site following the review of WB-PK1 part I results and approval by the relevant ethical and regulatory authorities.

π Following the review of PK and safety data children 20-<25kg receiving DTG 30mg dispersible tablets should be switched to DTG 50mg film-coated tablets. Those who prefer to remain on DTG 30mg DT will be able to do so until they move weight band.

DT=dispersible, otherwise film coated tables

38 APPENDIX XX ARRANGEMENTS FOR THE EXTENDED FOLLOW-UP OF ODYSSEY PARTICIPANTS

GENERAL INFORMATION

This appendix details planned extended follow-up for all children participating in the ODYSSEY (PENTA 20) trial.

Objectives are two-fold:

1. to provide safety data for ViiV Healthcare for participants who, in the opinion of the treating physician, continue to derive benefit from dolutegravir and receive dolutegravir from ViiV Healthcare where it is not available through their country's national HIV treatment programme;
2. to monitor long-term safety and effectiveness of dolutegravir versus standard of care (at selected sites, subject to sufficient funding).

All children who entered the main trial (weighing ≥14kg) will attend their end of study visit for the randomised phase on/after 24 April 2020 (when the last patient recruited into the main trial reaches 96 weeks follow-up). Children recruited weighing <14kg will be asked to attend their 96 week follow-up visit at/after 96 weeks from their randomisation visit and this will be their end of study visit for the randomised phase; they should move to the extended follow-up only after their 96 week visit is completed. The baseline visit for the extended follow-up will be the end of study visit for the randomised phase of the trial.

At the end of study visit for the randomised phase children and carers will be asked to consent to extended follow-up. Children's visit schedules (at least 6 monthly) and care will be as per local clinic guidelines. In addition to routine care, clinics will be asked to continue collecting urine dipsticks, Sleep and Mood Questionnaire data, waist and hip circumferences and bioelectric impedance analysis (BIA) measurements (the latter only at the sites where BIA machines are available) as per the Assessment schedule below. Pregnancy tests will also be required at every visit for females of childbearing potential. Clinicians will be able to change ART according to local supplies and/or in the patient's best interest. Laboratory tests will be according to local practice.

Children on DTG at the end of the randomised phase will be moved to local DTG where available (up to 6 months' supply of trial DTG will be provided for transition). Provided consent is given for extended follow-up, ViiV Healthcare DTG 5mg DT can continue to be provided for participants <20kg in South Africa, Uganda and Zimbabwe who are receiving DTG 5mg DT at their end of study visit for the randomised phase until DTG DTs are available locally or participants move to DTG FCTs or stop benefiting from DTG-based ART (i.e. require switching to another regimen). Similarly, provided consent is given for extended follow-up, ViiV Healthcare DTG 50mg FCT can continue to be provided for participants in Thailand receiving DTG 50mg FCT at their end of study visit for the randomised phase.

At each routine clinic visit during extended follow-up, a shortened version of the trial follow-up CRF will be completed. Serious adverse events must be reported to MRC CTU within 24 hours of the investigator becoming aware of the event. Annually we will collect participant and carer data on sleep and mood.

Participants receiving ViiV Healthcare DTG must remain in follow-up while this continues or they can no longer take ViiV Healthcare DTG provided for the trial. Follow-up of other participants will be at selected sites for 3 years after the randomisation phase is completed

(until May 2023) providing sufficient funding is available. If sufficient funding cannot be sourced then follow-up of these participants (those not receiving ViiV Healthcare DTG) will finish at their study visit for the end of the randomised phase on/after 24 April 2020.

ASSESSMENT SCHEDULE FOR EXTENDED FOLLOW- UP

WEEK	Study visit at end of randomised phase	Further follow-up (minimum of every 6 months)	End of extended follow-up visit
Informed consent for extended follow-up	X		
History and clinical assessment [a]	X	As per local practice	As per local practice
Tanner scale	X	N/A	N/A
Lipodystrophy assessment	X	N/A	N/A
Drug supply to next visit	X	As per local practice	As per local practice
HIV-1 RNA viral load	X	As per local practice	As per local practice
HIV-1 resistance tests		As per local practice	As per local practice
T cell lymphocyte subsets	X	As per local practice	As per local practice
Biochemistry [b]	X	As per local practice	As per local practice
Haematology	X	As per local practice	As per local practice
Lipids/glucose [b]	X	As per local practice	As per local practice
Bone profile [b]	X	As per local practice	As per local practice
Urine dipstick	X	Annual	Annual
Quality of Life questionnaire [c]	X	N/A	N/A
Pregnancy test [d]	X	Every clinic visit	X
Plasma storage	X	N/A	N/A
Adherence questionnaire	X	N/A	N/A
Acceptability, sleep & mood questionnaire [e]	X [d]	Annual [d]	X [d]
Body composition assessment [f]	N/A as full lipodystrophy assessment should be performed at this visit	Annual	Annual

(a) Clinical assessment: including presence of adverse events and change in HIV disease stage.
(b) Frequency of blood tests will be as per local practice but some specific tests above routine care may be required, subject to funding. These will be as per the trial assessment schedule for the randomised phase. No additional tests will be performed in extended follow-up that were not performed during the randomised phase.
(c) In children aged 8 or over
(d) Pregnancy test for females of childbearing potential only
(e) The full acceptability, sleep and mood questionnaire should be completed at the end of study visit for the randomised phase, however, only the sleep and mood section should be completed for the extended follow-up period. The sleep and mood section is only required to be completed for participants ≥6 years old.
(f) Weight, height, waist and hip circumferences and BIA measurements at the sites where BIA machines are available. Replaces previously collected Lipodystrophy assessment data.

SAFETY REPORTING

Any event fulfilling the criteria of an SAE should be reported within 24 hours of the site team becoming aware of the event. Other adverse events and pregnancies should be submitted within one week of the site team becoming aware of the event.

CO-ENROLMENT

Co-enrolment in other studies is allowed. Centres should also adhere to local guidelines concerning co-enrolment in other trials.