

Weight gain, body composition, and metabolic parameters of dolutegravir-based antiretroviral therapy versus standard of care in children and adolescents: an ancillary analysis of the ODYSSEY trial



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Summary

Background ODYSSEY trial showed superior efficacy of dolutegravir-based antiretroviral therapy (ART) versus then-current, non-dolutegravir standard of care over 96 weeks in children and adolescents living with HIV. The aim of this ancillary analysis was to compare anthropometric and body composition outcomes, including weight, height, BMI-for-age Z score, weight-for-age and height-for-age Z scores (<14 kg), mid-upper-arm circumference (MUAC), waist circumference, hip circumference, and body fat percentage, as well as metabolic outcomes (lipids and glucose), between dolutegravir and standard of care over approximately 5 years of follow-up.

Methods In this open-label, randomised, non-inferiority trial, children (aged ≥ 4 weeks and <18 years), weighing 3 kg or more, starting first-line ART (ODYSSEY-A) or switching to second-line ART (ODYSSEY-B) were enrolled in 29 centres in Germany, Portugal, South Africa, Spain, Thailand, Uganda, Zimbabwe, and the UK in two cohorts (children weighing ≥ 14 kg and children weighing <14 kg). Treatment effects (dolutegravir vs standard of care) were estimated on randomised allocation, accounting for treatment switches (substantial in standard of care arm during extended follow-up) through censoring and inverse-probability-of-censoring-weights. Changes in continuous outcomes were compared using linear mixed models, accounting for correlated slope and baseline value. Proportions of participants with unfavourable outcomes were compared using logistic mixed models. ODYSSEY is registered with ClinicalTrials.gov, NCT02259127, EUDRACT, 2014-002632-14, and ISRCTN, ISRCTN91737921.

Findings Between Sept 20, 2016, and Aug 26, 2019, 792 children were randomly assigned (392 to dolutegravir and 400 to standard of care). Of 707 children in the 14 kg or more cohort, 311 received first-line ART (ODYSSEY-A; 145 [92%] of 157 received efavirenz-based ART as standard of care) and 396 received second-line ART (ODYSSEY-B; 195 [98%] of 200 received boosted protease inhibitors as standard of care). Of 85 children in the less than 14 kg cohort, 72 received first-line ART (32 [74%] of 43 received lopinavir–ritonavir as first-line or second-line standard of care). Median follow-up on randomised allocation was 287 weeks (IQR 240–311) on dolutegravir-based ART and 205 weeks (168–240) on standard of care in the 14 kg or more cohort, and 220 weeks (208–232) on dolutegravir-based ART and 144 weeks (127–192) on standard of care in the less than 14 kg cohort. In the 14 kg or more cohort, 345 (49%) were female and 362 (51%) were male, 623 (88%) were Black African, median enrolment age was 12.2 years (IQR 9.1 to 14.9), weight 30.7 kg (23.4 to 43.0), and BMI-for-age Z score -0.6 (-1.4 to 0.1); 35 (5%) were overweight and six (1%) were obese. At week 240, adjusted mean differences (dolutegravir minus standard of care) were 1.0 kg for weight (95% CI -0.2 to 2.2 ; $p=0.095$) and 0.4 cm for MUAC (0.0 to 0.8 ; $p=0.030$), driven by differences in first-line participants, where higher increases were also observed in height, waist circumference, and hip circumference. Increases in BMI-for-age Z score, body fat percentage, and cross-sectional waist-to-height ratio were similar on dolutegravir-based ART and standard of care. Total cholesterol (-15.3 mg/dL [-21.0 to -9.5]; $p<0.0001$), triglycerides (-14.4 mg/dL [-25.2 to -3.6]; $p=0.0089$), and glucose (-4.4 mg/dL [-6.8 to -1.9]; $p=0.0004$) were lower with dolutegravir than standard of care. In the less than 14 kg cohort, 44 (52%) were female and 41 (48%) were male, 83 (98%) were Black African, median enrolment age was 1.4 years (IQR 0.6 to 2.0), weight 8.1 kg (5.4–10.0) and BMI-for-age Z score -0.8 (-1.9 to 0.2); three (4%) were overweight and none obese. Changes in weight, weight-for-age, BMI-for-age and height-for-age Z scores by 192 weeks were similar on dolutegravir and standard of care; there were small differences in MUAC (0.6 cm [-0.1 to 1.3]; $p=0.070$) and height (-2.5 cm [-4.5 to -0.5]; $p=0.016$). No significant differences in lipid biomarkers were observed; glucose decreased with standard of care but not with dolutegravir.

Interpretation Over approximately 5 years, indices defining excessive weight gain and central adiposity were similar with dolutegravir and other anchor drugs, and lipid and glycaemia profiles with dolutegravir were reassuring, providing supporting evidence for dolutegravir-based ART as the preferred treatment in children and adolescents.

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See Online for appendix

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Introduction

Over the past three decades, the proportion of children and adolescents with overweight or obesity has doubled globally, while obesity alone has tripled.¹ In light of this, there is a growing concern that children and adolescents living with HIV might be at increased risk of early metabolic and cardiovascular comorbidities compared with their peers without HIV.

Weight gain in children and adolescents living with HIV on antiretroviral therapy (ART) is influenced by a range of individual and environmental factors, which can generally be attributed to three main effects. The first effect, known as return to health, occurs when children and adolescents living with HIV initiate or switch to effective ART, resulting in a substantial catch-up in

weight. The second effect relates to comparator drugs, as weight gain with an investigational drug might appear greater when compared with agents known to attenuate weight.^{2,3} Population-wide secular increases in weight also have a role,³ and children and adolescents with well controlled HIV are expected to gain weight at similar rates to their peers without HIV.

Understanding the effect of ART on weight gain is important. Second-generation integrase strand transfer inhibitors (INSTIs) are highly effective, safe, and well tolerated in both adults and children.^{2,4-6} Dolutegravir is currently recommended as the preferred anchor drug, the principle antiretroviral agent in a multidrug regimen, by WHO⁷ and is the most commonly used anchor drug worldwide.⁸ However, concerns have been raised

Research in context

Evidence before this study

ODYSEY, an open-label, randomised controlled trial, showed superior virological and clinical outcomes with dolutegravir-based antiretroviral therapy (ART) compared with then-current non-dolutegravir standard of care regimens in children living with HIV initiating first-line or second-line treatment. In adult studies, dolutegravir has been associated with excessive weight gain, particularly among Black women. We searched PubMed on July 25, 2025, with no date or language restrictions, using the following search terms: ("weight" OR "body mass index" OR "body composition" OR "body fat") AND "dolutegravir" AND ("children" OR "adolescents"). We identified 97 publications, including 12 original studies with comparative data on weight or body composition before and after dolutegravir initiation versus other anchor agents (including two from ODYSSEY), and one systematic review. Ten paediatric studies (two randomised trials, SMILE and CHAPAS-4, and eight observational studies) varied in design, comparator regimens, and populations studied (initiating ART or changing to subsequent lines of treatment; virologically suppressed or unsuppressed). SMILE, a 48-week randomised controlled trial (RCT) in virologically suppressed children and adolescents, found greater gains in weight, weight-for-age, BMI, and BMI-for-age Z score on dolutegravir plus darunavir–ritonavir compared with standard of care (mostly efavirenz-based or lopinavir–ritonavir-based regimens). CHAPAS-4, a 96-week RCT in children initiating second-line ART, found greater increases in weight-for-age and BMI-for-age Z score on dolutegravir compared with lopinavir–ritonavir, but changes were similar on dolutegravir versus darunavir–ritonavir or atazanavir–ritonavir. Findings from the observational studies in children and adolescents were mixed: three reported higher weight, BMI, or BMI-for-age Z score with dolutegravir, whereas others found

no significant differences after switching to dolutegravir. A few studies, including a systematic review, reported favourable changes in atherogenic lipid fractions with dolutegravir compared with other anchor drugs.

Added value of this study

To our knowledge, this is the first long-term randomised comparison of weight gain, body composition, and metabolic outcomes in children and adolescents on dolutegravir versus non-dolutegravir ART. After approximately 5 years of follow-up, children in the 14 kg or more cohort initiating first-line dolutegravir-based ART had greater increases in mean weight, height, and body circumferences compared with those on non-dolutegravir standard of care (majority started efavirenz). We observed no differences between dolutegravir and other anchor drugs in anthropometric and body composition measures indicative of excessive weight gain or central adiposity. No differences between dolutegravir and non-dolutegravir standard of care were observed in children starting second-line ART (nearly all participants on standard of care started boosted protease inhibitors) or in the less than 14 kg cohort (most participants on standard of care started lopinavir–ritonavir). In both weight cohorts, few children became newly overweight, with no differences by dolutegravir versus non-dolutegravir based ART. Lipid and glycaemic profiles in children on dolutegravir were reassuring.

Implications of all the available evidence

Our findings provide reassurance that dolutegravir is not associated with excessive weight gain or fat gain or with abdominal adiposity in children and adolescents initiating first-line or second-line ART. Together with previous efficacy and safety data, these results support the continued use of dolutegravir as a preferred anchor agent for paediatric ART.

regarding the potential of dolutegravir to promote excessive weight gain. This effect has predominantly been observed in comparisons of dolutegravir combined with tenofovir alafenamide to regimens containing drugs with weight-suppressing effects, such as efavirenz, lopinavir–ritonavir, and tenofovir disoproxil fumarate.^{2,3}

While INSTIs, including dolutegravir, are associated with improved lipid profiles in adults, compared with other anchor drugs,⁹ concerns persist that these benefits could be offset by excessive weight gain and the development of metabolic syndrome. Metabolic syndrome—characterised by central obesity plus any two of glucose intolerance, hypertension, raised triglycerides, or reduced HDL cholesterol—predisposes individuals to cardiovascular disease, type 2 diabetes, and other non-communicable diseases.¹⁰ The association between dolutegravir and metabolic syndrome remains unclear, with some adult studies indicating a higher prevalence for dolutegravir, while others have found no association.^{11,12}

Data on dolutegravir-associated weight gain in children and adolescents living with HIV are scarce. Some studies have reported greater gains in weight and BMI or BMI-for-age Z score,^{5,13–17} while others have found no effect.^{18–21} A few studies have reported a better lipid profile with dolutegravir compared with other anchor drugs.^{5,22}

This paper presents a comprehensive analysis of the effect of dolutegravir compared with previous standard of care anchor drugs on weight gain, treatment-emergent overweight and obesity, body composition, and metabolic parameters in the ODYSSEY trial, including randomised follow-up and extended follow-up.

Methods

Study design

ODYSSEY was an open-label, multicentre, randomised, non-inferiority trial conducted in 29 centres in Germany, Portugal, South Africa, Spain, Thailand, Uganda, the UK, and Zimbabwe, which compared efficacy and safety of dolutegravir-based treatment (dolutegravir arm) with then-current non-dolutegravir-based standard of care (standard of care arm) in children starting first-line ART (ODYSSEY-A) or second-line ART (ODYSSEY-B).^{4,6,23} In the main trial, 707 children weighing 14 kg or more were recruited between Sept 20, 2016, and June 22, 2018. After dolutegravir dispersible tablets became available for younger children, an additional 85 children weighing less than 14 kg were recruited between July 5, 2018, and Aug 26, 2019 (appendix p 9).

Randomised follow-up was until the last participant reached week 96 (≥ 14 kg cohort, April 24, 2020; < 14 kg cohort, June 28, 2021); until these calendar dates trial clinicians retained participants on randomised allocation (dolutegravir or standard of care) unless clinical management required treatment switching. Each participant then attended an end of randomised phase visit; European participants then exited, and in African and Thai sites, participants could consent to extended

follow-up. Extended follow-up continued until May 1, 2023, when the last participant in the 14 kg or more cohort reached 240 weeks and the last participant in the less than 14 kg cohort reached 192 weeks. During extended follow-up, children in the standard of care arm transitioned to dolutegravir following national guidelines. We conducted an ancillary analysis of changes in anthropometric parameters, body composition, and metabolic parameters.

The initial trial protocol and subsequent amendments were approved by national and local ethics committees (appendix p 4).

Participants

Participants were children and adolescents living with HIV, aged 4 weeks to less than 18 years, weighing at least 3 kg and starting first-line ART or switching to second-line ART. Children eligible for ODYSSEY-B were those starting second-line ART after failure of first-line regimen, with an HIV-1 RNA viral load of 500 copies per mL or greater at or within 4 weeks before screening. Second-line ART was selected by the treating clinicians and should have included a new anchor drug and at least one NRTI likely to have preserved activity based on treatment history. Carers and children (or both) gave written informed consent and assent as appropriate to participate in the ODYSSEY trial and re-consented or re-assented for extended follow-up. ODYSSEY is registered with ClinicalTrials.gov, NCT02259127, EUDRACT, 2014-002632-14, and ISRCTN, ISRCTN91737921.

Randomisation and masking

Children were randomly assigned (1:1) to dolutegravir-based ART or non-dolutegravir-based standard of care, with allocation concealed at clinical site until after enrolment. Randomisation was stratified by ODYSSEY-A and ODYSSEY-B with additional stratification factors depending on the enrolment cohort.

Procedures

Children were seen at week 4 and week 12, and every 12 weeks in randomised follow-up and at least every 24 weeks in extended follow-up. Weight, height, and mid-upper-arm circumference (MUAC) were measured at baseline, once every 12 weeks in randomised phase, and every 12 weeks or every 24 weeks in extended follow-up, dependent on site. Waist circumference and hip circumference were measured in participants aged 5 years or older at baseline (introduced 1 year into study) and every 48 weeks during randomised and extended follow-up phases. Bioelectrical impedance analysis measures of body composition were taken in participants aged 5 years or older at the sites in Uganda and Zimbabwe at baseline and every 48 weeks during randomised and extended follow-up phases. Fat accumulation in the neck or upper back, breasts, and abdomen, was assessed by site clinicians at baseline and every 48 weeks during

the randomised phase, graded as mild, moderate, or severe, using Manual of Operations definitions, aligned with DAIDS lipohypertrophy severity grading. Total cholesterol, glucose, triglycerides, and cholesterol fractions (LDL and HDL) were measured at baseline and every 48 weeks during randomised and extended follow-up phases.

Outcomes

The primary outcome of the ODYSSEY trial, published previously, was the proportion of participants with virological or clinical treatment failure by 96 weeks.⁶ Here we report anthropometric parameters, body composition, and metabolic parameters. Change in total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol from baseline to week 48 and week 96 were pre-specified trial secondary outcomes. All other outcomes, including changes in weight, height, BMI-for-age Z score, weight-for-age Z score (<14 kg cohort) and height-for-age Z score (<14 kg cohort), body fat percentage and glucose, cross-sectional means of waist, hip circumferences, and waist-to-height ratio, as well as unfavourable outcomes indicating overweight or obesity and abnormal laboratory parameters (defined here), are considered exploratory but specified a priori. The ODYSSEY trial was designed before emerging concerns regarding anthropometric parameters and body composition outcomes associated with dolutegravir; therefore, these endpoints were not pre-specified as secondary outcomes. However, their comparison between dolutegravir and standard of care was included in the Statistical Analysis Plan. Analyses of outcomes beyond 96 weeks are considered exploratory, as they are observational in nature and depend on appropriate adjustment for treatment switching, but comparisons between treatment regimens were planned a priori. WHO reference data were used for age-standardisation of BMI;^{24,25} BMI-for-age Z scores in adolescents older than 19 years were estimated based on reference data for 19-year-olds.

Unfavourable anthropometric parameters, body composition, and metabolic parameters were defined as: BMI of 25 kg/m² or greater for participants aged at least 19 years, BMI-for-age Z score of more than 1SD for children aged 5 years to less than 19 years, and weight-for-height more than 2SD for children younger than 5 years;²⁶ body fat percentage categorised as overfat or obese per TANITA Corporation definitions;²⁷ waist-to-height ratio of 0·5 or more indicating central adiposity;²⁸ total cholesterol, glucose, triglycerides, and LDL cholesterol grade 1 or worse based on DAIDS grading (version 2.0, November 2014); and HDL cholesterol of less than 40 mg/dL.²⁹

Statistical analysis

All analyses were conducted separately for the 14 kg or more cohort and the less than 14 kg cohort, due to higher

variability in outcome measures in the 14 kg or more cohort and the different follow-up periods. Follow-up was censored at the earlier of May 1, 2023, or pregnancy.

Time-dependent measures were assigned to visit windows, which were –42 days to 41 days around the target date, except for week 4 where the window from –27 days to 27 days was used, and week 12 where the window from –28 days to 41 days was used. The closest measurement to the target date was used as the outcome measure for the window (using the later measurement if two were equidistant from the target date), with outcome set to missing where there was no measurement in the visit window or where the measurement was not scheduled in the protocol. 95% (12 216 of 12 897) of visits were performed within 1 week of the target date. Outcomes were not included for scheduled visits once the number of participants on dolutegravir or standard of care had dropped to fewer than ten.

Our analyses estimate the effects of being prescribed dolutegravir versus alternative non-dolutegravir-based ART; ie, the effects assuming participants remained on randomised allocation (similar to a per-protocol analysis, although the ODYSSEY protocol allowed for treatment switching during extended follow-up). Due to substantial treatment switching in the standard of care arm, an intention-to-treat analysis would probably underestimate differences between treatment regimens. Treatment regimens of interest were defined as dolutegravir-based ART for a participant assigned to the dolutegravir arm and alternative non-dolutegravir-based ART for a participant assigned to the standard of care arm. Participants were artificially censored after they switched from their allocated treatment regimen, defined as a participant in the dolutegravir arm starting non-dolutegravir-based ART or a participant in the standard of care arm starting dolutegravir-based ART. Inverse-probability weights were used to adjust for artificial censoring, essential to adjust appropriately for any non-random treatment switching, and were estimated by trial arm and ODYSSEY-A and ODYSSEY-B enrolment strata (≥14 kg cohort). Weights to account for censoring due to death, loss to follow-up, pregnancy, or administrative censoring were also estimated by trial arm and applied. Censoring weights were adjusted for most recent weight, BMI-for-age, CD4 (CD4% for <14 kg cohort), and log₁₀ viral load.

Mean change in continuous measures up to 240 weeks (≥14 kg cohort) and 192 weeks (<14 kg cohort) from baseline by dolutegravir and standard of care and difference between dolutegravir and standard of care (standard of care as reference) were calculated using linear mixed models. Models included a random intercept for participant and fixed effects for treatment regimen and visit week (3 knot cubic spline at 10th, 50th, 90th percentiles, specified according to weight cohort), interaction terms between treatment regimen and visit week spline variables, and other baseline variables:

ODYSSEY-A or ODYSSEY-B, country or region, calendar month of randomisation (3 knot cubic spline at 10th, 50th, 90th percentiles, specified according to weight cohort), sex, age, weight, BMI-for-age Z score, CD4 (CD4% for <14 kg cohort), and log₁₀ viral load. The model also included the outcome measure at baseline and interaction terms between the baseline measure (as categorical) and visit week spline variables, to model the outcome trajectory over time.³⁰ Cross-sectional means in anthropometric outcomes (if not measured from trial opening) were estimated similarly using linear mixed models, and proportions of participants with unfavourable outcomes were estimated using mixed logistic models. The probability of ever becoming overweight or obese by 240 weeks was estimated by treatment regimen based on estimates of the probability of becoming overweight or obese by visit window from a pooled logistic regression model in those not overweight or obese at enrolment or previously in follow-up.

Analyses of the 14 kg or more cohort were performed across the total population (adjusting for ODYSSEY-A and ODYSSEY-B strata), and for ODYSSEY-A and ODYSSEY-B strata separately, with interactions between treatment regimen and ODYSSEY-A and ODYSSEY-B strata tested in a joint model. Post-hoc exploratory subgroup analyses by age and sex were conducted in joint models for weight and BMI-for-age Z score in populations where a significant treatment effect was shown for weight. Analyses of the less than 14 kg cohort were performed across the total population (adjusting for ODYSSEY-A and ODYSSEY-B strata), as small numbers in ODYSSEY-B stratum precluded meaningful comparisons. Full details of statistical methods are given in the appendix (pp 5–8).

Young people with lived experience, represented through Youth Trial Boards, set up in ODYSSEY in African sites, contributed to trial conduct and participant materials; young people were not involved in the present ancillary analyses or manuscript preparation, which were undertaken after trial completion.

Role of the funding source

ViiV Healthcare reviewed and commented on the initial manuscript. Employees of the Medical Research Council Clinical Trials Unit (University College London, London, UK) and the Fondazione Penta ETS had a role in the study design, data collection, data analysis, data interpretation, and writing of the manuscript.

Results

Between Sept 20, 2016, and Aug 26, 2019, 792 children and adolescents living with HIV were randomly assigned (392 to dolutegravir, 400 to standard of care, figure 1), including 707 in the 14 kg or more cohort and 85 in the less than 14 kg cohort (table 1). Of 707 participants in the 14 kg or more cohort, 623 (88%) were Black African; 331 (47%) were enrolled in Uganda, 144 (20%) in

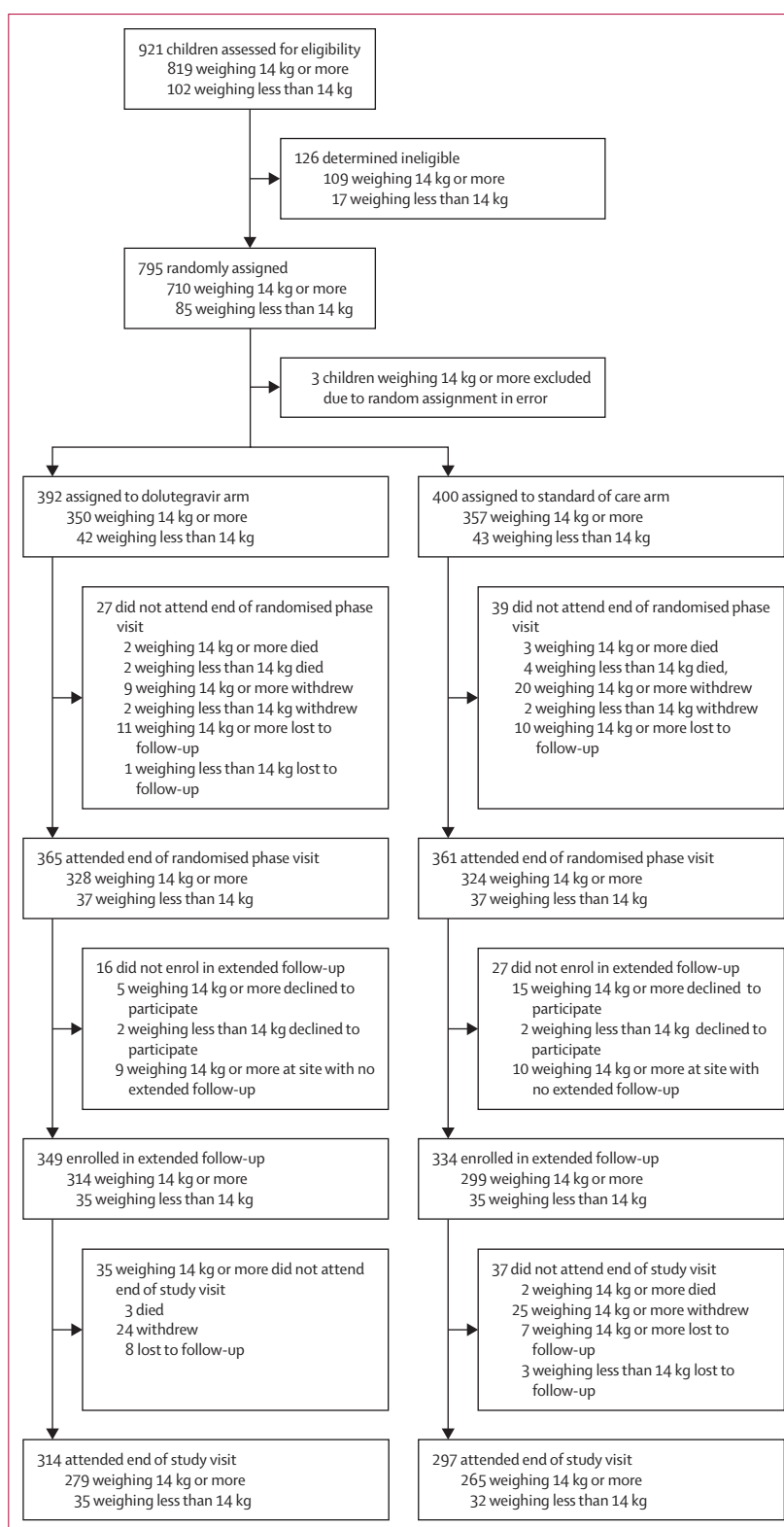


Figure 1: Trial profile

Further details on participant flow are provided in the appendix (pp 37–38).

	≥14 kg cohort (n=707)	<14 kg cohort (n=85)
Demographic characteristics		
Sex		
Male	362 (51%)	41 (48%)
Female	345 (49%)	44 (52%)
Race		
Black African	623 (88%)	83 (98%)
Asian	60 (8%)	0
White	6 (1%)	0
Other	18 (3%)	2 (2%)
Age, years	12.2 (9.1 to 14.9; 2.9 to 18.0)	1.4 (0.6 to 2.0; 0.1 to 5.9)
HIV infection characteristics		
WHO HIV-associated immunodeficiency (n=81 in the <14 kg cohort)*†		
Not significant	307 (43%)	22 (27%)
Mild	105 (15%)	9 (11%)
Advanced	58 (8%)	13 (16%)
Severe	237 (34%)	37 (46%)
Log ₁₀ viral load, copies per mL (n=706 in the ≥14 kg cohort; n=81 in the <14 kg cohort)†	4.4 (3.9 to 5.0)	5.3 (4.6 to 5.9)
NRTI backbone at randomisation		
Abacavir-lamivudine	463 (65%)	75 (88%)
Abacavir-tenofovir disoproxil fumarate	3 (<1%)	0
Tenofovir disoproxil fumarate or tenofovir alafenamide plus emtricitabine or lamivudine‡	164 (23%)	0
Zidovudine-lamivudine	77 (11%)	10 (12%)
Anchor drug class at randomisation		
INSTI	351 (50%)	44 (52%)
NNRTI	154 (22%)	9 (11%)
PI	202 (29%)	32 (38%)
Body composition		
Weight, kg	30.7 (23.4 to 43.0; 14.0 to 85.0)	8.1 (5.4 to 10.0; 3.4 to 13.4)
Height, cm	138.0 (124.9 to 152.5)	73.0 (61.0 to 80.3)
BMI, kg/m ²	16.3 (14.9 to 18.5)	15.0 (14.0 to 16.3)
BMI-for-age Z score	-0.6 (-1.4 to 0.1)	-0.8 (-1.9 to 0.2)
WHO nutritional status§		
Severely underweight or severe thinness	33 (5%)	26 (31%)
Moderately underweight or thinness	48 (7%)	13 (15%)
Normal or healthy weight	585 (83%)	43 (51%)
Overweight	35 (5%)	3 (4%)
Obese	6 (1%)	0
Waist-to-height ratio (n=188 in the ≥14 kg cohort)		
Median	0.45 (0.43 to 0.48)	..
<0.5	160 (85%)	..
≥0.5	28 (15%)	..
Bioelectrical impedance analysis: body fat percentage (n=461 in the ≥14 kg cohort)		
Median	15.4 (10.9 to 19.1)	..
Underfat	177 (38%)	..
Healthy	258 (56%)	..
Overfat	22 (5%)	..
Obese	4 (1%)	..

(Table 1 continues on next page)

South Africa, 146 (21%) in Zimbabwe, 61 (9%) in Thailand, eight (1%) in Germany, eight (1%) in Spain, eight (1%) in the UK, and one (<1%) in Portugal; 345 (49%) were female and 362 (51%) were male. At baseline, median age was 12.2 years (IQR 9.1 to 14.9), median weight 30.7 kg (23.4 to 43.0), height 138.0 cm (124.9 to 152.5), BMI 16.3 kg/m² (14.9 to 18.5), and BMI-for-age Z score -0.6 (-1.4 to 0.1). 35 (5%) participants were overweight and six (1%) were obese. Median waist-to-height ratio was 0.45 (0.43 to 0.48), with 28 (15%) of 188 participants having a ratio of 0.5 or more, indicating abdominal obesity. The median body fat percentage was 15.4% (10.9 to 19.1); 22 (5%) of 461 were classified as body fat percentage-defined overfat and four (1%) as obese. Of 85 participants in the less than 14 kg cohort, 83 (98%) were Black African and two (2%) reported race as other; all participants less than 14 kg were enrolled in Africa. 44 (52%) were female and 41 (48%) were male. At baseline, median age was 1.4 years (IQR 0.6 to 2.0), median weight was 8.1 kg (5.4 to 10.0), height 73.0 cm (61.0 to 80.3), and BMI-for-age Z score -0.8 (-1.9 to 0.2); three participants (4%) were overweight and none were obese.

ART at baseline is summarised in table 1. In the 14 kg or more cohort, 311 participants started first-line ART (in the standard of care arm 145 [92%] of 157 received efavirenz-based ART) and 396 initiated second-line ART (of 200 participants in the standard of care arm, 144 [72%] received lopinavir-ritonavir and 49 [25%] atazanavir-ritonavir; appendix pp 10–16). NRTI backbones were balanced across randomised arms: 463 (65%) participants received abacavir, 162 (23%) tenofovir disoproxil fumarate, and 77 (11%) zidovudine (table 1; appendix pp 10–23). In the less than 14 kg cohort, 72 (85%) of 85 children initiated first-line ART; among those in standard of care arm including children starting first-line and second-line ART 32 (74%) of 43 children received lopinavir-ritonavir. NRTI backbones were balanced: 75 (88%) participants received abacavir; ten (12%) received zidovudine (table 1; appendix pp 10–16).

In the 14 kg or more cohort, ten (1%) of 692 participants had elevated glucose, 103 (15%) of 684 had elevated total cholesterol, 81 (12%) of 692 had elevated triglycerides, and 84 (12%) of 692 elevated LDL cholesterol. In the less than 14 kg cohort, three (4%) of 76 participants had elevated glucose, ten (13%) of 77 had elevated total cholesterol, 34 (44%) of 77 had elevated triglycerides, and eight (11%) of 72 had elevated LDL cholesterol (table 1).

Median total follow-up (randomised phase and extended follow-up) to May 1, 2023, was 293 weeks (IQR 266–312) in the 14 kg or more cohort and 219 weeks (203–232) in the less than 14 kg cohort (appendix pp 37–38). In the 14 kg or more cohort, 95% in the dolutegravir arm and 83% in the standard of care arm remained on randomised allocation at 192 weeks, with 94% and 38% at 240 weeks, respectively; in the less

than 14 kg cohort, 100% in the dolutegravir arm and 72% in the standard of care arm remained on randomised allocation at 144 weeks, and 100% and 32% at 192 weeks, respectively (Kaplan–Meier estimates; appendix pp 24–25). 166 (23%) of 707 participants in the 14 kg or more cohort were censored before treatment switch by 240 weeks, and 15 (18%) of 85 participants in the less than 14 kg cohort by 192 weeks. In the 14 kg or more cohort, median follow-up on randomised allocation (excluding follow-up post-pregnancy) was 287 weeks (IQR 240–311) in the dolutegravir arm compared with 205 weeks (168–240) in the standard of care arm; and in the less than 14 kg cohort, 220 weeks (208–232) in the dolutegravir arm and 144 weeks (127–192) in the standard of care arm (appendix p 26).

For anthropometric parameters, in the 14 kg or more cohort, the mean weight gain over 240 weeks was 15.9 kg (SE 0.4) on dolutegravir and 14.9 kg (SE 0.4) on standard of care (dolutegravir minus standard of care 1.0 kg; 95% CI –0.2 to 2.2; $p=0.095$). The mean increase in MUAC on dolutegravir was 4.6 cm (SE 0.1), which was greater than on standard of care (4.1 [SE 0.1]; dolutegravir minus standard of care 0.4 cm; 95% CI 0.0 to 0.8; $p=0.030$). No differences were observed between dolutegravir and standard of care in height, BMI-for-age Z score, or body fat percentage (table 2, figure 2A).

In the 14 kg or more cohort, at week 240, an estimated 11% (95% CI 8 to 14) of children and adolescents living with HIV on dolutegravir and 10% (95% CI 7 to 13) on standard of care were overweight or obese, with no significant difference between dolutegravir and standard of care (table 3). Waist-to-height ratios were similar on dolutegravir and standard of care, and we found no difference between dolutegravir and standard of care in proportions of participants with central adiposity (waist-to-height ratio ≥ 0.5) or body fat percentage-defined overfat or obese status (table 3, appendix p 29). Treatment-emergent overweight or obesity was similar by treatment regimen (estimated proportions: dolutegravir 17%, standard of care 13%; dolutegravir minus standard of care 4%, 95% CI –3 to 9; $p=0.39$). New or increased abdominal fat accumulation assessed by visual inspection was reported at least once in five of 680 participants in the 14 kg or more cohort (in two [1%] of 338 participants on dolutegravir vs three [1%] of 342 participants on standard of care; all mild or moderate).

In analyses stratified by ODYSSEY-A and ODYSSEY-B within the 14 kg or more cohort, greater weight, height, and MUAC gains by 240 weeks on dolutegravir versus standard of care were seen in participants initiating first-line ART (ODYSSEY-A), where the standard of care comparator was mostly efavirenz, but not in those starting second line (ODYSSEY-B), where most participants on standard of care were receiving boosted protease inhibitors (figure 3, appendix p 27). Higher mean waist circumference and mean hip

	≥ 14 kg cohort (n=707)	<14 kg cohort (n=85)
(Continued from previous page)		
Metabolic parameters		
Glucose, mg/dL (n=692 in the ≥ 14 kg cohort; n=76 in the <14 kg cohort)		
Median	78 (70 to 85)	79 (70 to 92)
Not increased	682 (99%)	73 (96%)
Grade 1 or greater	10 (1%)	3 (4%)
Total cholesterol, mg/dL (n=684 in the ≥ 14 kg cohort; n=77 in the <14 kg cohort)		
Median	135 (117 to 155)	135 (101 to 154)
Not increased	581 (85%)	67 (87%)
Grade 1 or greater	103 (15%)	10 (13%)
Triglycerides, mg/dL (n=692 in the ≥ 14 kg cohort; n=77 in the <14 kg cohort)		
Median	88 (62 to 115)	146 (82 to 181)
Not increased	611 (88%)	43 (56%)
Grade 1 or greater	81 (12%)	34 (44%)
LDL cholesterol, mg/dL (n=692 in the ≥ 14 kg cohort; n=72 in the <14 kg cohort)		
Median	77 (62 to 97)	68 (46 to 89)
Not increased	608 (88%)	64 (89%)
Grade 1 or greater	84 (12%)	8 (11%)
HDL cholesterol, mg/dL (n=679 in the ≥ 14 kg cohort; n=67 in the <14 kg cohort)		
Median	41 (31 to 51)	35 (24 to 43)
≥ 40 mg/dL	360 (53%)	24 (36%)
<40 mg/dL	319 (47%)	43 (64%)

Data are n (%), median (IQR), or median (IQR; range). Percentages are for the non-missing proportion. Race was self-reported. INSTI=integrase inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor. *WHO 2007-defined HIV-associated immunodeficiency using CD4% or CD4 count, according to age. †At a participant level, the mean of the measured values was used if measured values were available at screening and randomisation. ‡Two participants in the standard of care group of the 14 kg or more cohort initiated tenofovir alafenamide and emtricitabine (one in ODYSSEY-A and one in ODYSSEY-B strata). §WHO classification of nutritional status in children younger than 5 years defined as: severely underweight weight-for-age Z score of less than –3SD; moderately underweight weight-for-age Z score of –3SD or greater to less than –2SD; overweight weight-for-height Z score more than 2SD to 3SD or less, and obese weight-for-height Z score of more than 3SD. In children aged 5 years or older, cutoffs were defined using BMI-for-age: severe thinness less than –3SD, thinness –3SD to less than –2SD, overweight more than 1SD to 2SD or less, and obese more than 2SD.²⁸ ¶Waist circumference and hip circumference were measured in participants aged 5 years or older at baseline (introduced 1 year into study; complete in 188 [27%] of 707 participants in the ≥ 14 kg cohort at baseline). ||Bioelectrical impedance analysis was performed at selected sites in Uganda (four sites) and Zimbabwe (one site) in participants at least 5 years old; body fat percentage categories defined by categorising body fat percentage, according to age and sex per TANITA Corporation definitions.²⁷

Table 1: Baseline characteristics

circumference at 240 weeks were also observed in participants in the ODYSSEY-A stratum who received dolutegravir compared with standard of care, but not in those in the ODYSSEY-B stratum (appendix p 30). We observed no differences between dolutegravir and standard of care in ODYSSEY-A or ODYSSEY-B strata in changes in BMI-for-age Z score, body fat percentage, or cross-sectional waist-to-height ratio (appendix pp 27–30) or proportions of participants with unfavourable anthropometric parameters and body composition endpoints (appendix p 31).

In the ODYSSEY-A stratum, where weight gain was higher on dolutegravir, there was no evidence of a difference in treatment effect for change in weight or BMI-for-age Z score by baseline age (<12 years vs ≥ 12 years) or sex or combined age and sex subgroups (all $p_{\text{interaction}} > 0.10$, appendix pp 32–35).

	≥14 kg cohort (baseline to week 240)						<14 kg (baseline to week 192)					
	Dolutegravir		Standard of care		Dolutegravir minus standard of care (95% CI)	p _{interaction (treatment arm × ODYSSEY-A or ODYSSEY-B)}	Dolutegravir		Standard of care		Dolutegravir minus standard of care (95% CI)	
	N*	Mean (SE)	N*	Mean (SE)			N*	Mean (SE)	N*	Mean (SE)		
Weight, kg	253	15.9 (0.4)	97	14.9 (0.4)	1.0 (−0.2 to 2.2); p=0.095	0.022	34	8.2 (0.2)	12	8.2 (0.3)	−0.1 (−0.8 to 0.7); p=0.83	
Height, cm	253	18.8 (0.4)	96	17.8 (0.4)	1.0 (−0.2 to 2.1); p=0.10	0.092	33	32.6 (0.8)	12	35.1 (0.7)	−2.5 (−4.5 to −0.5); p=0.016	
BMI-for-age Z score	253	0.34 (0.05)	96	0.22 (0.06)	0.11 (−0.03 to 0.26); p=0.13	0.19	33	0.19 (0.21)	12	−0.23 (0.28)	0.43 (−0.27 to 1.12); p=0.23	
Weight-for-age Z score	..	..	..	..	..	..	34	1.02 (0.12)	12	0.92 (0.18)	0.09 (−0.31 to 0.50); p=0.65	
Height-for-age Z score	..	..	..	..	..	..	33	1.48 (0.16)	12	1.61 (0.19)	−0.13 (−0.62 to 0.36); p=0.61	
MUAC, cm	252	4.6 (0.1)	97	4.1 (0.1)	0.4 (0.0 to 0.8); p=0.030	0.021	32	3.2 (0.2)	12	2.6 (0.3)	0.6 (−0.1 to 1.3); p=0.070	
Body fat percentage, %†	183	1.9 (0.4)	61	1.2 (0.5)	0.7 (−0.5 to 1.8); p=0.27	0.94	..	..	..	..	..	
Glucose, mg/dL	243	4.5 (0.7)	82	8.8 (1.0)	−4.4 (−6.8 to −1.9); p=0.0004	0.62	32	0.4 (2.2)	12	−13.5 (3.0)	13.9 (6.1 to 21.6); p=0.0005	
Total cholesterol, mg/dL	236	−1.9 (1.6)	84	13.3 (2.5)	−15.3 (−21.0 to −9.5); p<0.0001	0.39	33	11.8 (5.1)	12	14.6 (8.1)	−2.8 (−22.1 to 16.6); p=0.78	
Triglycerides, mg/dL	240	−6.5 (2.7)	84	8.0 (4.8)	−14.4 (−25.2 to −3.6); p=0.0089	0.1	32	−65.2 (8.6)	12	−36.2 (13.8)	−28.9 (−59.9 to 2.0); p=0.067	
HDL cholesterol, mg/dL	229	2.7 (0.7)	80	8.2 (1.1)	−5.5 (−8.0 to −2.9); p<0.0001	0.1	33	12.8 (1.7)	12	11.6 (2.7)	1.1 (−5.2 to 7.5); p=0.72	
LDL cholesterol, mg/dL	236	−3.4 (1.3)	78	0.1 (1.8)	−3.5 (−7.9 to 0.9); p=0.12	0.4	32	4.0 (4.1)	11	14.6 (7.1)	−10.6 (−26.3 to 5.2); p=0.19	

On-randomised allocation effects were estimated from marginal structural models with stabilised inverse probability weights to account for switch off randomised treatment regimen and censoring due to death, loss to follow-up, administrative censoring, or pregnancy (appendix pp 5–8). Mean change in continuous measures up to 240 weeks (≥14 kg cohort) and 192 weeks (<14 kg cohort) from baseline by trial arm and difference between trial arms (standard of care as reference) are calculated from linear mixed models with random intercept for participants and fixed effects for trial arm and visit weeks (3 knot cubic spline), including interaction between trial arm and visit weeks, adjusting for measure at baseline (plus interaction term between baseline measure [as categorical] and visit week) and other baseline variables: ODYSSEY-A or ODYSSEY-B, country or region, calendar month of randomisation (3 knot cubic spline), sex, age, weight, BMI-for-age Z score, CD4 (CD4% for <14 kg cohort), and log₁₀ viral load. Presenting mean change from a baseline weight 34.0 kg in the 14 kg or more cohort and 8.1 kg in the less than 14 kg cohort, height 138.5 cm and 71.9 cm, BMI-for-age Z score −0.7 and −0.9, weight-for-age Z score −2.2 (<14 kg cohort only), height-for-age Z score −2.5 (<14 kg cohort only), MUAC 20.0 cm and 13.1 cm, bioelectrical impedance analysis body fat percentage 15.2% (≥14 kg cohort only), total cholesterol 138.1 mg/dL and 127.9 mg/dL, glucose 78.2 mg/dL and 81.7 mg/dL, triglycerides 95.8 mg/dL and 159.2 mg/dL, HDL cholesterol 43.2 mg/dL and 34.0 mg/dL, LDL cholesterol 80.5 mg/dL and 69.8 mg/dL. MUAC=mid-upper-arm circumference. *Numbers of participants contributing to model at specified timepoint; ie, numbers remaining on randomised allocation with an observation available within the visit window; models are mixed models and include information across timepoints (using cubic splines for time) and observations are weighted to account for participants switching off randomised allocation and censoring. †Bioelectrical impedance analysis was performed at selected sites in Uganda (four sites) and Zimbabwe (one site) in participants aged at least 5 years. Analysis restricted to participants with a baseline age of at least 5 years (all in ≥14 kg cohort) at sites performing bioelectrical impedance analysis.

Table 2: Mean change in anthropometric, body composition, and metabolic endpoints from baseline comparing dolutegravir with standard of care, by weight cohort while on randomised allocation

In the less than 14 kg cohort, the mean weight gain over 192 weeks on dolutegravir was 8.2 kg (SE 0.2), with similar weight gain on dolutegravir and standard of care (−0.1 kg; 95% CI −0.8 to 0.7; p=0.83; table 2). At week 192, an estimated 1% (95% CI 0 to 5) of children on dolutegravir and 1% (95% CI 0 to 2) on standard of care were overweight or obese (dolutegravir minus standard of care 1%, 95% CI −3 to 4; p=0.80).

Although height gain was greater on standard of care (dolutegravir minus standard of care −2.5 cm; 95% CI −4.5 to −0.5; p=0.016; mean gain on dolutegravir 32.6 cm [SE 0.8] by week 192), we observed no difference in height-for-age Z score gains (table 2, appendix p 36). The mean MUAC gain over 192 weeks on dolutegravir was 3.2 cm (SE 0.2) and on standard of care was 2.6 cm (SE 0.3; dolutegravir minus standard of care 0.6 cm;

95% CI −0.1 to 1.3; p=0.070). No differences were observed between dolutegravir and standard of care in BMI-for-age Z scores, weight-for-age Z scores, or height-for-age Z scores (table 2). On dolutegravir and standard of care, BMI-for-age Z scores increased during the first 2 years of follow-up and subsequently declined (figure 2B), corresponding to a greater initial increase in weight-for-age Z score compared with height-for-age Z score in the first 2 years, followed by acceleration in height-for-age Z score gain thereafter (appendix p 36).

For metabolic parameters, in the 14 kg or more cohort total cholesterol remained unchanged and triglycerides decreased on dolutegravir, but both increased on standard of care, with statistically significant differences at 240 weeks favouring dolutegravir (dolutegravir minus standard of care −15.3 mg/dL, 95% CI

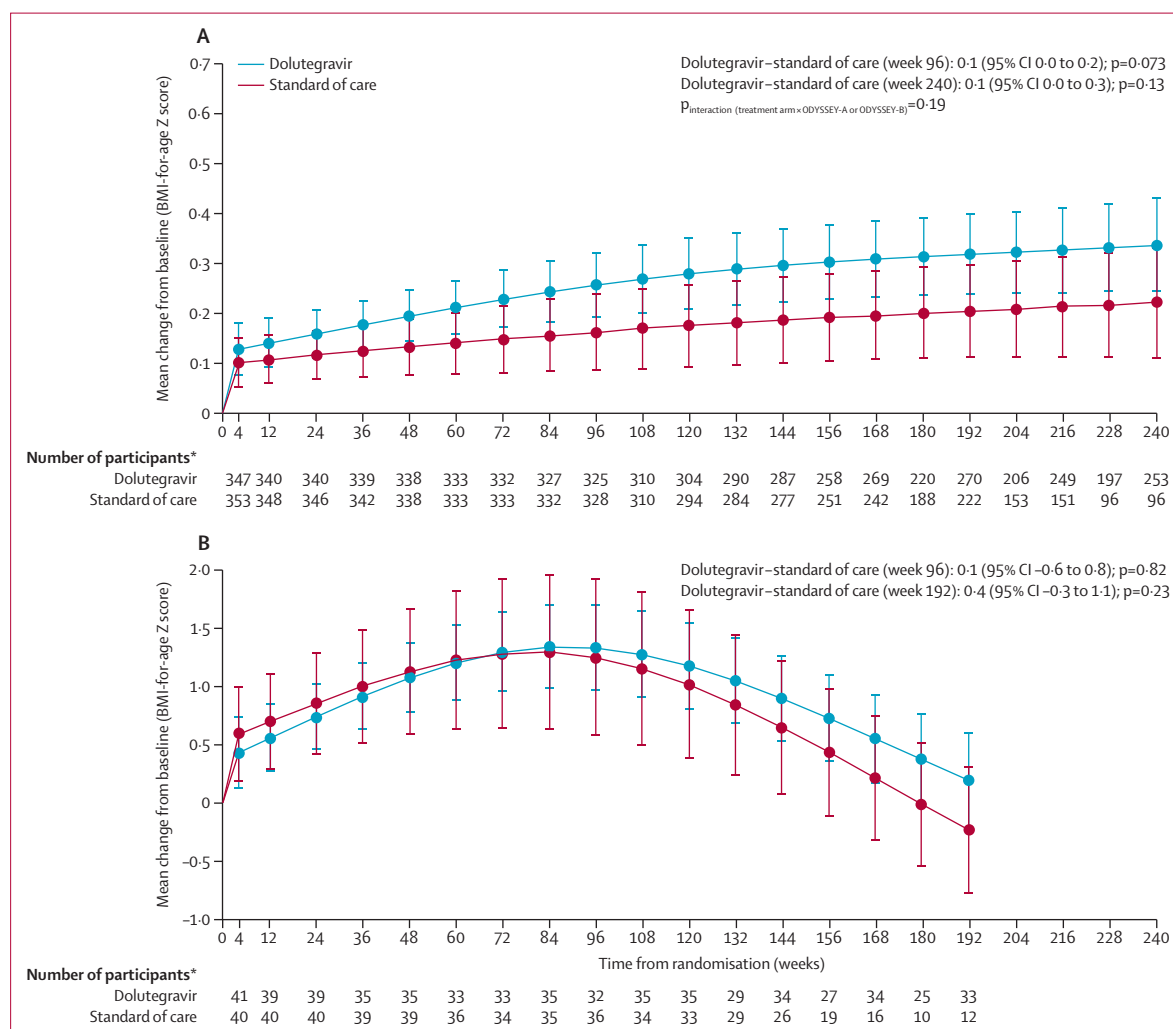


Figure 2: Change in BMI-for-age Z score by weight cohort while on randomised allocation

Change in BMI-for-age Z score in the 14 kg or more cohort (A) and in the less than 14 kg cohort (B). Vertical bars represent 95% CIs at each timepoint. Panel A and panel B use different scales. *Numbers of participants contributing to model at specified time point; ie, numbers remaining on randomised allocation with an observation available within the visit window. Models are mixed models and include information across time points (using cubic splines for time) and observations are weighted to account for participants switching off randomised allocation and censoring.

–21.0 to –9.5; $p<0.0001$ and –14.4 mg/dL, 95% CI –25.2 to –3.6; $p=0.0089$, respectively; table 2). LDL cholesterol decreased on dolutegravir but remained unchanged on standard of care, with no significant difference between dolutegravir and standard of care (–3.5 mg/dL; 95% CI –7.9 to 0.9; $p=0.12$). HDL cholesterol increased on dolutegravir and standard of care, but the increase was greater on standard of care (dolutegravir minus standard of care –5.5 mg/dL, 95% CI –8.0 to –2.9; $p<0.0001$). Higher proportions of participants on standard of care had grade 1 or worse increases in total cholesterol, triglycerides, but a lower proportion had low HDL cholesterol (<40 mg/dL). Glucose increased on dolutegravir and standard of care, with a smaller increase on dolutegravir (dolutegravir minus standard of care –4.4 mg/dL; 95% CI –6.8 to –1.9;

$p=0.0004$), and fewer children having grade 1 or worse increases (table 3).

In analyses stratified by ODYSSEY-A and ODYSSEY-B within the 14 kg or more cohort, the higher triglycerides concentration observed on standard of care primarily occurred in participants in ODYSSEY-B where most received boosted protease inhibitors (dolutegravir minus standard of care –9.2 mg/dL, 95% CI –22.3 to 3.8; $p=0.16$ for ODYSSEY-A; –18.9 mg/dL, 95% CI –34.1 to –3.8; $p=0.014$ for ODYSSEY-B; $p_{\text{interaction}}=0.10$; appendix p 27).

In the less than 14 kg cohort, total cholesterol, LDL cholesterol, and HDL cholesterol increased on both treatment regimens, with no significant differences between dolutegravir and standard of care (table 2). Triglyceride concentrations decreased on dolutegravir by

	Dolutegravir		Standard of care		Dolutegravir minus standard of care (95% CI)	P _{interaction} (treatment arm × ODYSSEY-A or ODYSSEY-B)
	N*	Proportion (95% CI)	N*	Proportion (95% CI)		
WHO-defined overweight or obese†	253	11% (8 to 14)	96	10% (7 to 13)	1 (−3 to 5); p=0.50	0.025
Body fat percentage overfat or obese‡	186	10% (7 to 13)	63	10% (6 to 15)	0 (−6 to 5); p=0.87	0.77
Waist-to-height ratio 0.5 or greater§	240	11% (7 to 14)	95	11% (7 to 15)	0 (−5 to 5); p=0.99	0.66
Glucose DAIDS grade 1 or worse¶	247	1% (0 to 3)	87	3% (1 to 6)	−2 (−5 to 1); p=0.19	0.48
Total cholesterol DAIDS grade 1 or worse¶	248	10% (7 to 13)	87	18% (12 to 25)	−9 (−16 to −1); p=0.018	0.70
Triglycerides DAIDS grade 1 or worse¶	247	7% (4 to 10)	87	15% (10 to 20)	−8 (−14 to −2); p=0.0089	0.12
LDL cholesterol DAIDS grade 1 or worse¶	243	6% (4 to 9)	81	7% (3 to 12)	−1 (−6 to 4); p=0.71	0.70
HDL cholesterol less than 40 mg/dL¶	245	35% (30 to 40)	83	21% (15 to 27)	14 (7 to 22); p=0.0003	0.25

On-randomised allocation effects were estimated from marginal structural models with stabilised inverse probability weights to account for switch off randomised treatment regimen and censoring due to death, loss to follow-up, administrative censoring, or pregnancy (appendix pp 5–8). Estimated proportions with unfavourable outcomes (95% CI) up to 240 weeks (≥14 kg cohort) by trial arm and difference between trial arms (standard of care as reference) are marginal estimates calculated from logistic mixed models with random intercept for participants and fixed effects for trial arm and visit weeks (3 knot cubic spline), including interaction between trial arm and visit weeks, adjusting for baseline variables: ODYSSEY-A or ODYSSEY-B, country or region, calendar month of randomisation (3 knot cubic spline), sex, age, weight, BMI-for-age Z score, CD4, and log₁₀ viral load. DAIDS=Division of AIDS. *Numbers of participants contributing to model at specified timepoint; ie, numbers remaining on randomised allocation with an observation available within the visit window; models are mixed models and include information across timepoints (using cubic splines for time) and observations are weighted to account for participants switching off randomised allocation and censoring. †WHO-defined overweight or obesity defined as: BMI of 25 and greater for participants aged at least 19 years, BMI-for-age Z score greater than 1 for children aged 5 years to less than 19 years, and weight-for-height Z score more than 2SD for children younger than 5 years.²⁶ ‡Body fat percentage defined as overfat or obese (versus underfat or healthy) using TANITA Corporation definition.²⁷ §Body circumference measures collected in participants at least 5 years old; analysis restricted to participants with a baseline age of at least 5 years (all in ≥14 kg cohort); body circumference measures introduced 1 year after start of trial recruitment, therefore adjustment for baseline not possible; unfavourable central adiposity defined as waist-to-height ratio of 0.5 or more.²⁸ ¶Metabolic parameters (total cholesterol, glucose, triglycerides, LDL cholesterol) were defined as grade 1 or worse laboratory event according to DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version 2.0); unfavourable HDL cholesterol defined as HDL cholesterol of less than 40 mg/dL.²⁹

Table 3: Proportion with unfavourable anthropometric parameters and metabolic outcomes at week 240 comparing dolutegravir with standard of care while on randomised allocation (≥14 kg cohort)

mean of 65.2 mg/dL (SE 8.6) and on standard of care by mean of 36.2 mg/dL (SE 13.8; dolutegravir minus standard of care −28.9 mg/dL; 95% CI −59.9 to 2.0; p=0.067). Glucose concentration decreased on standard of care but remained unchanged on dolutegravir (dolutegravir minus standard of care 13.9 mg/dL; 95% CI 6.1 to 21.6; p=0.0005).

Discussion

In the ODYSSEY trial, over approximately 5 years of follow-up, we found no evidence for excessive weight or body fat gain and no excess in central adiposity in children and adolescents living with HIV on dolutegravir-based ART, with reassuring metabolic outcomes on dolutegravir.

At 240 weeks an estimated 11% on dolutegravir in the 14 kg or more cohort were overweight or obese, while at 192 weeks, 1% of children living with HIV on dolutegravir in the less than 14 kg cohort were overweight or obese, with no significant differences between dolutegravir and non-dolutegravir regimens. These figures are comparable with current estimates in the general population in Africa, where overweight (including obesity) affects 15% of those aged 5–14 years and 5% of children younger than 5 years.^{1,31}

Children weighing 14 kg or more (535 [76%] of whom were aged ≥9 years at baseline) on dolutegravir experienced greater increase in MUAC compared with those on non-dolutegravir regimens, although absolute

differences were small (0.4 cm in the context of 4.6 cm gain on dolutegravir over 240 weeks). Overall, weight gain was similar on dolutegravir and standard of care (15.9 kg and 14.9 kg, respectively). Greater differences between treatment regimens in MUAC and weight, as well as height and waist circumference and hip circumference were seen in participants starting first-line ART (ODYSSEY-A), where the comparator anchor drug was primarily efavirenz, a drug known to have a weight-suppressing effect.³

In ODYSSEY overall and among participants on first line, we found no evidence of differences between dolutegravir and standard of care in anthropometric measures used to assess overweight and abdominal obesity, including BMI-for-age Z score, body fat percentage, and waist-for-height ratio. Furthermore, few cases of newly developed overweight or obesity were observed, with no differences between treatment regimens. While these findings and the estimated mean differences in these outcomes between regimens provide reassurance, the absence of significant differences between dolutegravir and standard of care regimens does not confirm that there are no differences, and interpretation should still consider the upper confidence limits, which indicate the worst-case scenarios. Clinical vigilance and monitoring for children on dolutegravir remains necessary.

Overall, our findings contrast with the adult ADVANCE and NAMSAL RCTs, conducted in Africa, which showed

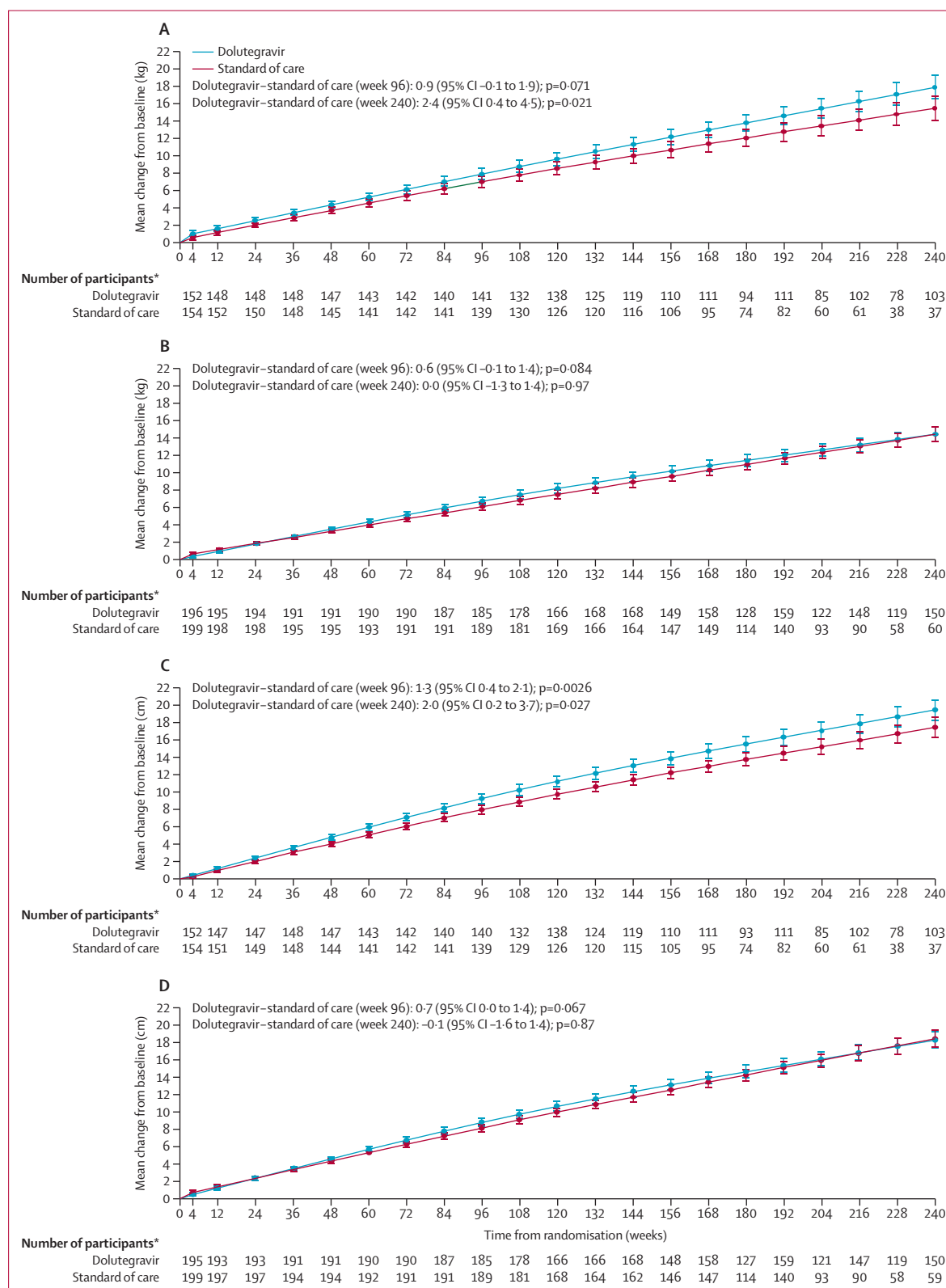


Figure 3: Change in weight and height by ODYSSEY-A and ODYSSEY-B strata in children weighing 14 kg or more while on randomised allocation

Change in weight in the ODYSSEY-A (A) and the ODYSSEY-B (B) strata and change in height in the ODYSSEY-A (C) and the ODYSSEY-B (D) strata. Vertical bars represent 95% CIs at each time point. *Numbers of participants contributing to model at specified time point; ie, numbers remaining on randomised allocation with an observation available within the visit window. Models are mixed models and include information across time points (using cubic splines for time) and observations are weighted to account for participants switching off randomised allocation and censoring. Weight $p_{\text{interaction}}(\text{treatment arm} \times \text{ODYSSEY-A or ODYSSEY-B}) = 0.022$, height $p_{\text{interaction}}(\text{treatment arm} \times \text{ODYSSEY-A or ODYSSEY-B}) = 0.092$.

significantly higher obesity rates in adults initiating dolutegravir-based versus efavirenz-based regimens, particularly among women.^{32,33} Our results also differ from adult studies reporting greater increases in waist circumference on dolutegravir compared with protease inhibitors,² but are consistent with those reporting greater increases on dolutegravir compared with NNRTIs.³⁴ Adult studies have not reported on waist-for-height ratio, which is considered a more reliable marker of abdominal obesity,²⁸ where we saw no difference between dolutegravir and non-dolutegravir regimens. The absence of difference in body fat percentage observed in our study also aligns with findings of no differences in trunk fat in the ADVANCE trial.³³

Although the paediatric CHAPAS-4 trial showed significantly greater weight-for-age Z score and BMI-for-age Z score gains on dolutegravir compared with lopinavir–ritonavir,⁵ their estimated differences were only marginally higher than those observed in participants in the ODYSSEY-B strata in the 14 kg or more cohort, receiving second-line dolutegravir versus standard of care (144 [72%] of 200 received lopinavir–ritonavir). We found no significant differences in weight, weight-for-age Z score, and BMI-for-age Z score gains in the less than 14 kg cohort, which included predominantly children younger than 2 years, with most (32 [74%] of 43) in the standard of care arm receiving lopinavir–ritonavir. On both dolutegravir and standard of care, gains in BMI-for-age Z scores, weight-for-age Z scores, and height-for-age Z scores over 192 weeks in this cohort likely reflect a return to health, characterised by rapid catch-up in weight and a delayed catch-up in height, patterns consistent with observations from African paediatric cohorts.³⁵

Data on the effect of dolutegravir on body composition in children and adolescents living with HIV remain scarce. A small cohort study using dual-energy X-ray absorptiometry (DEXA) in adolescents switching from protease inhibitors or NNRTIs to dolutegravir reported no significant changes in BMI, body fat, or limb fat, but a significant increase in median trunk fat after 12 months.²² However, the absence of a concurrent non-dolutegravir comparison arm makes it difficult to attribute the observed changes solely to dolutegravir exposure, as age-related pubertal development might have contributed.

In the ODYSSEY trial, total cholesterol and triglycerides were lower overall on dolutegravir; the clinical relevance of this is unclear but lower concentrations could be associated with better health outcomes in later life. These findings align with adult and paediatric studies indicating that the observed differences in atherogenic lipid fractions (total cholesterol, LDL cholesterol, and triglycerides) are driven primarily by comparator anchor drugs, with efavirenz and boosted protease inhibitors associated with more adverse lipid profiles than dolutegravir.^{5,9,22}

In ODYSSEY, glucose increase was lower on dolutegravir compared with standard of care in the 14 kg or more cohort. In the less than 14 kg cohort, glucose concentration decreased on standard of care, where most children received lopinavir–ritonavir, but remained stable on dolutegravir. Evidence for an association between dolutegravir and hyperglycaemia in adult studies is conflicting. A large network meta-analysis reported a higher incidence of grade 2 or worse hyperglycaemia with dolutegravir compared with efavirenz and atazanavir–ritonavir, but not when compared with other anchor drugs.² A 2023 systematic review and meta-analysis reported a lower overall risk of type 2 diabetes with INSTIs compared with other antiretroviral classes, but a higher risk associated with INSTIs in the subgroup of African populations.³⁶

Conducted at 29 sites in Africa, Europe, and Asia, ODYSSEY enrolled predominantly Black African children, largely recruited in African countries, representing the population most affected by paediatric HIV. Most sites were urban, and the absence of socioeconomic or family-structure data limits assessment of their influence on treatment outcomes. This study has other limitations. The interpretation of the effect of anchor drugs was limited by the use of different comparators in the standard of care arm. However, randomisation was stratified by ODYSSEY-A (first line) and ODYSSEY-B (second line), and most standard of care participants received efavirenz for first line and boosted protease inhibitors for second line, which enabled interpretation of changes attributable to the comparator drugs. Notably, only two participants initiated tenofovir alafenamide, thus we were unable to evaluate weight gain associated with dolutegravir used with tenofovir alafenamide. Additionally, subgroup analyses by age and sex in the ODYSSEY-A stratum in the 14 kg or more cohort and analyses in the less than 14 kg cohort were constrained by small sample sizes, which limited statistical power and might have led to an underestimation of differences between dolutegravir and standard of care regimens. Moreover, we did not have access to DEXA, the gold standard for assessing body composition, which might have limited our ability to detect subtle differences in fat distribution between dolutegravir and non-dolutegravir regimens, and we did not measure HbA_{1c}, a more reliable marker of glycaemic control. We also did not systematically collect blood pressure, precluding assessment of treatment effects on blood pressure or the prevalence of hypertension.

In conclusion, comparative long-term data from the ODYSSEY trial indicate a favourable safety profile for dolutegravir versus non-dolutegravir regimens across the paediatric age range for weight, body composition, and metabolic parameters, supporting dolutegravir's continued use as a preferred anchor drug for children and adolescents. Given the increasing global prevalence of childhood obesity, ongoing monitoring of metabolic health is essential.

Contributors

AT and DF designed the substudy. AT, EW and DF had full access to all the data in the study. EW and AT performed the statistical analysis, and EW, AT and DF verified the data reported. AT led the writing the paper. EW and DF critically reviewed and edited the first draft. All authors reviewed, made updates to, and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

AT, EW, AV, HAM, ARK, ALu, EK, SN-R, GMA, EV, MA, YA, TP, MB-D, DB, MK, ALi, CKö, SBW, YR, AB, TRC, PM, CKi, CG, DMG, and DF were investigators in the ODYSSEY trial funded by ViiV Healthcare via Penta Foundation. AT received funding from the UK Medical Research Council. MA received funding for research studies from Gilead Sciences and MSD paid to their institution and speaking fees from ViiV Healthcare. TP received research funding from ViiV Healthcare and Penta Foundation paid to their institution. AB has received fixed-term consultancy fees from the WHO-hosted Global Accelerator for Paediatric Formulations. PR received consulting fees from ViiV Healthcare and Gilead Sciences. AT is a co-chair of the WHO-led Paediatric Antiretroviral Working Group. AB and SBW are co-chairs of the Penta–European AIDS Clinical Society Paediatric HIV Treatment Guidelines Working Group. AT and AB are members of the Penta ID Scientific Steering Committee. MA is a vice chair of the IMPAACT Therapeutic Scientific Committee. CKö is a member of the Advisory Council for Robert Koch Institute and German AIDS Society. SBW is a chair of the Penta Training Committee; Penta Foundation has received educational grants from ViiV Healthcare and Gilead Sciences. All other authors declare no competing interests.

Data sharing

The ODYSSEY data are held at the Medical Research Council Clinical Trials Unit at University College London (London, UK), which encourages optimal use of data by using a controlled access approach to data sharing, incorporating a transparent and robust system to review requests, and provide secure data access consistent with the relevant ethics committee approvals. We will consider all requests for data sharing, which can be initiated by contacting mrcctu.ctuenquiries@ucl.ac.uk.

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