*Open Forum Infectious Diseases*

**MAJOR ARTICLE**

# Changes in body mass index in children and adolescents living with HIV in Europe and Thailand starting dolutegravir

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***Background:*** Excess weight gain has been reported in some adults on dolutegravir (DTG), but data in children/adolescents living with HIV (CALHIV) are limited.

***Methods:*** CALHIV aged 2-<18 years (yrs) at DTG start from 15 observational cohorts across Europe and Thailand were included. Mixed-models described changes in body mass index-for-age z-score(zBMI). We assessed (i) zBMI change 48 weeks(wks) before versus after DTG start; (ii) zBMI change up to 96wks on DTG and associated factors; and (iii) zBMI changes over 96wks in CALHIV aged 6-<18yrs at start of DTG versus protease inhibitor(PI)-based regimens using propensity score weighting.

***Results:*** Of 948 CALHIV on DTG, 50% were female, median[IQR] age 13.7[11.1,15.6] years, zBMI 0.31[-0.64,1.19], 48% Black, 30% overweight or obese at DTG start. Among 741 with zBMI available pre/post DTG start, zBMI (95% CI) increased by 0.07(0.03,0.11) versus 0.13(0.09,0.16) (p=0.087), in the 48wks before and after DTG start, respectively.

Mean zBMI change by 96wks on DTG was 0.20(0.14,0.27). In multivariable models, greatest increases in zBMI were in those aged 6-<12yrs at DTG start (0.34(0.23,0.44)), males of 'Other' ethnicity(0.39(0.10,0.68)), Black females(0.27(0.15,0.39)), and those on tenofovir alafenamide(TAF) (0.39(0.17,0.61)). There was no difference in mean zBMI change at 96wks among those on DTG versus PI-based regimens (0.21(0.13,0.30) vs 0.30(0.13,0.48), p=0.354).

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***Conclusions:*** CALHIV experienced zBMI increases on DTG with largest gains in children aged 6-<12yrs, on TAF, with low baseline zBMI, and some variation by sex and ethnicity. However, zBMI changes over 96 weeks were comparable between those on DTG and PI-based regimens.





## BACKGROUND

Dolutegravir (DTG), a second-generation integrase strand transfer inhibitor(INSTI), is recommended as part of first-line and subsequent-line treatment for children (aged ≥4 weeks, weighing ≥3 kg), adolescents and adults living with HIV[1]. Some adult studies have reported excess weight gain and/or increased body mass index(BMI) on INSTIs as compared to other regimens[2], particularly when co-administered with tenofovir alafenamide(TAF)[3, 4]. Recent studies have highlighted the importance of accounting for the effect of prior regimens, in particular switches from tenofovir disoproxil fumarate(TDF) and efavirenz(EFV), both of which are weight suppressing, to other antivirals that have been associated with weight gain [5] [6] [7]. There are limited data on weight gain in children and adolescents living with HIV(CALHIV) on DTG which is being rolled out globally.

The ODYSSEY trial, where CALHIV started first- or second-line ART, largely in sub-Saharan Africa, reported a small but statistically significantly higher weight gain (mean difference=1kg over 96 weeks) on DTG compared to standard of care (non-nucleoside reverse transcriptase inhibitor(NNRTI) or protease inhibitor(PI)-based regimen), that was not considered clinically significant[8]. The CHAPAS-4 trial of CALHIV starting second-line ART in sub-Saharan Africa, reported increases in BMI-for-age z-score(zBMI) by 96 weeks on DTG, which were comparable to darunavir/ritonavir(DRV/r) or atazanavir/ritonavir(AZT/r)-based regimens but higher than lopinavir/ritonavir(LPV/r), which is thought to reflect poorer growth on LPV/r[8, 9].

Studies of growth in children on DTG from real-world settings have reported mixed results, some reported no change in zBMI [10-12], others reported significant increases [13-15] or increases in zBMI that were comparable to trends before DTG start[16]. Most studies have small sample sizes (n<200), and few have explored short and long-term growth trajectories and factors associated with zBMI increase.

The aim of this study was to explore short and long-term zBMI changes in CALHIV on DTG in routine-care and compared to those on PI-based regimens.

## METHODS

Individual patient data of CALHIV who started DTG aged <18 years from 15 cohorts in 14 countries in Europe and Thailand were pooled in 2023, as part of the Epidemiology of Pregnancy and Paediatric Infections International Cohort Collaboration (EPPICC)(ClinicalTrials.gov ID NCT04677842), using a standardised data specification(www.hicdep.org) [17]. Data included

routine demographic, clinical and treatment-related variables throughout paediatric care and in some cohorts into adult care.

Inclusion criteria for analysis were: age 2-<18 years at DTG start, ≥24 weeks follow-up on DTG, and ≥1 zBMI measurement within 96 weeks on DTG. Children aged <2 years were excluded as BMI is less reliable in this age group[18]. CALHIV who received DTG as part of a clinical trial were excluded. Data were censored at last visit or seven days after DTG discontinuation (defined as stopping DTG for >30 days).

zBMI is a measure of BMI relative to median BMI of children of the same age and sex, and therefore accounts for expected increases in BMI that occur as children grow. This was calculated using the British 1990 growth reference[19], where zBMI in the 2$^{nd}$ to <85$^{th}$ centile is classified as normal weight, 85$^{th}$ to <95$^{th}$ as overweight, and ≥95$^{th}$ as obese.

**Ethics and Patient Consent Statement**

This study is based on secondary analysis of routine care data of contributing cohorts. EPPICC has ethics committee approval from University College London (reference 17493/001) and all cohorts received approval or exemptions from local/national ethics committees. Some cohorts have informed consent for use of routine care data while other cohorts have a waiver of consent.

**Statistical methods**

Mixed models were used to describe zBMI changes over time (see Table S1 for full details). Models included linear splines for time, with placement of knots (the points at which the slope of the trajectory changes) selected based on 'best' model fit using Akaike's Information Criterion. Mixed models included random intercepts for patient and slopes for time, and an exponential residual correlation structure to account for repeated measures over time.

Differences in zBMI were explored by baseline demographic and clinical characteristics at DTG start: age (2-<6, 6-<12, 12-<18 years), sex at birth (male, female), ethnicity (Black, White, Asian, Other), region (UK/Ireland, Thailand, Ukraine, rest of Europe), ART/viral load(VL) status (naïve, ART-experienced/suppressed (VL<200 copies/mL(c/mL)), ART-experienced/unsuppressed (VL≥200c/mL) and ART-experienced/unknown VL; using nearest VL within -24/+1 week of DTG start), WHO immunosuppression for age (none/mild, advanced/severe; using nearest CD4 within -24/+4 weeks)[20], NRTI backbone (TAF, TDF, other), zBMI (nearest within -24/+4 weeks) and, among those ART-experienced, regimen immediately prior to DTG (contained any of TDF, EFV or LPV/r versus not), zBMI (<-1, -1 to <0, 0 to <1, ≥1).

**Change in zbmi in the 48 weeks before and after DTG start**

First, we compared short-term rate of zBMI change in the 48 weeks before versus after DTG start by ART/viral load(VL) status in CALHIV with ≥1 zBMI measurement available in both

periods. zBMI measurements from 96 weeks before to 96 weeks after DTG start were included with a linear spline with knots at -48, 0, 24 and 48 weeks used to model time. Next, we restricted the analysis to the subgroup ART-experienced/VL<200c/mL at DTG start, who are less likely to experience weight gain as a 'return to health' effect after DTG start[21]. Univariable mixed models were used to explore whether (change in mean zBMI in first 48 weeks after DTG start) – (change in mean zBMI in 48 weeks before DTG start) differed by demographic and clinical characteristics at DTG start.

**Factors associated with change in zBMI over 96 weeks on DTG**

Second, we described the long-term changes in zBMI and percentage of CALHIV moving between zBMI category over 96 weeks on DTG. zBMI measurements from DTG start to 96 weeks were included.

In multivariable analyses, characteristics associated with mean zBMI change, overall or with significant interactions with time on DTG (indicating rate of change in zBMI differed across groups), were identified (see Table S1 for further details). Time since DTG start was fitted using a linear spline with knots at 0 and 24 weeks.

In the main analysis, WHO immunological stage and zBMI at DTG start were not adjusted for due to >10% missing data. Three separate subgroup analyses were carried out using the main multivariable model, (a) adjusting for ART regimen prior to DTG among ART-experienced, (b) adjusting for WHO immunological stage among those with available data, (c) adjusting for zBMI at DTG start among those with available data.

**Comparison of change in zBMI over 96 weeks on DTG versus PI**

Third, CALHIV on DTG were compared to those on boosted-PI based regimens using data pooled in a previous EPPICC merger in 2021. Thailand was excluded from this analysis as they were not included in the 2021 merger. To maximise comparability of groups, CALHIV aged 6-<18 years at start of DTG or PI combined with 2 or 3NRTIs after 2012 were included. Propensity score weighting balanced differences in characteristics at DTG/PI start (see Table S1 for further details). Weighted mixed models were used to compare zBMI change over 96 weeks on DTG vs. PIs, overall and by ART/VL status at drug start. CALHIV on eligible DTG and PI-based regimens were included in both groups with a patient level random effect used to account for repeated measures.

**Sensitivity analyses**

Sensitivity analyses for the first and second analyses above explored (1) the potential impact of the COVID-19 pandemic by excluding data after January 2020 as countries such as the UK saw overall increases in overweight and obesity in children during the pandemic[22], (2) differences by NRTI backbone at DTG start excluding Ukraine and Thailand (as no access to TAF) (3)

zBMI trajectories using WHO growth standards/reference[18, 23]. For the second analysis an additional sensitivity analysis was carried out restricted to CALHIV who were suppressed at DTG start.

All analyses were conducted in Stata, Version 18.

## RESULTS

### Baseline characteristics

Overall, 1230 CALHIV started DTG aged <18 years, of whom 948 (77%) met the inclusion criteria for analysis with ≥1 zBMI measurement in first 96 weeks on DTG (Figure 1). Half (50%) were female; 48% Black, 32% White, 11% Asian, and 9% Other ethnicity; 33% in the UK/Ireland, 17% Ukraine, 8% Thailand, and 41% in the rest of Europe, 39% were born abroad (Table 1). At start of DTG the median age was 13.7[IQR 11.1, 15.6] years, 10% were treatment naïve, 13% ART-experienced/unsuppressed, 51% ART-experienced/suppressed, 25% ART-experienced/unknown viral load, and 14% had WHO advanced or severe immunosuppression-for-age. Seven percent started DTG on a TAF-containing regimen, 20% TDF and 73% on other NRTIs. Among those ART-experienced at DTG start, 57% switched from LPV/TDF/EFV-based regimens. Characteristics by country/region are given in Table S2.

Median baseline zBMI at DTG start was 0.31[-0.64, 1.19], although this varied significantly across regions with markedly lower median zBMI in Ukraine and Thailand. Median duration of follow-up after DTG start was 107[64, 173] weeks. CALHIV on DTG who were excluded from analyses due to no BMI measurement during 96 weeks on DTG (n=126), were older, more likely to be White, from Ukraine, have unknown viral load and on TDF at DTG start, and have shorter duration of follow-up on DTG than those included (Table S3).

### Change in zBMI in 48 weeks before and after DTG start

741/948 CALHIV (78%) had ≥1 BMI measurements in both the 48 weeks before and after DTG start and included in analyses of change in zBMI pre/post DTG start (Figure 1). The zBMI increased by a mean of 0.07 (95% CI 0.03, 0.11) in the 48 weeks before versus 0.13 (0.09, 0.16) in the 48 weeks after DTG start(p=0.087)(Table S5). Difference in the change in mean zBMI before versus after DTG start did not vary significantly by ART/VL status at DTG start (Figure 2, panel a).

In analysis restricted to those virally suppressed at DTG start (n=425, characteristics shown in Table S4), the difference in the change in mean zBMI before and after DTG start varied by age (p=0.069), previous ART regimen (p=0.024) and baseline zBMI (p<0.001) (Figure 2, panels b-d). A significantly larger increase in zBMI in the post-DTG period (vs pre-DTG) was seen in those aged 6-<12 years at DTG start (p=0.09), among those with a prior ART regimen containing

LPV/EFV/TDF, and those with zBMI <-1 at DTG start (p<0.001) (Table S5). There was no effect of sex, region, ethnicity or NRTI backbone (Table S5, Figure S1).

**Factors associated with change in zBMI over 96 weeks on DTG**

Among the 948 CALHIV with zBMI data in the first 96 weeks on DTG, the unadjusted change in mean zBMI by 96 weeks was 0.20 (0.14,0.27). Among 316 CALHIV with zBMI at both DTG start and 96 weeks, 43(14%) were classed overweight and 53(17%) as obese at DTG start. By 96 weeks, 15% of those classed as normal weight moved to the overweight category, and 37% classed as overweight moved to the obese category, with females more likely to develop obesity than males (Table S6).

In multivariable analysis, there was evidence that zBMI differed across regions (p<0.001) and by age at DTG start (p-for interaction=0.002), NRTI backbone (p-for-interaction=0.031), and ethnicity/sex (p-for interaction=0.09)(Table S7). Compared to the UK/Ireland the mean zBMI throughout follow-up was lower in other regions, by 0.64(0.31,0.98) in Ukraine, 0.23(-0.33,0.80) in Thailand and 0.21(0.02,0.40) in the rest of Europe.

The largest increases in mean zBMI were in the 6-<12-year age group (Figure 3, panel a), and those starting DTG with TAF (Figure 3, panel b). In terms of ethnicity and sex, the most rapid increase was among males of 'Other' ethnicity (Figure 3, panel c, Table S7) including those of Mixed race. The next largest increase was among Black females(Figure 3, panel d). In contrast, Asian females had a decrease in mean zBMI.

In subgroup analysis of ART-experienced CALHIV at DTG start (n=744), prior ART regimen was also associated with zBMI change on DTG, independently of NRTI backbone at DTG start, with largest increases in those previously on LPV/TDF/EFV-based regimens (p-for-interaction=0.003, Figure S2). In a second subgroup with WHO immunological stage data at DTG start (n=621), those with advanced/severe immunosuppression had a more rapid increase in zBMI in the first 24 weeks compared to the none/mild group, but a similar rate of change after 24 weeks on DTG (p-for-interaction=0.079)(Figure S2).

In a third subgroup analysis of CALHIV with zBMI data at DTG start (n=790), lower baseline zBMI was associated with larger increases in zBMI over 96 weeks(p-for-interaction<0.001)(Figure S3). When adjusting for zBMI at DTG start, interactions between time on DTG and age group and ethnicity/sex interaction remained significant (p-for-interaction=0.011 and 0.042, respectively)(Figure S3). However, the interaction between time on DTG, NRTI backbone and region were no longer significant (p=0.442 and 0.199).

**Propensity scoring analysis comparing zBMI change on DTG versus PI**

A subset of 467 CALHIV age 6-<12 years on 2 or 3NRTI+DTG and were compared to 308 on 2 or 3NRTI+PI regimens (163(53%) on darunavir, 98(32%) atazanavir, 45(15%) lopinavir and 2(1%) fosamprenavir), of whom 34 contributed to both analysis groups (Figure 1, sub-group B).

Before weighting, characteristics at DTG/PI start were broadly similar, though those on DTG were more likely to start the regimen virally suppressed<200c/mL or be from Ukraine (Table 1). After propensity score weighting, characteristics were well balanced, though some regional differences remained (Table S8). Over 96 weeks, there was no difference in weighted change in mean zBMI on DTG and PI (0.21(0.13,0.30) vs. 0.30(0.13,0.48), p=0.354; Figure 4). When stratified by ART and VL status, zBMI change remained similar.

In sensitivity analyses, where we restricted calendar years of observations (to assess potential impact of COVID-19 pandemic), excluded Ukraine and Thailand (due to no access to TAF), used WHO growth reference, and restricted to those suppressed at DTG start, findings were consistent with the main analysis (Table S9).

## DISCUSSION

Our large study of CALHIV in routine-care in Europe and Thailand included multiple approaches to assessing the short and long-term change in zBMI on DTG. We observed weak evidence of a larger increase in mean zBMI in the 48 weeks after DTG start as compared to before DTG start (p=0.087). There was significant evidence of larger increases in zBMI post-DTG start in some subgroups such as children aged 6-12 years at DTG start. These findings persisted when restricting analyses to the subgroup virally suppressed at DTG start who are less likely to experience a 'return to health' weight gain[21].

Other paediatric observational studies have reported conflicting results. A small French cohort (n=97) reported no difference in zBMI change in 12 months pre/post DTG start[24]. Another small study of 38 children and adolescents on INSTIs in the USA, of whom 28 were on DTG, found zBMI increased by 0.02(95% CI -0.09,0.13) per year prior to INSTI start, rising to 0.21(0.08,0.35) after INSTI start[25]. An Eswatini cohort (n=460) reported significantly larger gains in zBMI after DTG start at 1.2(1.1,1.3) per year on DTG versus 0.3(0.2,0.4) before DTG start. However the latter cohort had a low zBMI at DTG start and this may reflect a 'return to health' effect, although all were virally suppressed at DTG start[26]. We observed significantly larger post-DTG increases in zBMI in those previously on LPV/EFV/TDF-based regimens, and weak evidence suggesting larger increases in those starting DTG with TAF. These findings are consistent with previous studies showing the weight suppressing effect of TDF and EFV, and poor growth among those on LPV/r which may lead to weight gain when discontinued[5, 8, 27, 28]. The findings also align with previous research showing greatest weight gains associated with DTG+TAF based regimens in adults[3, 4]. We also found significantly larger post-DTG increases

in zBMI in CALHIV with low zBMI (< -1) at DTG start but not for higher zBMI groups. This aligns with evidence from DTG studies with low median zBMI that show more rapid gains[26].

Our second finding is that over 96 weeks on DTG, the largest zBMI increases were in those aged 6-<12 years, males of 'other' ethnicity, Black females, and those on DTG with TAF. In separate analyses of growth using EPPICC data, which compared growth by NRTI backbone in children/young people on a range of anchor drugs, we observed no differences in zBMI change in the following analyses: in the 48 weeks before versus after TAF start among those never been on TDF; in growth on TAF versus abacavir; and between NRTI backbones combined with DTG versus other anchor drugs [29]. However, as with this analysis the numbers on TAF+DTG were low, and may lack power to detect differences.

In our analysis, children aged 6-<12 years at DTG start had largest gains over 96 weeks on DTG. The age effect was not observed in the ODYSSEY or CHAPAS-4 trials and has not been reported in other paediatric cohort studies although few explored associated factors. We also observed larger zBMI gains in males of 'other' ethnicity and in Black females; the latter finding is consistent with reports in adult studies[30] [31]. Among the black female group, over half were born abroad. There is a complex interplay between ethnicity, migrant status, socio-economic status, lifestyle and cultural factors which are known to be associated with childhood obesity and are not captured here. Therefore caution is needed in interpretation of these findings and further research is warranted[32, 33].

The average zBMI increase on DTG was not large, at 0.13 over 48 weeks, and 0.2 over 96 weeks. This is well below the definition of 'Rapid' growth which is an increase of >0.67-1.28 over 48 weeks, which correspond to crossing over major percentile lines traditionally shown on growth charts (i.e. the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th) [34-36].

Though zBMI increases were small on average, 15% of children/adolescents with normal BMI at DTG start were classified as overweight by 96 weeks. This may reflect trends in the general population[37]. In sensitivity analyses with follow-up time censored at 2020 (to take into account of potential impact of COVID-19 pandemic) and when using WHO growth reference, similar trends in zBMI increases were observed. In these sensitivity analyses the sex/ethnicity association was no longer significant, although the sample sizes were considerably smaller. Results also persisted when this analysis was restricted to those virally suppressed only.

The third key finding of our study was that zBMI changes over 96 weeks on DTG were comparable to those on PI-based regimens within the same cohort, using propensity scoring analysis. This is consistent with findings from the CHAPAS-4 trial where DTG was not associated with excess absolute weight gain compared darunavir or atazanavir-based regimens, though weight gain was higher on DTG than lopinavir[8]. The ODYSSEY trial reported a small but significant change in zBMI that was 0.13(95% CI 0.01,0.25) higher on DTG compared to PI/NNRTI-based regimens, but was not considered clinically significant[8].

This study has important strengths in terms of comprehensive analysis of patterns of growth, and inclusion of a large geographically diverse sample with long duration of follow-up on DTG. However, there were important limitations. Firstly, while we controlled for region in our analysis, there is heterogeneity between cohorts in terms of population characteristics which are challenging to fully control for. Secondly, we used the British 1990 growth reference to derive z-scores. The WHO growth standards[18] and reference[23] may be more representative of the diverse population but are limited to those aged<19 years. Similar findings were observed in our sensitivity analyses using WHO references, and in previous EPPICC analyses using setting specific reference data e.g. for Thailand[38]. Third, some CALHIV experience delayed pubertal growth spurts which can result in a decline followed by rapid increase in zBMI[39]. For those who started ART late at older ages (e.g. 6-<12 years), this could result in later and more intense growth spurts[40] and potentially lead to bias. Finally, in our propensity scoring analysis of DTG versus PI-based regimens, while weighting was used to balance clinical characteristics, we were unable to include calendar year at regimen start as there was little overlap between the calendar years in start of PIs and DTG-based regimens. Therefore residual confounding may remain.

In conclusion, this study explored zBMI trajectories in children and adolescents on DTG using multiple methods. We observed long-term increases in zBMI over time on DTG, although this was comparable to trends observed in CALHIV on PI-based regimens. Some subgroups had greater zBMI increases on DTG, in particular those aged 6-<12 years at DTG start, specific sex/ethnic groups, those who switched from TDF, EFV or LPV/r, those on TAF with DTG, and those with a low baseline zBMI below -1. Data on outcomes beyond 96 weeks are needed along with data on clinical impact of excess weight gain such as dyslipidaemia, hypertension, diabetes, anxiety and depression[41, 42]. People living with HIV are at greater risk of comorbidities than the general population[43] and it is therefore important to monitor weight in these groups and screen for associated co-morbidities.

**Potential conflicts of interest**

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**Data sharing statement**

The EPPICC data are held at MRC CTU at UCL, which encourages optimal use of data by employing 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. The rationale for this approach has been published (doi:10.1186/s13063-015-0604-6). Ethics committee approval for use of EPPICC data restrict the ability for EPPICC data to be shared publicly without request. Rather, ethics approval does allow a controlled access approach. All requests for data are considered and can be initiated by contacting mrcctu.datareleaserequest@ucl.ac.uk.

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## TABLES AND FIGURES

**Table 1: Characteristics of children and adolescents living with HIV (CALHIV) included in analyses**

| | Included in analysis of zBMI over 96 weeks on DTG | Included in comparative analysis of zBMI change on DTG vs. PI-based regimens* | |
|---|---|---|---|
| | DTG (n=948) | DTG (n=467) | PI (n=308) |
| **Age at DTG/PI start (years)** | 13.7 [11.1, 15.6] | 13.6 [11.1, 15.6] | 13.5 [10.9, 15.3] |
| 2 to <6 | 46 (5%) | . | . |
| 6 to <12 | 263 (28%) | 153 (33%) | 104 (34%) |
| 12 to <18 | 639 (67%) | 314 (67%) | 204 (66%) |
| **Sex** | | | |
| Male | 477 (50%) | 227 (49%) | 148 (48%) |
| Female | 471 (50%) | 240 (51%) | 160 (52%) |

| | | | |
|---|---|---|---|
| **Ethnicity** (n=925)** | | | |
| Black | 442 (48%) | 280 (60%) | 225 (73%) |
| White | 300 (32%) | 130 (28%) | 46 (15%) |
| Asian | 103 (11%) | 13 (3%) | 1 (0%) |
| Other | 80 (9%) | 44 (9%) | 36 (12%) |
| **Region** | | | |
| UK/Ireland | 315 (33%) | 57 (12%) | 31 (10%) |
| Ukraine | 165 (17%) | 223 (48%) | 37 (12%) |
| Thailand | 77 (8%) | 0 (0%) | 0 (0%) |
| Rest of Europe[†] | 391 (41%) | 187 (40%) | 240 (78%) |
| **ART and viral load status at DTG/PI start** | | | |
| Naive | 99 (10%) | 60 (13%) | 97 (31%) |
| ART-experienced and unsuppressed (VL≥200c/mL) | 124 (13%) | 67 (14%) | 89 (29%) |
| ART-experienced and suppressed (VL<200c/mL) | 488 (51%) | 340 (73%) | 122 (40%) |
| ART-experienced, VL unknown | 237 (25%) | . | . |
| **WHO immunological stage for age (n=733, n=425, n=280)** | | | |
| None/mild | 629 (86%) | 381 (90%) | 201 (72%) |
| Advanced/severe | 104 (14%) | 44 (10%) | 79 (28%) |
| **Prior AIDS diagnosis (n=938)** | | | |
| AIDS-free at DTG start | 744 (78%) | 367 (79%) | 250 (81%) |
| AIDS at DTG start | 194 (20%) | 100 (21%) | 58 (19%) |
| **NRTI backbone at DTG/PI start** | | | |
| TAF | 67 (7%) | 49 (10%) | 110 (36%) |
| TDF | 190 (20%) | 49 (10%) | . |
| Other | 691 (73%) | 369 (79%) | 191 (62%) |
| **Time since ART initiation (years)*** ** | 8.9 [5.1, 12.1] | 8.6 [5.2, 12.1] | 8.3 [4.6, 11.9] |
| **ART regimen prior to DTG start*** ** | | | |
| No EFV, LPV or TDF | 324 (43%) | 298 (73%) | 137 (65%) |
| Contained EFV, LPV or TDF | 437 (57%) | 109 (27%) | 74 (35%) |
| **Previous treatment failure*** ** | | | |
| No | 633 (75%) | 318 (78%) | 114 (54%) |
| Yes | 211 (25%) | 89 (22%) | 97 (46%) |
| **Born abroad (n=920)** | | | |
| Yes | 372 (39%) | 215 (46%) | 155 (50%) |

| | | | |
|---|---|---|---|
| No | 548 (58%) | 250 (54%) | 150 (49%) |
| **zBMI at DTG/PI start (n=780)** | 0.31 [-0.64, 1.19] | 0.53 [-0.45, 1.37] | 0.39 [-0.48, 1.16] |

Data shown are n (%) or median [IQR]. AIDS = Acquired Immunodeficiency Syndrome, ART = antiretroviral treatment, EFV = efavirenz, DTG = dolutegravir, LPV = ritonavir-boosted lopinavir, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, UK = United Kingdom, VL = viral load, WHO = World Health Organisation, zBMI = BMI-for-age z score

[†]Rest of Europe includes Belgium. Denmark, Germany, Greece, Italy, Poland, Romania, Spain, Sweden, and Switzerland

*35 CALHIV contributed to both the DTG and PI groups; **Black (218 male, 224 female), White (141 male, 159 female), Asian (62 male, 41 female), Other (43 Male (23/43 Mixed Race), 37 Female (28/37 Mixed Race), Other ethnicity also included Hispanic, 'other ethnic groups', Maghrebian, and Roma people); ***ART-experienced CALHIV only.

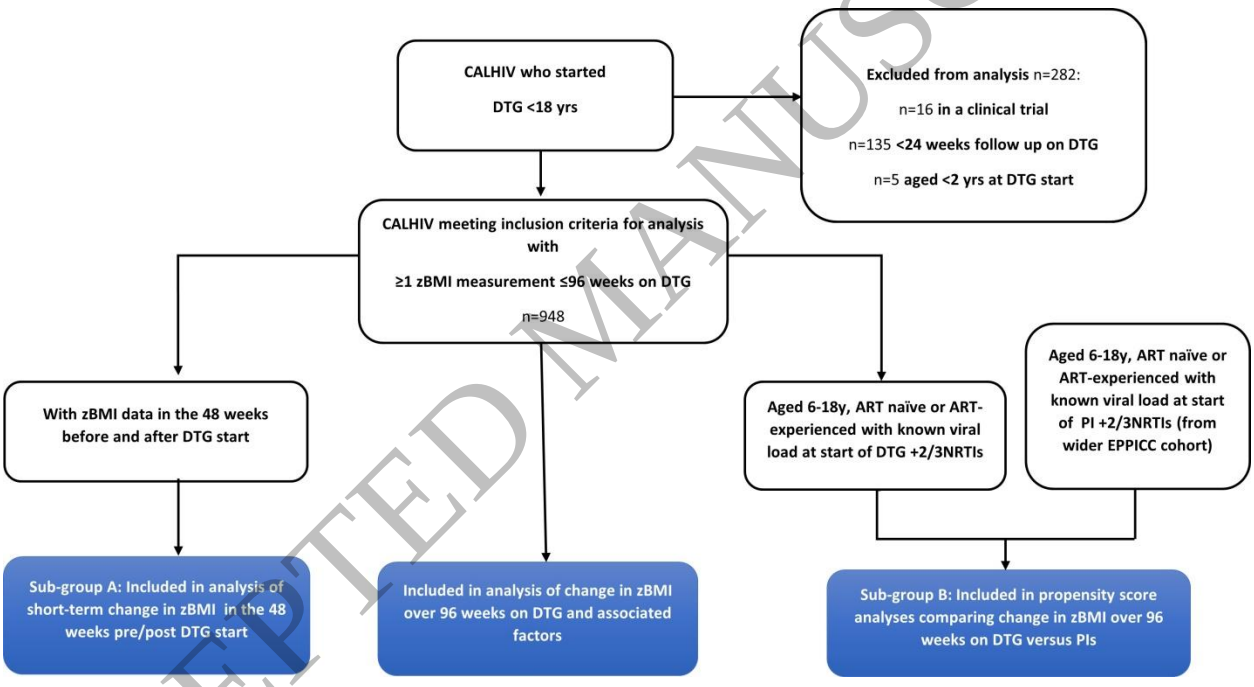
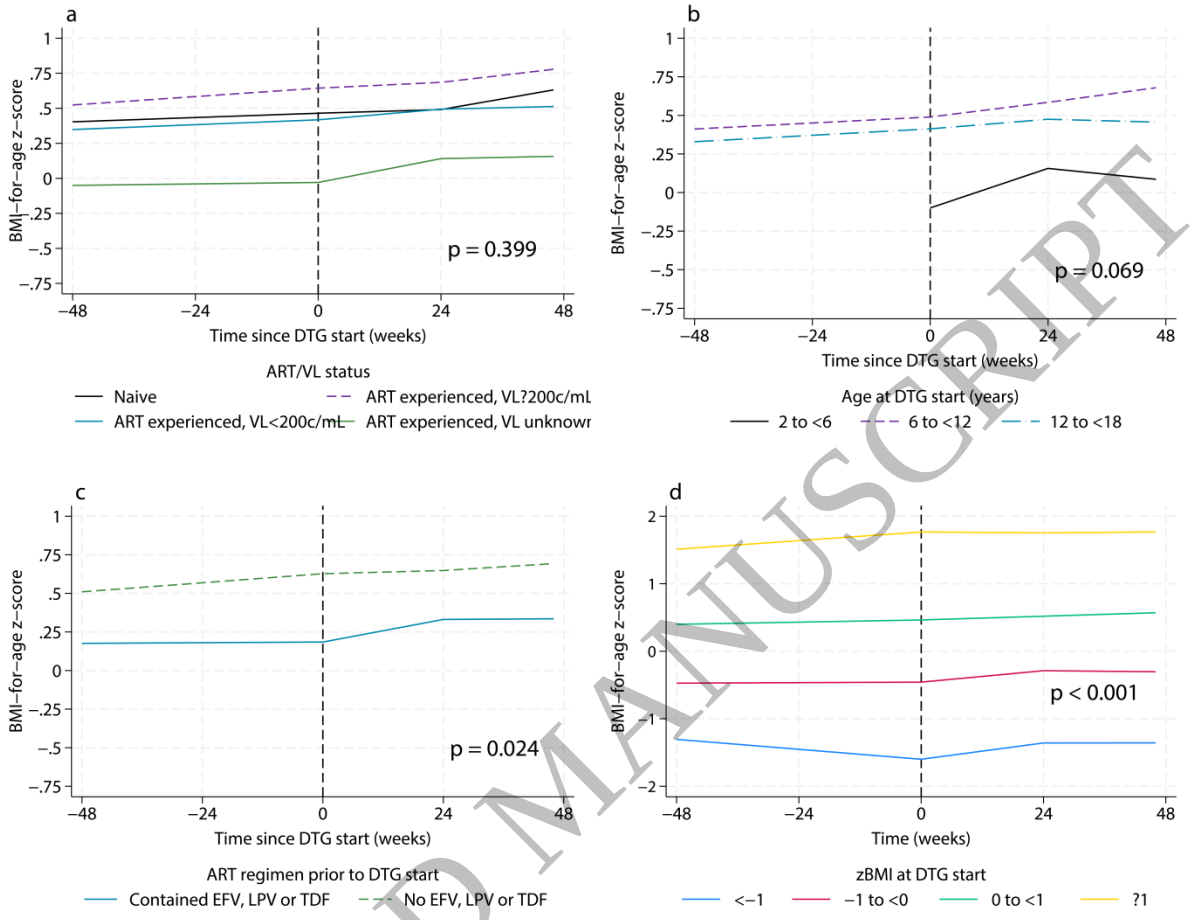



Figure 1: Flow diagram of children and adolescents living with HIV (CALHIV) included in each analysis

*35 CALHIV contributed to both the DTG and PI groups

ALT TEXT: Flow diagram showing numbers of children included in analysis and numbers excluded with reasons, and numbers of children included in the different analyses in the study

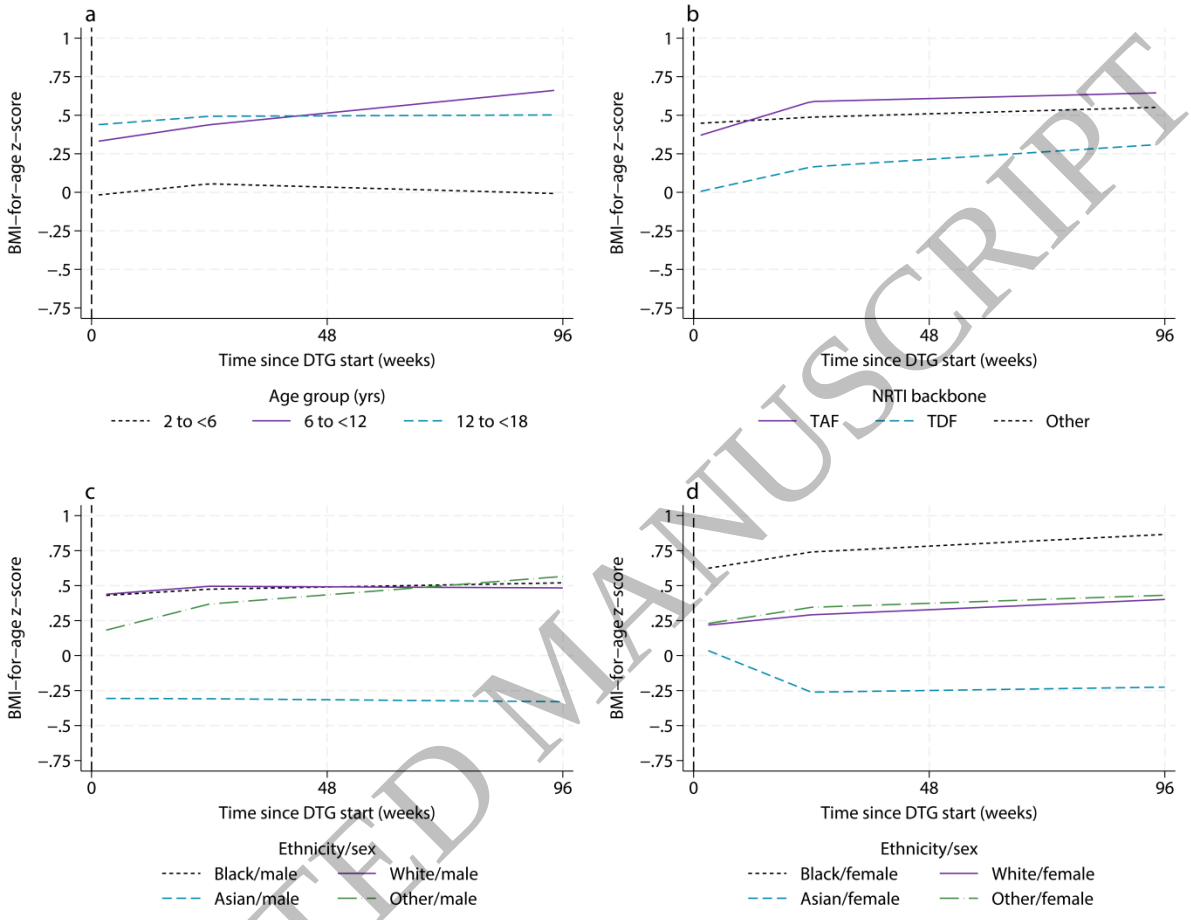



Mean BMI-for-age z-score was estimated using mixed effects models with linear splines for time since DTG start with a knot at 0 and 24 weeks, random intercept for patient, random slope for time, and correlated residuals with an exponential structure. P-values test for differences across groups in change in zBMI over 48 weeks on DTG minus change in zBMI over 48 weeks before DTG start. zBMI was not calculated before age 2 years, therefore the mean zBMI is not shown for the 2 to <6 age group pre DTG start in panel a), and this category is not included in estimation of p-value. ART = antiretroviral treatment, EFV = efavirenz, DTG = dolutegravir, LPV = ritonavir-boosted lopinavir, NRTI = nucleoside reverse transcriptase inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, zBMI = BMI-for-age z score

**Figure 2:** Mean BMI-for-age z-score in the 48 weeks pre/post DTG start by a) ART/VL status, and for CALHIV virally suppressed (VL<200c/mL) at DTG start only by: b) age group c) previous ART regimen d) zBMI at DTG start

ALT TEXT: Four graphs showing change in BMI-for-age z score over time in the 48 weeks before and after dolutegravir start, by different factors. The lines and p-values on the graphs

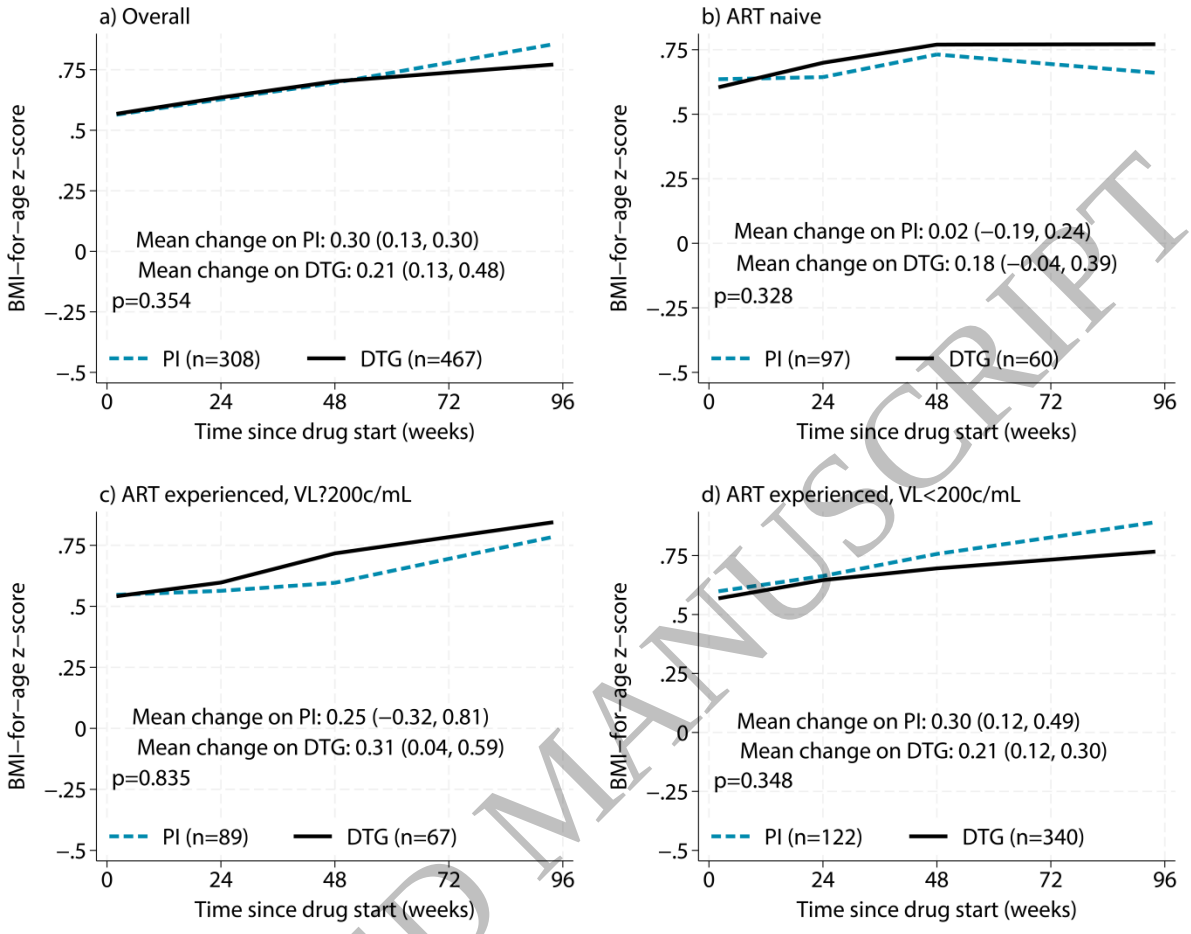
show how the difference in change in zBMI before and after dolutegravir start varies significantly by ART regimen prior to DTG start, and by zBMI at DTG start.




Mean BMI-for-age z-score (adjusted) was estimated using mixed effects models with linear splines for time since DTG start with a knot at 24 weeks, adjusting for sex, ART backbone, ethnicity, and region, with time interactions for ethnicity*sex, and NRTI backbone. ART = antiretroviral treatment, EFV = efavirenz, DTG = dolutegravir, LPV = ritonavir-boosted lopinavir, NRTI = nucleoside reverse transcriptase inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, zBMI = BMI-for-age z score

**Figure 3:** Mean BMI-for-age z-score up to 96 weeks after DTG start by a) Age group b) NRTI backbone c) Ethnicity in males d) Ethnicity in females

ALT TEXT: Four graphs show change in BMI-for-age z score over 96 weeks on dolutegravir by age group, NRTI backbone, ethnicity in males and females.




ART = antiretroviral treatment, DTG = dolutegravir, PI = protease inhibitor, zBMI = BMI-for-age z score

**Figure 4:** BMI for age z score in those on DTG or PI, a) Overall b) ART naive c) ART experienced, VL≥200c/mL d) ART experienced, VL<200c/mL.

ALT TEXT: Four graphs show change in BMI-for-age z score over 96 weeks, for children on DTG versus PI based regimens. Each graph is for a different ART/VL status group, and all show no significant difference in growth between regimens.