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

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Abstract (word count 375)

Background: ODYSSEY demonstrated superior efficacy of dolutegravir (DTG)-based antiretroviral therapy (ART) versus then-current non-DTG standard-of-care (SOC), over 96 weeks in children starting first- or second-line treatment, and in cohorts enrolled weighing ≥14kg and <14kg. During extended follow-up children in the SOC arm switched to DTG. This secondary analysis compares anthropometric, body fat percentage (BF%) and metabolic outcomes between DTG and SOC.

Methods: Treatment effects (DTG-SOC) were estimated on randomised allocation, accounting for treatment- switches 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.

Findings: 792 children were randomised (392 DTG,400 SOC): 707 ≥14kg, including 311 first-line (SOC 92% efavirenz); 396 second-line (SOC 98% boosted protease inhibitors), 85 <14kg, 72 first-line (first- and second-line SOC 74% lopinavir/ritonavir). 576(81%) children ≥14kg and 70(82%) <14kg were followed to 240 and 192 weeks, respectively.

In the ≥14kg cohort, 49% were female, enrolment median age(IQR) was 12.2years(9.1-14.9), weight 31kg(23-43) and body-mass-index (BMI)-for-age Z-score(BAZ) -0.6 (-1.4-0.1); 5% were overweight, 1% obese. Increases in weight and mid-upper-arm circumference (MUAC) were marginally higher on DTG than SOC; adjusted differences in means (DTG-SOC) at 240 weeks were 1.0kg(95%CI -0.2 to 2.2; P=0.095) and 0.4cm(0 to 0.8; P=0.030), driven by differences in first-line participants, where higher increases were also observed in height, waist and hip circumference. Increases in BAZ, BF% and cross-sectional waist-to-height ratios were similar on DTG and SOC. Total cholesterol, triglycerides and glucose were lower on DTG than SOC (-15.3mg/dL(-21.0, -9.5); P<0.0001; -14.4mg/dL (-25.2, -3.6); P=0.0089; -4.4mg/dL(-6.8, -1.9); P=0.00039).

In the <14kg cohort, 52% were female, enrolment age(IQR) was 1.4years(0.6-2.0), weight 8kg(5-10) and BAZ -0.8(-1.9-0.2); 4% were overweight, none obese. Changes in weight, weight-for-age, BMI-for-age and height-for-age Z-scores by 192 weeks were similar on DTG and SOC; there were small differences in MUAC and height (0.6cm(-0.1, 1.3); P=0.07; -2.5cm(-4.5, -0.5); P=0.016). No significant differences in lipid biomarkers were observed; glucose decreased on SOC but not on DTG.

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

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Keywords:

HIV; children; adolescents; dolutegravir; weight-gain; body fat percentage; lipid profile; glycaemia

Research in context

Evidence before this study

ODYSSEY, an open-label, randomised controlled trial, demonstrated superior virological and clinical outcomes with dolutegravir (DTG)-based antiretroviral therapy (ART) compared to then-current non-DTG standard-of-care regimens in children initiating first- or second-line treatment. In adult studies, DTG has been associated with excess 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 DTG initiation or 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 RCT in virologically-suppressed children and adolescents, found greater gains in weight, weight-for-age, BMI and BAZ on DTG plus darunavir/ritonavir compared to SOC (mostly efavirenz- 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 BAZ on DTG compared to lopinavir/ritonavir, but changes were similar on DTG versus darunavir/ritonavir or atazanavir/ritonavir. Findings from the observational studies in children and adolescents were mixed: three reported higher weight, BMI and/or BAZ with DTG, while others found no significant differences after switching to DTG. A few studies, including a systematic review, reported favourable changes in atherogenic lipid fractions with DTG compared to other anchor drugs.

Added value of this study

This is the first long-term randomised comparison of weight gain, body composition and metabolic outcomes in children and adolescents on DTG versus non-DTG ART. After approximately 5 years of follow-up, children in the ≥14 kg cohort initiating first-line DTG-based ART (three quarters aged ≥9 years) had greater increases in mean weight (DTG-SOC 2.4kg), height (2.0cm), MUAC (1.1cm), and waist (2.6cm) and hip (4.6cm) circumferences compared with those on non-DTG SOC (92% started efavirenz). Reassuringly, there were no differences between DTG and other anchor drugs in anthropometric and body composition measures indicative of excessive weight gain or central adiposity, including BMI-for-age Z-score, body fat percentage, and waist-to-height ratio. No differences between DTG and non-DTG SOC were observed in children starting second-line ART (98% SOC participants started boosted protease inhibitors) or in the <14 kg cohort (three quarters <2

years of age at enrolment; 74% SOC participants started lopinavir/ritonavir). In both weight cohorts, few children became newly overweight, with no differences by DTG versus non-DTG based ART. Lipid and glycaemic profiles in children on DTG were reassuring.

Implications of all the available evidence

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

Manuscript (word count 3968)

Introduction

Over the past three decades, the proportion of children and adolescents who are overweight or obese 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 (CALHIV) may be at increased risk of early metabolic and cardiovascular comorbidities compared to their HIV-negative peers.

Weight gain in CALHIV 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 CALHIV initiate or switch to effective ART, resulting in a significant catch-up in weight. The second effect relates to comparator drugs, as weight gain with an investigational drug may appear greater when compared with agents known to attenuate weight.[2,3] Lastly, increasing weight gain in the general population ("societal norm") play a role,[3] and CALHIV with well-controlled HIV are expected to gain weight at similar rates to their HIV-negative peers.

Understanding the impact 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 (DTG) is currently recommended as the preferred anchor drug by the World Health Organization (WHO)[7] and is the most commonly used anchor drug worldwide.[8] However, concerns have been raised regarding the potential of DTG to promote excessive weight gain. This effect has predominantly been observed in comparisons of DTG combined with tenofovir alafenamide (TAF) to regimens containing drugs with weight-supressing effects, such as efavirenz (EFV), lopinavir/ritonavir (LPV/r) and tenofovir disoproxil fumarate (TDF).[2,3]

While INSTIs, including DTG, are associated with improved lipid profiles in adults, compared to other anchor drugs,[9] concerns persist that these benefits may be offset by excessive weight gain and the development of metabolic syndrome. Metabolic syndrome, characterised by central obesity along with glucose intolerance, hypertension and/or dyslipidaemia, predisposes individuals to cardiovascular disease, type II diabetes and other non-communicable diseases.[10] The association between DTG and metabolic syndrome remains unclear, with some adult studies indicating a higher prevalence for DTG, while others have found no association.[11,12]

Data on DTG-associated weight gain in CALHIV are limited. Some studies have reported greater gains in weight and BMI and/or BAZ,[5,13-17] while others have found no impact.[18-21] A few studies have reported a better lipid profile with DTG compared to other anchor drugs.[5,22]

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

Methods

Study design

ODYSSEY (ClinicalTrials.gov NCT02259127) was an open-label multicentre, randomised, non-inferiority trial which compared efficacy and safety of DTG-based treatment (DTG arm) with then-current non-DTG-based standard of care (SOC 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 ≥14kg were recruited between 20 September 2016 and 22 June 2018. After DTG dispersible tablets became available for younger children, an additional 85 children weighing <14kg were recruited between 05 July 2018 and 26 August 2019.

Randomised follow-up was until the last participant reached week 96 (≥14kg cohort, 24 April 2020; <14kg cohort, 28 June 2021). Extended follow-up in African and Thai sites continued until 01 May 2023, when the last participant in the ≥14kg cohort reached 240 weeks and the last participant in the <14kg cohort reached 192 weeks. During extended follow-up, children in the SOC arm transitioned to DTG following national guidelines. We conducted a secondary analysis of changes in anthropometric, body composition and metabolic parameters.

Participants

Participants were CALHIV, aged 4 weeks or older and below 18 years, and weighing at least 3 kg, starting first-line 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 within 4 weeks of 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. Children or their carers (or both) gave written informed consent and assent as appropriate to participate in the ODYSSEY trial and re-consented/re-assented for extended follow-up.

Randomisation and masking

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

Procedures

Children were seen at weeks 4, 12 and 12-weekly 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, 12-weekly in randomised phase, and 12- or 24-weekly in extended follow-up, dependent on site. Waist and hip circumferences were measured in participants aged ≥5 years at baseline (introduced 1 year into study; complete in 27% of ≥14kg participants at baseline) and 48-weekly during randomised and extended follow-up phases. Bioelectrical impedance analysis (BIA) measures of body composition were taken in participants aged ≥5 years at the sites in Uganda and Zimbabwe (66% of ≥14kg participants) at baseline and 48-weekly during randomised and extended follow-up phases. Clinical assessments of fat accumulation (mild/moderate/severe in neck/upper back, breast and abdomen) were made at baseline and 48-weekly during the randomised phase. Total cholesterol (TC), glucose, triglycerides, cholesterol fractions (LDL-C, HDL-C) were measured at baseline and 48-weekly 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, body composition and metabolic parameters. Change in TC, triglycerides , LDL-C and HDL-C from baseline to weeks 48 and 96 were pre-specified trial secondary outcomes. Outcomes beyond week-96 and all other outcomes are exploratory. WHO reference data were used for age-standardisation of BMI;[24,25] BMI-for-age Z-scores (BAZ) in adolescents >19 years of age were estimated based on reference data for 19-year-olds.

Unfavourable anthropometric, body composition and metabolic parameters were defined as follows: BMI≥25 for participants aged at least 19, BAZ >+1 SD for children aged 5–<19 years, and weight-for-height >+2 SD for children under 5 years,[26] indicating overweight/obesity; body fat percentage (BF%) categorised as overfat/obese per TANITA Corporation definitions;[27] waist-to-height ratio ≥0.5 indicating central adiposity;[28] TC, glucose, triglycerides, and LDL-C ≥Grade 1 based on DAIDS grading (Version 2.0, November 2014); and HDL-C <40 mg/dL.[29]

Statistical analysis

All analyses were conducted separately for the ≥14kg and <14kg cohorts, due to higher variability in outcome measures in the ≥14kg cohort and the different follow-up periods. Follow-up was censored at the earlier of 01 May 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 -27 days to + 27 days was used, and week 12 where the window -28 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 2 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. Outcomes were not included for scheduled visits once the number of participants on DTG and/or SOC had dropped <10.

Analysis is "on-randomised allocation". Treatment regimens of interest were defined as DTG-based ART for a participant assigned to the DTG arm and alternative non-DTG-based ART for a participant assigned to the SOC arm. Participants were artificially censored after they switched from their allocated treatment regimen, defined as a participant in the DTG arm starting non-DTG-based ART or a participant in the SOC arm starting DTG-based ART. Inverse-probability weights were used to adjust for artificial censoring and were estimated by trial arm and ODYSSEY A and B (≥14kg 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 <14kg cohort) and $\log_{10}$ viral load.

Mean change in continuous measures up to 240 weeks (**≥**14kg cohort) and 192 weeks (<14kg cohort) from baseline by DTG and SOC and difference between DTG and SOC (SOC 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 10^{th}, 50^{th}, 90^{th} percentiles, specified according to weight cohort), interaction terms between treatment regimen and visit week spline variables, and other baseline variables: ODYSSEY A/B, country or region, calendar month of randomisation (3 knot cubic spline at 10^{th}, 50^{th}, 90^{th} percentiles, specified according to weight cohort), sex, age, weight, BMI-for-age Z-score, CD4 (CD4% for <14kg cohort), and $\log_{10}$ 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/obese by 240 weeks was estimated by trial arm based on estimates of the probability of becoming overweight/obese by visit window from a pooled logistic regression model in those not overweight/obese at enrolment or previously in follow-up.

Analyses of the ≥14kg cohort were performed across the total population (adjusting for ODYSSEY A/B), and for ODYSSEY A and B separately, with interactions between treatment regimen and ODYSSEY A/B tested in a joint model. Exploratory subgroup analyses by age and sex were conducted in joint models for weight and BAZ in populations where a significant treatment effect was shown for weight. Analyses of the <14kg cohort were performed across the total population (adjusting for ODYSSEY A/B), as small numbers in ODYSSEY B precluded meaningful comparisons.

Full details of statistical methods are given in the appendix.

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

Baseline characteristics

A total of 792 CALHIV were randomised (392 to DTG, 400 to SOC), including 707 in the ≥14kg cohort and 85 in the <14kg cohort (table 1). **In the ≥14kg cohort (n=707)**, 88% participants were enrolled in Africa (47% Uganda, 20% South Africa, 21% Zimbabwe), 9% Thailand, 4% Europe; 49% were female. At baseline, median age was 12.2 years (IQR 9.1, 14.9), median weight 30.7kg (23.4, 43.0), height 138.0cm (124.9, 152.5), BMI 16.3kg/m^2 (14.9, 18.5) and BAZ -0.6(-1.4, 0.1). Thirty-five participants (5%) were overweight and six (1%) were obese. Median waist-to-height ratio was 0.45 (0.43, 0.48), with 28 participants (15%) having a ratio ≥0.5, indicating abdominal obesity. The median BF% was 15.4% (10.9, 19.1); 5% were classified as BF%-defined overfat and 1% as obese. **In the <14kg cohort (n=85)**, all participants were enrolled in Africa. 52% were female. At baseline, median age was 1.4 years (0.6, 2.0), median weight 8.1kg (5.4, 10.0), height 73.0cm (61.0, 80.3) and BAZ -0.8 (-1.9 to 0.2); three participants (4%) were overweight and none obese.

ART at baseline is summarised in table 1. **In the ≥14kg cohort**, 311 participants started first-line ART (in the SOC arm 145(92%) received EFV-based ART) and 396 initiated second-line ART (in the SOC arm 144(72%) received LPV/r and 49(25%) atazanavir/ritonavir (ATV/r)). NRTI backbones were balanced across randomised arms: 463(65%) received abacavir, 162(23%) TDF and 77(11%) zidovudine (appendix tables S1, S2). **In the <14kg cohort,** 72 children (85%) children initiated first-line ART; among those in SOC across both first and second lines, 32(74%) received LPV/r. NRTI backbones were balanced: 75(88%) received abacavir; 10(12%) zidovudine (appendix table S1).

Metabolic parameters at baseline are presented in table 1. **In the ≥14kg cohort,** 10(1%) had elevated glucose, 103(15%) elevated TC, 81(12%) elevated triglycerides and 84(12%) elevated LDL-C. **In the <14kg cohort,** three participants (4%) had elevated glucose, 10(13%) elevated TC, 34(44%) elevated triglycerides and 8 (11%) elevated LDL-C.

Median follow-up was 293 weeks (IQR 266 to 312) in the ≥14kg cohort and 219 weeks (IQR 203 to 232) in the <14kg cohort. In the ≥14kg cohort, 95% in DTG arm and 83% in SOC arm remained on randomised allocation at 192 weeks, with 94% and 38% at 240 weeks, respectively; in the <14kg cohort, 100% in DTG arm and 72% in SOC arm remained on randomised allocation at 144 weeks, and 100% and 32% at 192 weeks, respectively (Kaplan-Meier estimates). 23% (166/707) in the ≥14kg cohort were censored prior to treatment switch by 240 weeks, and 18% (15/85) in the <14kg cohort by 192 weeks.

Anthropometric parameters

In the ≥14kg cohort, the mean weight gain over 240 weeks on DTG was 15.9kg, with a borderline higher weight gain observed on DTG compared to SOC (DTG-SOC 1.0kg; 95%CI -0.2, 2.2; P=0.095). The mean increase in MUAC on DTG was 4.6cm, greater on DTG than SOC (0.4cm; 95%CI 0, 0.8; P=0.030). No differences were observed between DTG and SOC in height, BAZ or BF% (table 2, figure 1).

At week 240, 11.2% (95%CI 8.3 to 14.0) of CALHIV on DTG and 9.8% (95%CI 6.8 to 12.8) on SOC were overweight or obese, with no difference between DTG and SOC (table 3). Waist-to-height ratios were similar on DTG and SOC, and there was no difference between DTG and SOC in proportions of participants with central adiposity (waist-to-height ratio ≥0.5) or BF%-defined overfat or obese status (tables 3, 4). Treatment emergent overweight or obesity was similar by treatment regimen (DTG 16.9%, SOC 12.9%; DTG-SOC 4.0%, 95%CI -3.5, 8.9; P=0.39). New or increased abdominal fat accumulation assessed by visual inspection was reported at least once in 5 of 680 participants in the ≥14kg cohort (2/338 (0.6%) DTG vs. 3/342 (0.9%) SOC; all mild or moderate).

In analyses stratified by ODYSSEY A and ODYSSEY B within the ≥14kg cohort, greater weight, height and MUAC gains by 240 weeks on DTG versus SOC were seen in participants initiating first-line ART (ODYSSEY A), where the SOC comparator was mostly EFV, but not in those starting second line (ODYSSEY B) where most participants on SOC receiving boosted protease inhibitors (PIs) (figure 2, appendix table S3). Higher mean waist and hip circumferences at 240 weeks were also observed in ODYSSEY A participants on DTG compared to SOC, but not in ODYSSEY B (appendix table S4). There were no differences between DTG and SOC in ODYSSEY A or ODYSSEY B in change in BAZ, BF% or cross-sectional waist-to-height ratio (appendix tables S3, S4) or proportions of participants with unfavourable anthropometric and body composition endpoints (appendix table S5).

In ODYSSEY A, where weight gain was higher on DTG, there was no evidence of a difference in treatment effect for change in weight or BAZ by baseline age and sex (interaction P=0.60 and P=0.36, respectively, appendix figure S2).

In the <14kg cohort, the mean weight gain over 192 weeks on DTG was 8.2kg, with no difference between DTG and SOC (-0.1kg; 95%CI -0.8, 0.7; P=0.83) (table 2). At week 192, 1.1% (95%CI 0 to 4.7) of CALHIV on DTG and 0.6% (95%CI 0 to 1.6) on SOC were overweight or obese, with no difference between DTG and SOC (P=0.80).

Although height gain was greater on SOC (-2.5cm; 95%CI -4.5, -0.5; P=0.016; mean gain on DTG 32.6cm by week 192), there was no difference in height-for-age Z-score gains (table 2, figure S4). MUAC gain was borderline higher on DTG (0.6cm; 95%CI -0.1, 1.3; P=0.07). No differences were observed between DTG and SOC in BAZ, WAZ or HAZ scores (table 2). On DTG and SOC, BAZ

increased during the first two years of follow-up and subsequently declined (figure 1, panel B), corresponding to a greater initial increase in WAZ compared to HAZ in the first two years, followed by acceleration in HAZ gain thereafter (figure S4).

Metabolic parameters

In the ≥14kg cohort: TC remained unchanged and triglycerides decreased on DTG but both increased on SOC, with statistically significant differences at 240 weeks favouring DTG (DTG-SOC -15.3mg/dL, 95%CI -21.0, -9.5; P<0.0001 and -14.4 mg/dL, 95%CI -25.2, -3.6; P=0.0089, respectively) (table 2). LDL-C decreased on DTG but remained unchanged on SOC, with no significant difference between DTG and SOC (-3.5mg/dL; 95%CI -7.9, 0.9; P=0.12). Glucose increased on DTG and SOC, with a smaller increase on DTG (-4.4mg/dL; 95%CI -6.8, -1.9; P=0.00039), and fewer children having grade ≥1 elevations (table 3). HDL-C increased on DTG and SOC, but the increase was greater on SOC (-5.5mg/dL, 95%CI -8.0, -2.9; P<0.0001). Higher proportions of participants on SOC had grade ≥1 elevations in TC, triglycerides, but a lower proportion had low HDL-C (<40mg/dL).

In analyses stratified by ODYSSEY A and B within the ≥14kg cohort, the higher triglycerides levels observed on SOC primarily occurred in participants in ODYSSEY B where most received boosted PIs (DTG-SOC ODYSSEY A -9.2mg/dL, 95%CI -22.3, 3.8; P=0.16; ODYSSEY B -18.9mg/dL, 95%CI -34.1, -3.8; P=0.014; interaction P=0.10; table S3).

In the <14kg cohort, TC, LDL-C, as well, as HDL-L increased in both groups, with no significant differences between DTG and SOC (table 2). Triglyceride levels decreased on both treatment regimens, with a greater reduction observed on DTG (DTG-SOC -28.9mg/dL; 95%CI -59.9, 2.0; P=0.067). Glucose levels decreased on SOC but remained unchanged on DTG (DTG-SOC 13.9mg/dL; 95%CI 6.1, 21.6; P=0.00049).

Discussion

ODYSSEY is the first paediatric RCT to present comparative long-term data on the impact of DTG versus non-DTG regimens on weight gain, body composition and metabolic parameters across a wide age range, from >4 weeks of age through adolescence. The trial demonstrates that DTG-based ART is not associated with excessive weight or body fat gain in CALHIV over approximately five years of follow-up; metabolic outcomes on DTG were also reassuring.

At 240 weeks 11% on DTG in the ≥14 kg cohort were overweight or obese, while at 192 weeks, 1.1% of CALHIV on DTG in the <14kg cohort were overweight or obese, with no significant differences between DTG and non-DTG regimens. These figures are comparable to current estimates in the general population in Africa, where overweight (including obesity) affects 15% of those aged 5-14 years and 5% of children <5 years.[1,31]

Children weighing ≥14 kg (75% of whom were aged ≥9 years at baseline) on DTG experienced borderline higher weight gain and greater MUAC increases compared to those on non-DTG regimens, although absolute differences were small (1kg and 0.4cm respectively in the context of gains of 15.9kg and 4.6cm on DTG over 240 weeks). These differences, as well as greater increases in height and waist and hip circumferences were driven by participants starting first-line ART (ODYSSEY A), where the comparator anchor drug was primarily EFV, a drug known to have a weight-suppressing effect.[3]

It is reassuring that in ODYSSEY overall and among participants on first line, we found no evidence of differences between DTG and SOC in anthropometric measures used to assess overweight and abdominal obesity, including BAZ, BF% and waist-for-height ratio. Furthermore, few cases of newly developed overweight or obesity were observed, with no differences between treatment regimens.

Overall, our findings contrast with the adult ADVANCE and NAMSAL RCTs, conducted in Africa, which showed significantly higher obesity rates in adults initiating DTG-based versus EFV-based regimens, particularly among women.[32,33] Our results also differ from adult studies reporting greater increases in waist circumference on DTG compared to PIs,[2] but are consistent with those reporting greater increases on DTG compared to 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 DTG and non-DTG regimens. The lack of difference in BF% in our study also aligns with findings for no differences in trunk fat in the ADVANCE trial.[33]

In contrast to the paediatric CHAPAS-4 trial, which showed greater WAZ and BAZ gains on DTG compared to LPV/r,[5] we observed similar BAZ in ODYSSEY B participants in the ≥14kg cohort, receiving second-line DTG and SOC (72% received LPV/r). Also, we found no significant differences in weight, WAZ and BAZ gains in the <14 kg cohort, which included predominantly children <2 years of age, with most (74%) in the SOC arm receiving LPV/r. On both DTG and SOC, gains in BMI-, weight-, and height-for-age Z-scores over 192 weeks in this cohort likely reflected 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 DTG on body composition in CALHIV remain limited. A small cohort study using dual-energy X-ray absorptiometry (DEXA) in adolescents switching from PIs or NNRTIs to DTG 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-DTG comparison group makes it difficult to attribute the observed changes solely to DTG exposure, as age-related pubertal development may have contributed.

In the ODYSSEY trial, TC and triglycerides were lower overall on DTG; the clinical significance of this is unclear but lower levels could be associated with better health outcomes in later life. These findings align with adult and paediatric studies demonstrating lower atherogenic lipid fractions (TC, LDL-C and triglycerides) with DTG than with NNRTIs or PIs.[5,9,22]

In ODYSSEY, glucose increase was lower on DTG compared to SOC in the ≥14kg cohort, and there was a trend towards fewer participants on DTG experiencing grade ≥1 hyperglycaemia. In the <14 kg cohort, glucose levels decreased on SOC, where most children received LPV/r, but remained stable on DTG. Evidence for an association between DTG and hyperglycaemia in adult studies is conflicting. A large network meta-analysis reported a higher incidence of grade ≥2 hyperglycaemia with DTG compared to EFV and ATV/r, but not when compared to other anchor drugs.[2] A recent systematic review and meta-analysis reported a lower overall risk of type II diabetes with INSTIs compared to other antiretroviral classes, but a higher risk associated with INSTIs in the subgroup of African populations.[36]

In ODYSSEY, interpretation of the effect of anchor drugs was limited by the use of different comparators in the SOC arm. However, randomisation was stratified by ODYSSEY A (first line) and

ODYSSEY B (second line), and most SOC participants received EFV for first line and boosted PIs for second line, which enabled interpretation of changes attributable to the comparator drugs. Notably only 2 participants initiated TAF, thus we were unable to evaluate weight gain associated with DTG used with TAF. Additionally, subgroup analyses by age and sex in ODYSSEY A in the ≥14kg cohort and analyses in the <14 kg cohort were constrained by small sample sizes, which limited statistical power and may have led to an underestimation of differences between DTG and SOC regimens. Moreover, we did not have access to DEXA, the gold standard for assessing body composition, which may have limited our ability to detect subtle differences in fat distribution between DTG and non-DTG regimens, and we did not measure HbA1c, a more reliable marker of glycaemic control.

In conclusion, over approximately five years of follow-up, the ODYSSEY trial demonstrated that DTG-based ART was not associated with excessive weight gain, increase in body fat percentage or central adiposity in children and adolescents. Furthermore, reassuring lipid and glycaemic profiles were seen in children on DTG. These findings highlight the favourable safety profile of DTG regarding weight and metabolic parameters, supporting its continued use as a preferred anchor treatment option 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 on 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.

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.

Declaration of interests

AT, EW, AV, HM, ARK, ALu, EK, SNR, GMA, EV, MA, YA, TP, MBD, DB, MK, ALi, CKö, SBW, YR, AB, TC, PM, CKi, CG, DMG, 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 SW are cochairs 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.

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Figure 1. Change in BMI-for age Z-scores (≥14kg cohort and <14kg cohort)

Figure 2. Change in weight and height by ODYSSEY A and B (≥14kg cohort)

Figure 3. Change in BMI-for-age, body fat percentage by ODYSSEY A and B (≥14kg cohort)

Appendix

ODYSSEY Trial Team

Supplementary statistical methods

Figure S1. ODYSSEY trial schema

Figure S2. ODYSSEY CONSORT diagram (randomised and extended follow-up)

Table S1. Baseline characteristics by weight cohort

Table S2. Baseline characteristics by ODYSSEY A and B (≥14kg cohort)

Table S3. On-randomised allocation: mean change in anthropometric, body composition and metabolic endpoints from baseline to 240 weeks comparing dolutegravir with standard of care, by ODYSSEY A/B (≥14kg cohort)

Table S4. On randomised allocation: cross-sectional means in anthropometric outcomes at week 240 comparing dolutegravir with standard of care, by ODYSSEY A/B (≥14kg cohort)

Table S5. On randomised allocation: proportion with unfavourable anthropometric and metabolic outcomes at week 240 comparing dolutegravir with standard of care, by ODYSSEY A/B (≥14kg cohort)

Figure S3. On-randomised allocation: change in weight and BAZ from baseline, by sex and age at baseline in ODYSSEY A (≥14kg cohort)

Figure S4. On-randomised allocation: change in WAZ and HAZ (<14kg cohort)

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Table 1. Baseline characteristics by weight cohort

	≥14kg cohort	<14kg cohort
Participants randomised	**707**	**85**
Demographic characteristics		
Sex		
female	345 (49%)	44 (52%)
Age (years)		
median	12.2 [9.1, 14.9; 2.9, 18.0]	1.4 [0.6, 2.0; 0.1, 5.9]
HIV infection characteristics		
WHO HIV-associated immunodeficiency ¥ §	707	81
Not significant	307 (43%)	22 (27%)
Mild	105 (15%)	9 (11%)
Advanced	58 (8%)	13 (16%)
Severe	237 (34%)	37 (46%)
Log10 Viral load (copies/mL) §	706	81
median	4.4 [3.9, 5.0]	5.3 [4.6, 5.9]
NRTI backbone at randomisation		
ABC 3TC	463 (65%)	75 (88%)
ABC TDF	3 (<1%)	0 (0%)
TDF/TAF 3TC/FTC¶	164 (23%)	0 (0%)
ZDV 3TC	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)		
median	30.7 [23.4, 43.0; 14.0, 85.0]	8.1 [5.4, 10.0; 3.4, 13.4]
Height (cm)		
median	138.0 [124.9, 152.5]	73.0 [61.0, 80.3]
BMI (kg/m2)		
median	16.3 [14.9, 18.5]	15.0 [14.0, 16.3]
BMI-for-age Z-score		
median	-0.6 [-1.4, 0.1]	-0.8 [-1.9, 0.2]
WHO nutritional status Ω		
Severely underweight/severe thinness	33 (5%)	26 (31%)
Moderately underweight/thinness	48 (7%)	13 (15%)
Normal/healthy weight	585 (83%)	43 (51%)
Overweight	35 (5%)	3 (4%)
Obese	6 (1%)	0 (0%)
BIA: Body fat percentage, % †	461	0
median	15.4 [10.9, 19.1]	---
Underfat	177 (38%)	---
Healthy	258 (56%)	---
Overfat	22 (5%)	---
Obese	4 (1%)	---
Metabolics		
Glucose (mg/dL)	692	76
median	78 [70, 85]	79 [70, 92]
Not increased	682 (99%)	73 (96%)
≥Grade 1	10 (1%)	3 (4%)
Total cholesterol (mg/dL)	684	77
median	135 [117, 155]	135 [101, 154]
Not increased	581 (85%)	67 (87%)

≥Grade 1	103	(15%)	10	(13%)
Triglycerides (mg/dL)	692		77	
median	88 [62, 115]		146 [82, 181]	
Not increased	611	(88%)	43	(56%)
≥Grade 1	81	(12%)	34	(44%)
LDL-C (mg/dL)	692		72	
median	77 [62, 97]		68 [46, 89]	
Not increased	608	(88%)	64	(89%)
≥Grade 1	84	(12%)	8	(11%)
HDL-C (mg/dL)	679		67	
median	41 [31, 51]		35 [24, 43]	
≥40mg/dl	360	(53%)	24	(36%)
<40mg/dl	319	(47%)	43	(64%)

Data are n(%), median [IQR], or median [IQR; range]. Percentages are for the non-missing proportion. 3TC=lamivudine. ABC=abacavir. BIA=bioelectrical impedance analysis. BMI=body max index. FTC=emtricitabine. HDL-C=high-density lipoprotein cholesterol. INSTI=integrase inhibitor. LDL-C=low-density lipoprotein cholesterol. NRTI=nucleoside reverse transcriptase inhibitors. NNRTI=non-nucleoside reverse transcriptase inhibitors. PI=protease inhibitor. TAF=tenofovir alafenamide. TDF=tenofovir disoproxil fumarate. WHO=World Health Organization. ZDV=zidovudine.

¥ WHO HIV-associated immunodeficiency defined using CD4%/CD4 count, according to age.[1]
§ At a participant level, the mean of the measured values was used if measured values were available at screening and randomisation.
¶ Two ≥14kg cohort participants in the SOC group initiated tenofovir alafenamide and emtricitabine (one in ODYSSEY A and one in ODYSSEY B).
Ω World Health Organization (WHO) classification of nutritional status in 0-<5 year olds defined as: severely underweight weight-for-age Z-score <−3; moderately underweight weight-for-age Z-score ≥−3 to <−2; overweight weight-for-height Z -score >2 to ≤ 3 and obese weight-for-height Z-score >3.[2] In ≥5 year olds, cut-offs were defined using BMI-for-age: severe thinness <-3, thinness -3 to <-2SD, overweight >1 to ≤2, and obese >2.[3]
† Bioelectrical impedance analysis (BIA) was performed at selected sites in Uganda (4 sites) and Zimbabwe (1 site) in participants at least 5 years old. BIA body fat percentage categories defined by categorising BIA body fat percentage, according to age and sex.[4]

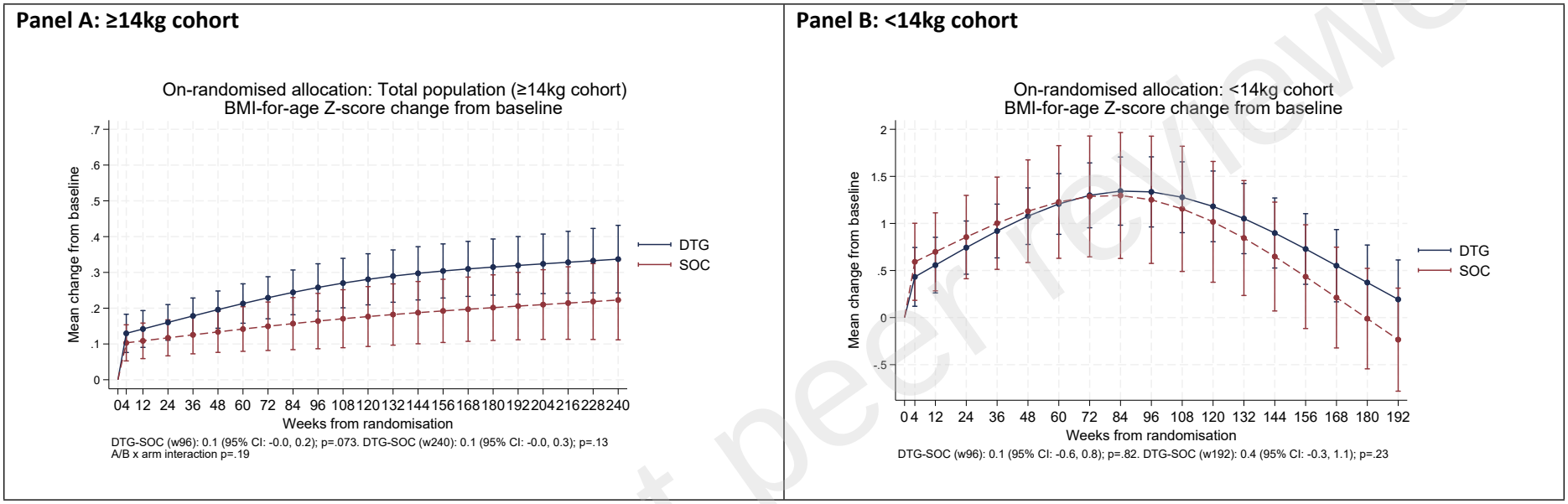
Table 2. On-randomised allocation: mean change in anthropometric, body composition and metabolic endpoints from baseline comparing dolutegravir with standard of care, by weight cohort

On-randomised allocation: mean change in continuous outcomes from baseline to 240 weeks (≥14kg cohort) and 192 weeks (<14kg cohort)							
	>=14kg cohort				<14kg		
	Dolutegravir	Standard of care	Dolutegravir versus standard of care (95% CI)	Pinteraction (treatment group vs ODYSSEY A/B)	Dolutegravir	Standard of care	Dolutegravir versus standard of care (95% CI)
Weight, kg	15.9±0.4	14.9±0.4	1.0 (-0.2, 2.2);P=0.095	0.022	8.2±0.2	8.2±0.3	-0.1 (-0.8, 0.7);P=0.83
Height, cm	18.8±0.4	17.8±0.4	1.0 (-0.2, 2.1);P=0.10	0.092	32.6±0.8	35.1±0.7	-2.5 (-4.5, -0.5);P=0.016
BMI-for-age Z-score	0.34±0.05	0.22±0.06	0.11 (-0.03, 0.26); P=0.13	0.19	0.19±0.21	-0.23±0.28	0.43 (-0.27, 1.12); P=0.23
Weight-for-age Z-score	---	---	---	---	1.02±0.12	0.92±0.18	0.09 (-0.31, 0.50); P=0.65
Height-for-age Z-score	---	---	---	---	1.48±0.16	1.61±0.19	-0.13 (-0.62, 0.36); P=0.61
MUAC, cm	4.6±0.1	4.1±0.1	0.4 (0, 0.8);P=0.030	0.021	3.2±0.2	2.6±0.3	0.6 (-0.1, 1.3);P=0.07
Body fat percentage, % †	1.9±0.4	1.2±0.5	0.7 (-0.5, 1.8);P=0.27	0.94	---	---	---
Total cholesterol, mg/dl	-1.9±1.6	13.3±2.5	-15.3 (-21.0, -9.5);P<0.0001	0.39	11.8±5.1	14.6±8.1	-2.8 (-22.1, 16.6);P=0.78
Glucose, mg/dl	4.5±0.7	8.8±1.0	-4.4 (-6.8, -1.9);P=0.00039	0.62	0.4±2.2	-13.5±3.0	13.9 (6.1, 21.6);P=0.00049
Triglycerides, mg/dl	-6.5±2.7	8.0±4.8	-14.4 (-25.2, -3.6);P=0.0089	0.1	-65.2±8.6	-36.2±13.8	-28.9 (-59.9, 2.0);P=0.067
HDL-C, mg/dl	2.7±0.7	8.2±1.1	-5.5 (-8.0, -2.9);P<0.0001	0.1	12.8±1.7	11.6±2.7	1.1 (-5.2, 7.5);P=0.72
LDL-C, mg/dl	-3.4±1.3	0.1±1.8	-3.5 (-7.9, 0.9);P=0.12	0.4	4.0±4.1	14.6±7.1	-10.6 (-26.3, 5.2);P=0.19

Plus–minus values are means ± SE within the treatment groups. 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, Supplementary statistical methods). Mean change in continuous measures up to 240 weeks (≥14kg cohort) and 192 weeks (<14kg cohort) from baseline by trial arm and difference between trial arms (SOC 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/B, country/region, calendar month of randomisation (3 knot cubic spline), sex, age, weight, BMI-for-age Z-score, CD4 (CD4% for <14kg cohort), and log10 viral load. Presenting mean change from a baseline weight 34.0kg in ≥14kg cohort and 8.1kg in <14kg cohort, height 138.5cm and 71.9cm, BMI-for-age Z-score -0.7 and -0.9, weight-for-age Z-score -2.2 (<14kg cohort only), height-for-age Z-score -2.5 (<14kg cohort only), MUAC 20.0cm and 13.1cm, BIA body fat percentage 15.2% (≥14kg cohort only), total cholesterol 138.1mg/dl and 127.9mg/dl, glucose 78.2mg/dl and 81.7mg/dl, triglycerides 95.8mg/dl and 159.2 mg/dl, HDL-C 43.2 mg/dl and 34.0 mg/dl, LDL-C 80.5 mg/dl and 69.8 mg/dl. BMI=body max index. CI=confidence interval. HDL-C=high-density lipoprotein cholesterol. LDL-C=low-density lipoprotein cholesterol. MUAC=mid-upper arm circumference.

† Bioelectrical impedance analysis was performed at selected sites in Uganda (4 sites) and Zimbabwe (1 site) in participants at least 5 years old. Analysis restricted to participants with a baseline age of at least 5 years (all in ≥14kg cohort) at sites performing bioelectrical impedance analysis.

Figure 1. Change in BMI-for-age Z-score (≥14kg cohort and <14kg cohort)



Note differences in figure scales in Panel A and B. A=ODYSSEY A. B=ODYSSEY B. BMI=body max index. CI=confidence interval. DTG=dolutegravir. SOC=standard of care. w=week.

Table 3. On randomised allocation: proportion with unfavourable anthropometric and metabolic outcomes at week 240 comparing dolutegravir with standard of care (≥14kg cohort)

	≥14kg cohort			
	Dolutegravir	**Standard of care**	**Dolutegravir versus standard of care (95% CI)**	**Pinteraction (treatment group vs ODYSSEY A/B)**
WHO-defined overweight/obese #	11.2% (8.3, 14.0)	9.8% (6.8, 12.8)	1.4 (-2.7, 5.5); P=0.50	0.025
Body fat percentage overfat/obese ‡	10.0% (6.6, 13.3)	10.4% (5.5, 15.3)	-0.5 (-6.3, 5.4); P=0.87	0.77
Waist-to-height ratio≥0.5 ¶	10.8% (7.4, 14.3)	10.9% (7.1, 14.7)	0.0 (-5.1, 5.1); P=0.99	0.66
Total cholesterol DAIDS grade≥1 Ω	9.8% (6.7, 13.0)	18.3% (12.0, 24.6)	-8.5 (-15.5, -1.5); P=0.018	0.70
Glucose DAIDS grade≥1 Ω	1.4% (0.0, 2.8)	3.4% (0.7, 6.0)	-2.0 (-5.0, 1.0); P=0.19	0.48
Triglycerides DAIDS grade≥1 Ω	7.3% (4.3, 10.2)	15.2% (10.0, 20.4)	-8.0 (-13.9, -2.0); P=0.0089	0.12
LDL-C DAIDS grade≥1 Ω	6.4% (3.8, 9.0)	7.4% (3.1, 11.6)	-1.0 (-5.9, 4.0); P=0.71	0.70
HDL-C<40mg/dl Ω	35.4% (30.4, 40.5)	21.0% (15.0, 26.9)	14.5 (6.6, 22.3); P=0.00029	0.25

Estimated proportion with unfavourable endpoint (95% CI) within the treatment groups. 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, Supplementary statistical methods). Estimated proportions with unfavourable outcomes up to 240 weeks (≥14kg cohort) by trial arm and difference between trial arms (SOC as reference) are 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/B, country/region, calendar month of randomisation (3 knot cubic spline), sex, age, weight, BMI-for-age Z-score, CD4, and log10 viral load. CI=confidence interval. DAIDS=Division of AIDS. HDL-C=high-density lipoprotein cholesterol. LDL-C=low-density lipoprotein cholesterol. WHO=World Health Organization.

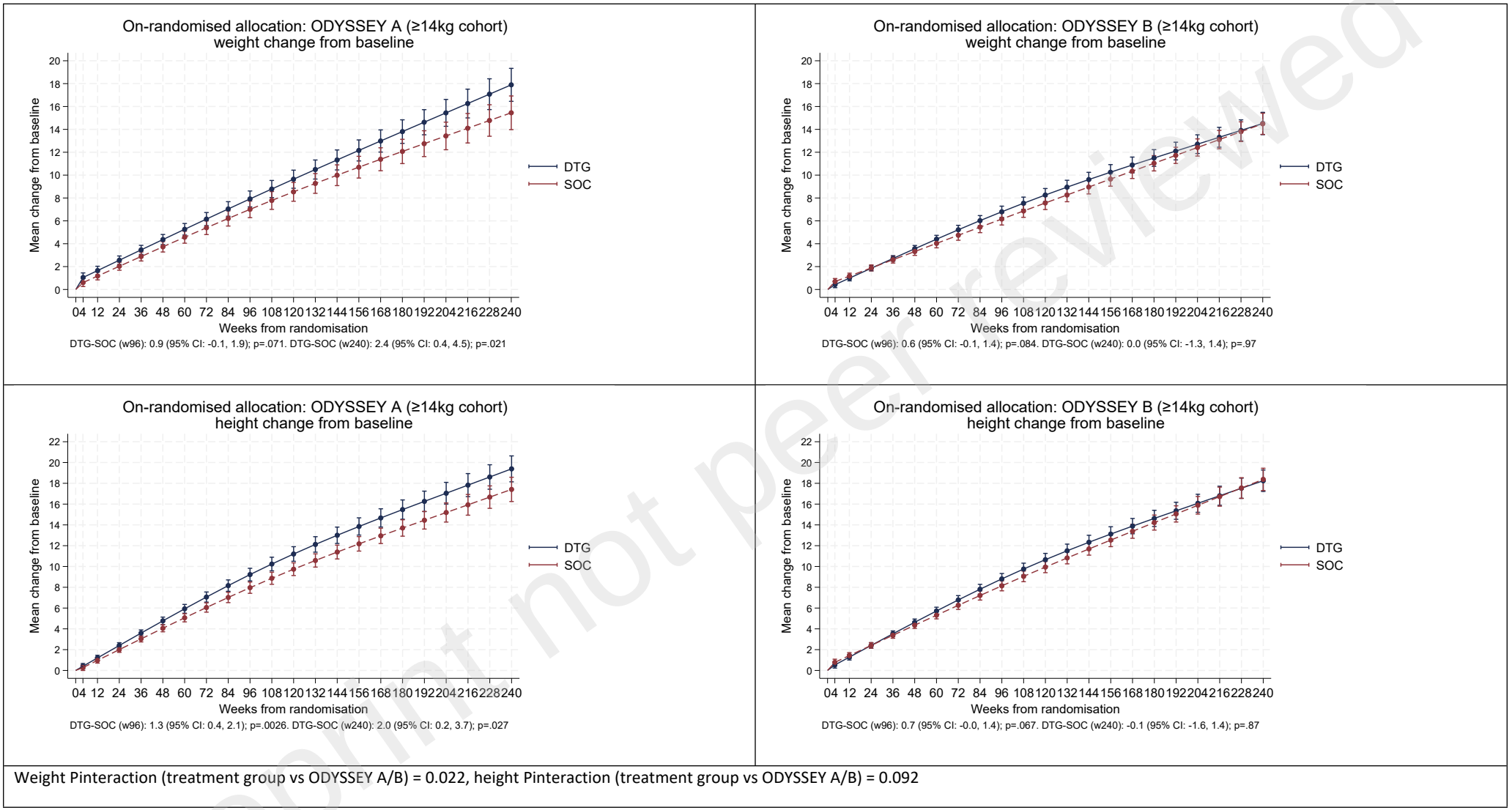
WHO-defined overweight/obesity defined as: BMI≥25 for participants aged at least 19, BMI-for-age Z-score >1 for children aged 5–<19 years, and weight-for-height Z-score >2 SD for children under 5 years.[5]
‡ Body fat percentage defined as overfat/obese (versus underfat/healthy) using TANITA Corporation definition.[4]
¶ 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 ≥14kg cohort). Body circumference measures introduced one year after start of trial recruitment, therefore adjustment for baseline not possible. Unfavourable central adiposity defined as waist-to-height ratio ≥0.5.[6]
Ω Metabolic parameters (total cholesterol, glucose, triglycerides, LDL-C) were defined as ≥Grade 1 laboratory event according to Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014].[7] Unfavourable HDL-C defined as HDL-C<40mg/d.[8]

Table 4. On randomised allocation: cross-sectional means in anthropometric outcomes at week 240 comparing dolutegravir with standard of care (≥14kg cohort)

On-randomised allocation: mean continuous outcomes at 240 weeks				
	≥14kg cohort			
	Dolutegravir	**Standard of care**	**Dolutegravir versus standard of care (95% CI)**	**Pinteraction (treatment group vs ODYSSEY A/B)**
Waist-to-height ratio	0.445±0.002	0.448±0.003	-0.003 (-0.010, 0.005);P=0.46	0.47
Waist circumference, cm	69.8±0.4	69.5±0.4	0.3 (-0.8, 1.4);P=0.56	0.016
Hip circumference, cm	83.5±0.5	82.3±0.5	1.3 (-0.2, 2.7);P=0.089	0.0044

Plus–minus values are means ± SE within the treatment groups. On-randomised allocation effects were estimated from marginal structural models with stabilised inverse probability weights to account for switch off randomised treatment regime and censoring due to death, loss to follow-up, administrative censoring or pregnancy (appendix, Supplementary statistical methods). Mean in continuous measures up to 240 weeks by trial arm and difference between trial arms (SOC 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, and baseline variables: ODYSSEY A/B, country/region, calendar month of randomisation (3 knot cubic spline), sex, age, weight, BMI-for-age Z-score, CD4 (CD4% for <14kg cohort), and log10 viral load. Body circumference measures were collected in participants at least 5 years old; analysis restricted to participants with a baseline age of at least 5 years (all in ≥14kg cohort). Body circumference measures introduced one year after start of trial recruitment, therefore adjustment for baseline not possible. CI=confidence interval.

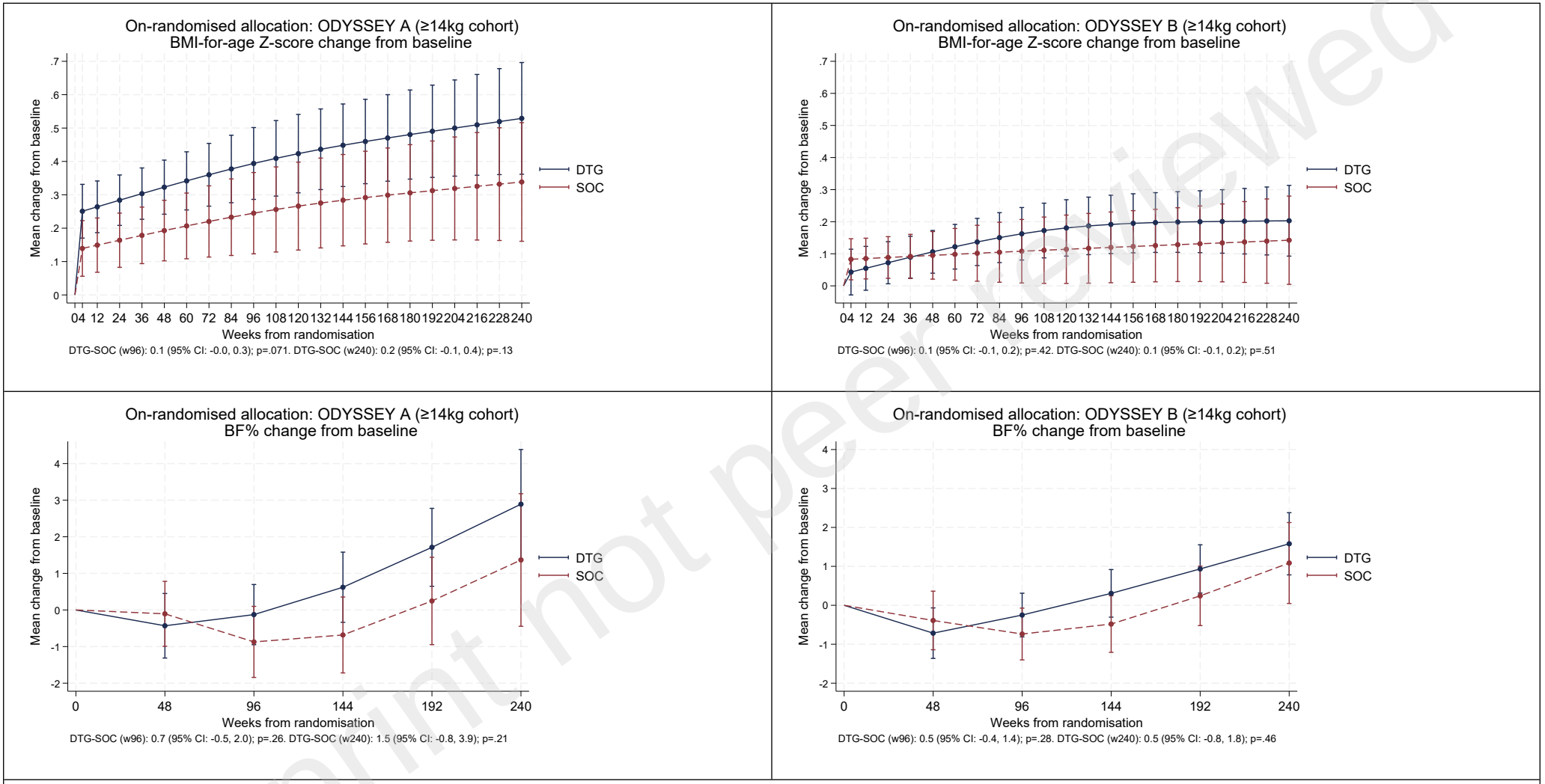
Figure 2. Change in weight and height by ODYSSEY A and B (≥14kg cohort)



Weight Pinteraction (treatment group vs ODYSSEY A/B) = 0.022, height Pinteraction (treatment group vs ODYSSEY A/B) = 0.092

CI=confidence interval. DTG=dolutegravir. SOC=standard of care. w=week.

Figure 3. Change in BMI-for-age, body fat percentage by ODYSSEY A and B (≥14kg cohort)



BMI-for-age Z-score Pinteraction (treatment group vs ODYSSEY A/B) = 0.19, body fat percentage Pinteraction (treatment group vs ODYSSEY A/B) = 0.94

BF%=body fat percentage. BMI=body max index. CI=confidence interval. DTG=dolutegravir. SOC=standard of care. w=week.