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Effects of the initiation of Dolutegravir-based ART regimens on growth indicators among children and adolescents living with HIV. Insights from the IeDEA global cohort.

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Glossary of Abbreviations

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
PLHIV	People Living with HIV
CALHIV	Children and Adolescents Living with HIV
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization
FDA	Food and Drug Administration
ART	Antiretroviral Therapy
HAART	Highly Active Antiretroviral Therapy
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
INSTIs	Integrase Strand Transfer Inhibitors
PIs	Protease Inhibitors
DTG	Dolutegravir
BIC	Bictegravir
LPV/r	Lopinavir/Ritonavir
FDC	Fixed Dose Combination
EVG	Elvitegravir
EFV	Efavirenz
TDF	Tenofovir Disoproxil Fumarate
TAF	Tenofovir Alafenamide
ABC	Abacavir
ZDV	Zidovudine
IeDEA	International epidemiology Databases to Evaluate AIDS
zBMI	BMI-for-age z-score
CCASAnet	Caribbean, Central and South America network for HIV epidemiology

Abstract

Background:
Global guidelines now prioritize early and universal ART initiation in children and adolescents living with HIV (CALHIV) with dolutegravir (DTG)-based regimens, due to their efficacy, safety, and child-friendly formulations. However, emerging evidence suggests that DTG, especially when used with tenofovir alafenamide (TAF), may be associated with excess weight gain and potential metabolic disturbances in older populations, underscoring the need for careful regimen selection amongst CALHIV and long-term monitoring.

Aim:
This study aims to assess growth trajectories among CALHIV following initiation or switch to DTG-based ART, using data from the global IeDEA pediatric cohort. Specifically, it examines changes in BMI-for-age z-scores (zBMI).

Methods:
The analysis includes CALHIV aged >30 days to <19 years with at least one valid anthropometric measurement within 24 months of DTG initiation, across six IeDEA regions. Longitudinal zBMI trends were modeled using linear mixed-effects models with linear splines, adjusting for demographic and clinical covariates.

Results:
A total of 29,663 children and adolescents living with HIV were included in analyses. The cohort counted with 13,671 males (46.1%) and 15,992 females (53.9%). At the time of DTG start, the median age was 12.9 years (interquartile range [IQR]: 9.2–15.9). The Southern Africa region contributed the largest proportion of participants (50%), followed by East Africa (33%), West Africa (7%), and Central Africa (5%). The median baseline zBMI was –0.62 (IQR: –1.47 to 0.16) and was significantly lower among males compared to females (−0.84 vs. −0.45, p<0.001). At DTG initiation, 66.3% of participants were on regimens that included Tenofovir d, ZDV or ABC, and 4.3% were on TAF+DTG regimens; 100% of these patients came from the Southern Africa region. In longitudinal analyses difference in zBMI slope showed a borderline significance for females with an annual increase of 0.08 (95% CI: 0.01 to 0.16) pre DTG to 0.18 (95% CI: 0.11 to 0.26) (p = 0.06). Adolescents ≥12 years exhibited a borderline significant acceleration in zBMI gain post-DTG, with the rate increasing from 0.04 (95% CI: −0.03 to 0.11) pre-DTG to 0.14 (95% CI: 0.07 to 0.22) post-DTG (p = 0.04). The most pronounced increase in zBMI was observed among patients who initiated DTG in combination with TAF, with the rate rising from 0.06 (95% CI: −0.02 to 0.14) pre-DTG to 0.22 (95% CI: 0.14 to 0.30) post-DTG. In a secondary analysis, zBMI increased modestly in the first year after DTG initiation (annual change: 0.19 95% CI: −0.09 to 0.30), followed by stabilization in the second year (–0.02 95% CI: −0.25 to 0.21). This trend was consistent across sexes and most age groups. The most pronounced regional effect occurred in West Africa (p< 0.001). DTG+TAF regimens were associated with the greatest initial zBMI increase (0.30 95% CI: 0.18 to 0.49) (p = 0,319), which then declined in the second year (-0.08 IC 95% : -0.32 to 0.16).

Discussion:

In this large, multicenter cohort of nearly 30,000 CALHIV from predominantly low- and middle-income countries, we observed a modest and non-significant increase in zBMI following DTG initiation, with a trend toward early weight gain that plateaued by the second year. This pattern was consistent across regions and subgroups, though more pronounced in adolescent females and those receiving DTG with TAF. These findings support a “return-to-health” effect in undernourished populations and suggest that DTG-related weight gain may be transient rather than progressive. While overall growth trends were reassuring, our results highlight the importance of continued monitoring in specific subgroups and underscore the need for further research into long-term metabolic outcomes.

Introduction

Background:

Since its emergence, Human Immunodeficiency Virus (HIV) has remained a persistent global public health challenge, claiming an estimated 42.3 million lives to date (1). However, the development and widespread use of antiretroviral therapy (ART) over the past three decades has fundamentally transformed the epidemic. ART effectively inhibits viral replication and prevents progression to AIDS, reducing HIV-related morbidity and mortality by over 80%(2). HIV is now considered a manageable chronic condition, allowing people living with HIV (PLHIV) to live longer, healthier lives. In 2012 approximately 9.7 million people in low- and middle-income countries were on ART resulting in an increase in the number of PLHIV and a decrease in new infections (3). In 2023 almost 31 million people were receiving lifesaving ART, and according to The United Nations Program on HIV/AIDS (UNAIDS) its expected that by 2025 95% of all people living with HIV should have a diagnosis, 95% of whom should be taking lifesaving antiretroviral treatment, and 95% of people living with HIV on treatment should achieve a suppressed viral load, an effort aligned with the Sustainable Development Goal of ending the HIV epidemic by 2030 (4,5).

Significant progress has been made in reducing HIV incidence among children, with a 52% decline over the past decade (5). This remarkable achievement is largely due to advances in treatment, particularly highly active antiretroviral therapy (HAART), which has drastically reduced vertical transmission rates, the primary mode of transmission in children, historically linked to the absence of ART during pregnancy or breastfeeding.

Despite this progress, an estimated 2.38 million children and adolescents aged 0–19 years old were living with HIV in 2023 (6). This global figure masks significant disparities in regional burden, treatment access, and outcomes. For instance, 84% of adolescents (10–19 years old) with HIV reside in sub-Saharan Africa (7), and while infections in Eastern and Southern Africa have declined by an impressive 82% since 2010, this progress has unfortunately stalled (5).

To address these ongoing challenges, the World Health Organization (WHO) now recommends that all children and adolescents living with HIV initiate ART regardless of age, weight, or clinical stage (8). Nevertheless, treatment coverage for children remains inadequate, with a growing gap between adult and child treatment coverage since 2010(5). By 2022, only 57% of children living with HIV were receiving ART, compared to 77% among adults. This disparity is further exacerbated by regional inequalities; only 35% of children in

West/Central Africa are on ART, compared to 76% in Eastern/Southern Africa (3,5,9). As of most recent data, related to the 95-95-95 goals:

- 66% of children living with HIV know their status
- 86% of those who know their status are on ART
- 84% of those on ART are virally suppressed.(6,10)

However, non-adherence to ART remains a critical challenge and has been consistently associated with poor outcomes. This issue is strongly linked to factors such as cost and access to medication, the persistent stigma associated with HIV, and, crucially, the lack of pediatric-friendly formulations (10,11). These factors collectively lead to poor adherence, treatment fatigue, virologic failure, and decreased survival among HIV-positive children (12). Recognizing this, as of July 2022, a total of 73 countries recommended dolutegravir-based regimens for children living with HIV, citing its safety, dosage variety, and convenient presentation (5).

Treatment/ Management for Children and adolescents:

The primary goal of ART is sustained virologic suppression. Choosing appropriate ART regimens requires consideration of drug safety, toxicity, tolerability, and availability of age- and weight-appropriate formulations(13). Regulatory approvals, such as those from the Food and Drug Administration (FDA), often guide selection based on these parameters.

ART regimens include a broad spectrum of drugs that can be divided into eight drug classes, categorized by their mechanism of action in disrupting the HIV life cycle. The four most used and preferred for ART are:

- **Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)**: Block reverse transcriptase and prevent RNA-to-DNA conversion.
- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**: Bind directly to reverse transcriptase to inhibit its function.
- **Integrase Strand Transfer Inhibitors (INSTIs)**: Inhibit integrase, preventing viral DNA integration into host genomes.
- **Protease Inhibitors (PIs)**: Block the protease enzyme, preventing the maturation of new viral particles.

Recommended regimens for initial ART in infants aged < 30 days with HIV-1 infection is a backbone of two NRTIs, that can be nevirapine (NVP), regardless of weight, or raltegravir (RAL) if weight ≥2 kg (12).

For infants aged >= 30 days and adolescents, INSTI- based regimens (one INSTI plus two NRTIs) or NNRTI - based regimens are recommended, Dolutegravir (DTG) is the preferred drug for use, and for children aged >= 2 years and weighing >=14 kg, Dolutegravir or Bictegravir are the preferred options (14).

This recommendation is based on dolutegravir's (DTG) superior efficacy and tolerability, fewer adverse drug reactions, minimal drug-drug interactions, and a higher genetic barrier to resistance compared to other available ART options (15). Additionally, the availability of DTG in dispersible tablet form addresses several challenges associated with pediatric treatment, particularly those related to palatability and administration(11). For example, protease inhibitors such as Lopinavir/Ritonavir (LPV/r) are known for their bitter taste, which has negatively impacted adherence in young children. DTG also mitigates the need to crush pills or open capsules, practices that can reduce the bioavailability of antiretrovirals by compromising dosage accuracy and therapeutic exposure(16). Furthermore, DTG is available as part of a fixed-dose combination (FDC) formulation (12), which enables once-daily dosing. This simplifies administration and reduces pill burden, improving adherence and therefore the rates of viral suppression, making it a more practical and effective option for children living with HIV (17).

Overall, DTG represents a clinically superior, child-friendly, and programmatically efficient choice for pediatric ART, aligning with global targets for universal access and sustained viral suppression in children living with HIV. Nevertheless, its increasing adoption has brought attention to potential adverse effects, particularly emerging signs of metabolic dysregulation.

Dolutegravir and its supposed effects on weight gain and metabolic disorders:

As previously mentioned, since 2019, DTG based ART regimens have been recommended as the preferred initial treatment for individuals living with HIV, including infants who are at least 30 days old and weigh a minimum of 3 kg (12,13,18). Despite these clinical advantages, DTG has increasingly been associated with an emerging concern: excess weight gain.

Initially, this weight gain was interpreted as part of a "return-to-health" phenomenon, whereby undernourished or immunocompromised individuals experience improved nutritional status and body mass after initiating effective ART(19). The mechanisms underlying this process are thought to involve the reduction of HIV-associated inflammation and the reversal of accelerated catabolism (20,21).

Numerous adult cohort studies and randomized trials have documented these trends(22–26), For instance, a 96-week trial showed that patients initiating DTG- or BIC-based regimens experienced significantly greater weight gain than those starting Elvitegravir(EVG)-containing regimens. Investigators also found higher odds of >10% weight change with any INSTI's compared to efavirenz (EFV) (21). Most recently data from the **IeDEA cohort in West Africa** demonstrated an average annual weight gain of 3.1 kg following transition to DTG, compared to only 0.6 kg in the two years prior to the switch. These gains were most pronounced among individuals switching from EFV or PI-based regimens, lending support to the theory that previous therapies may have had weight-suppressive effects (26).

On a switch study where participants were randomized to either switch from a boosted PI to DTG or continue with the boosted PI, greater weight gain was evidenced at 48 weeks in the DTG switch group. Researchers found decreased levels of adiponectin (chemokine involved in regulation of glucose and lipid metabolism), that could cause insulin resistance and weight gain, this hypothesis has generated controversy, as there are other possible alternatives to this downregulation and to the role that it has towards weight gain (23,27).

Finally it has been argued that weight gain could be associated with viral kinetics and the capacity to decrease viral load faster than other ARV drugs, leading to a more pronounced return to health changes, a theory that has been debunked by studies analyzing weight gain at time points with equivalent viral suppression rates(28,29).

Additional factors associated with weight gain among people living with HIV include female sex, older people, ethnicity, lower baseline CD4+ T lymphocyte counts, and high pretreatment HIV RNA levels(19,21,30–32). The physiological mechanisms underlying this phenomenon are not yet fully understood, but can be resumed as:

- **Direct drug effects**: DTG may influence appetite regulation or adipocyte function through hormonal or metabolic pathways, causing insulin resistance and potentially leading to increased fat accumulation(23,27). Also the inclusion of TAF based regimen was associated with increased risk of >10% weight gain when compared with ABC or TDF(23).

- **Loss of suppressive effect from previous regimens**: NNRTIs and NRTIs (such as efavirenz (EFV) or Tenofovir disoproxil fumarate(TDF), Abacavir (ABC) or Zidovudine (ZDV)) and protease inhibitors (PIs) may exert appetite-suppressive or metabolism-modulating effects. Switching from these regimens to DTG could remove those

effects, revealing a predisposition to weight gain (23,26).

- **Accelerated viral suppression**: DTG's rapid suppression of viral load may lead to a more pronounced "return to health" effect compared to slower-acting ARVs. However, this hypothesis remains challenged by studies controlling for viral suppression (22,23).

While these effects have been more extensively documented in adolescent and adult populations (25,33), they are now receiving growing attention in pediatric populations, where the implications for growth, development, and long-term health are still being explored (18). Understanding the mechanisms behind these hypotheses is especially critical in children, given the developmental characteristics of this population, children can be more susceptible to the long-term effects of excess weight gain and metabolic disruption.

Some studies have reported an increased rate of BMI change in cohorts initiating INSTIs (primarily DTG) (21,34) such as the study performed by Thivalapill et al. (2020) where a substantial increase in BMI z-score, from 0.8 kg/m²/year to 1.2 kg/m²/year, in children initiating DTG-based regimens was reported, though the follow-up was limited to one year, and the study had a high risk of bias due to exclusion of patients with viral load >200 copies/ml and the studied population (18).
In contrast, others have found limited or no impact on weight gain. For example, the randomized ODYSSEY trial compared DTG to standard care, concluding after 48 weeks that total cholesterol decreased with DTG and increased with the standard care, they also reported minimal additional weight gain with dolutegravir therapy, alongside a small increase in height, suggesting improvement in normal weight. Similarly the European Pregnancy and Pediatric Infections Cohort Collaboration (EPPICC) describe zBMI increases after starting DTG similar to increases after starting PI, with increased gains in children aged 6-<12 years at DTG start, black females and those on DTG+TAF(35).

Given these mixed findings, there is a critical need for long-term, large-scale, pediatric-specific studies. Understanding the full spectrum of DTG's impact on growth, weight, and metabolic parameters in **children and adolescents living with HIV (CALHIV)** is essential to prevent undesired long term metabolic side effects.

Aims:

General objectives and potential scope of the study:

This study aims to contribute to the growing body of evidence on growth trajectories and metabolic abnormalities in CALHIV following initiation or switch to DTG-based ART, using the **IeDEA global cohort**. with a goal of informing evidence-based treatment strategies that ensure both viral suppression and metabolic health, balancing the short-term efficacy of DTG with its potential long-term consequences in pediatric HIV care.

Specific objectives:

Through this analysis, the study seeks to clarify:

- Describe growth patterns before and after DTG initiation, and whether they differ significantly according to sex, age group, geographic region and prior ART regimen.
- To assess the prevalence of metabolic abnormalities before and after DTG initiation, related to cholesterol, glucose, and creatinine based on standardized grading criteria before and after DTG initiation.

Methods:

Study design and participants

The International epidemiology Database to Evaluate AIDS (IeDEA) global pediatric collaboration is part of the global IeDEA research consortium (https://www.iedea.org/), established in 2006 by the U.S. National Institutes of Allergy and Infectious Diseases (NIAID), aimed at identifying and addressing high priority research questions in the field of HIV/AIDS care and treatment using routine data from multicentric HIV/AIDS children cohorts(36).

For this analysis, data from six IeDEA regions were included: West, Central, Eastern, and Southern Africa; Asia-Pacific; and the Caribbean, Central and South America (CCASAnet).

Inclusion criteria for this analysis were: a documented date of dolutegravir (DTG) initiation; age greater than 30 days and less than 19 years at the time of DTG initiation; and the availability of at least one valid anthropometric measurement (weight and height) recorded within the 24-month period before or after the initiation of DTG.
In order to reduce noise and data entry errors rigorous criteria was employed to exclude Implausible or outlier anthropometric values (defined below and in appendices (figure 1))

Data management

Participating HIV care clinics in these regions contributed anthropometric, sociodemographic, clinical, and laboratory data, which were harmonized and merged into 12 primary datasets: BAS (Basic information, such as date of enrollment in HIV treatment and care program, date of first ART treatment, etc.), LTFU (Death and dropout information), VIS (Visit related information, Weight and Height) LAB_CD4 (Laboratory values - CD4+ cell count tests), LAB_RNA (Laboratory values - viral assay) ART (Antiretroviral medication history), DIS (CDC-C and WHO stage diseases) CENTER (Site-specific information) PROGRAM (Linkage of care programs/sites to region), LAB (Laboratory values - general), LAB_B (Laboratory values - blood pressure), MED (Other medications).

The ART data set was used to establish the date of initiation of DTG for each patient, using the variable ART_ID, containing the ATC code for ARV medications. Patients were classified as DTG users if any ART line included DTG, with the earliest DTG initiation date recorded as the index point (Week 0). This information was then merged into the VIS dataset to extract anthropometric measures for each clinical visit.

Variables definitions

The primary outcome assessed was weight change, using BMI for age z-scores (zBMI). zBMI is a measure that expresses a child's BMI relative to a population of the same age and sex, quantifying how many standard deviations (SD) a child's BMI is above or below the average BMI for their age and sex group, this way accounting for normal growth changes, Weight for age z-score (zWFA) and Height for age z-score (zHFA) were also calculated. Z-scores were computed using the **'zscorer'** package in R, based on the **2006 WHO Child Growth Standards** for children <5 years and **2007 WHO Reference** for those aged 5–19 years (20, 21, 39).

BMI categories were defined based on the WHO standards as:

- Severe underweight: zBMI < -3
- Underweight: -3 ≤ zBMI < -2
- Normal: -2 ≤ zBMI ≤ 2
- Overweight: 2 < zBMI ≤ 3
- Obese: zBMI > 3

Overweight and obese categories were merged due to limited sample size in the obesity category (0.3%). BMI for age Z-scores lower than -5 and greater than 5 as well as Weigh for age Z-scores and Height for Age Z-scores lower than -7 and greater than 7 were considered outliers (incorrect entries or growth abnormalities). Measurements with negative growth in

height over time (i.e., lower height than prior visit) were assumed to reflect data entry error and removed. zBMI changes of >2 SD compared to both neighboring points (or >4 SD if at either endpoint) were flagged and excluded to avoid outliers influencing slope estimates. Finally, Patients were censored at either the date of their last clinical visit or the last date before DTG discontinuation (defined as absence of DTG in any future ART regimen).

Covariates and Stratification Variables

Baseline characteristics were measured at DTG initiation and included:

Age category (defined according to NICHD Pediatric terminology)(40):

- Infants/toddlers: <2 years
- Early childhood: 2–<6 years
- Middle childhood: 6–<12 years
- Adolescents: 12–<19 years

Sex at birth: Male, Female

Geographic region: West, Central, Eastern, Southern Africa; Asia-Pacific; CCASAnet

Healthcare facility location: Rural/semi-rural, urban/semi-urban or Unknown. (from CENTER dataset)

Baseline ART regimen:

- PI-based: The presence of a protease inhibitor was prioritized.
- NRTI/NNRTI-based
- ART-naïve
- Prior regimen unknown: Patients that had a date of ART start prior to the beginning of DTG but patient prior regimen wasn't registered.

NRTI backbone at DTG start:

- DTG+others
- DTG+TAF
- DTG+TDF|ZDV|ABC

CD4 cell count was categorized into immunologic stages (Stage 1, 2, and 3) to age-specific thresholds (based on the CDC Pediatric HIV CD4 Cell Count Categorization), as follows:

Children aged <1 year:

- Stage 1: CD4 ≥1,500 cells/mm³
- Stage 2: CD4 between 750–1,499 cells/mm³
- Stage 3: CD4 <750 cells/mm³

Children aged 1 to <6 years:

- Stage 1: CD4 ≥1,000 cells/mm³
- Stage 2: CD4 between 500–999 cells/mm³
- Stage 3: CD4 <500 cells/mm³

Children aged ≥6 years:

- Stage 1: CD4 ≥500 cells/mm³
- Stage 2: CD4 between 200–499 cells/mm³
- Stage 3: CD4 <200 cells/mm³

Viral load categories:

- < 50 copies/mL
- 50- 100 copies/mL
- >= 1000 copies/mL.

To merge laboratory values with anthropometric measurements, **rolling joins** in R were used to match the closest CD4 or VL value within ±180 days of each clinical visit. Later, for the classification of immunologic state, viral load and zBMI category at DTG start, values were retrieved from up to 6 months before DTG start.

Ethics approval

Each participating IeDEA region obtained local institutional review boards' approvals to participate. Consent requirements were deferred to the local institutional review boards. The analysis only used anonymized data that had been collected as part of routine clinical care.

Statistical analysis:

Patient characteristics were summarized at the time of DTG initiation. Categorical variables were expressed as counts and percentages, and continuous variables as medians with interquartile ranges (IQR). Analyses were conducted on a complete-case basis. Characteristics of included vs. excluded patients (due to missing or implausible data) were compared to assess potential selection bias.

Changes in zBMI over time were measured using linear mixed-effects models (LMMs), allowing for repeated measures and within subject variability. The dependent variable was zBMI and the primary independent variable was **time in weeks**.
A series of nested models with increasing complexity were compared using likelihood ratio tests and information criteria (AIC/BIC) to determine the optimal random effects structure. A model with both random intercepts and random slopes (by time) for individual patients provided the best fit.
Each covariate was tested for interaction with time to explore effect modification of zBMI trajectory and for stratification purposes. Variables showing statistically significant interaction terms ($p < 0.05$) were included in the multivariable model to assess their independent contribution to weight trajectory.

Final model (Statistical formula):

$$Y_{ij} = \beta_0 + \beta_1 \cdot \text{lspline1}_{ij} + \beta_2 \cdot \text{lspline2}_{ij} + \sum_k \gamma_k X_{ik} + \sum_k \delta_k (X_{ik} \cdot \text{lspline1}_{ij}) + \sum_k \theta_k (X_{ik} \cdot \text{lspline2}_{ij}) + b_{0i} + b_{1i} \cdot \text{weeks}_{ij} + \epsilon_{ij}$$

Where:

- *Yij*: be the BMI z-score for individual i at time j
- *lspline1ij, lspline2ij* = the linear spline components of weeks (e.g. before/after a knot)
- The summations represent the interaction terms (e.g., region * lspline1, region * lspline2, etc.)
- *Xi* = fixed effects covariates (region, sex, rurality, age_class, priorcombo, actualcombo, and their interactions with lspline terms)
- *b0i, b1i*= random intercept and slope (for weeks) for patient i
- *ϵij* = residual error

Linear spline terms were introduced at clinically relevant time points to allow for distinct estimation of zBMI trajectories across key periods surrounding DTG initiation. Two models were constructed:

- **Model 1: Single knot at week 0 (DTG initiation):** Estimated separate slopes over the 96-week period prior to and following DTG initiation.
- **Model 2: Knots at weeks -48, 0 and 48:** Estimate three separate slopes reflecting the periods: pre-DTG initiation (-48–0 weeks), early post-DTG (0–48 weeks), and late post-DTG (48–96 weeks). Allowing the assessment of changes in BMI z-score trajectory across distinct phases of overall antiretroviral (ARV) treatment exposure.

Model-based marginal means (predicted zBMI) at specific time points (e.g., 0, 48 and 96 weeks pre- and post-DTG) were estimated using the 'emmeans' package in R. Visualization of predicted trajectories was done using ggplot.

Slopes before and after DTG initiation were compared using the '**contrast'** function from the **emmeans** package, which performs Wald tests on estimated marginal trends. Providing estimates of slope differences along with 95% confidence intervals and p-values, allowing statistical assessment of whether the rate of change in zBMI differed significantly across time periods or between subgroups.

Sensitivity analyses:

Analyses were performed to assess the robustness of the findings across different data availability scenarios. Including a subset of patients with at least one anthropometric

measurement both before and after DTG initiation, to ensure assessment of longitudinal trends. A subset with at least two measurements either before or after DTG initiation, allowing evaluation of within-period changes, and finally, restricted cohort of patients with data exclusively within 48 weeks before and after DTG initiation, to standardize the observation window.

Results

A total of 29,663 children and adolescents living with HIV (CALHIV) from the six IeDEA regional cohorts initiated dolutegravir (DTG) and had at least one zBMI measurement recorded either before or after DTG initiation. Descriptive results are presented in Table 1, both overall and stratified by sex. Cohort counted with 13,671 males (46.1%) and 15,992 females (53.9%). At the time of DTG start, the median age was 12.9 years (interquartile range [IQR]: 9.2–15.9), with females initiating DTG at a significantly older age than males (13.3 vs. 12.4 years, $p<0.001$).

The Southern Africa region contributed the largest proportion of participants (50%), followed by East Africa (33%), West Africa (7%), and Central Africa (5%). The Asia-Pacific and the Caribbean, Central and South America (CCASAnet) regions were less represented, accounting for 3% and 1% of the cohort, respectively. A higher proportion of males were from West Africa and Central Africa, while more females were from Southern Africa. The majority (75.2%) lived in urban or mostly urban areas. (Table 1).

The median baseline zBMI was –0.62 (IQR: –1.47 to 0.16) and was significantly lower among males compared to females (−0.84 vs. −0.45, $p<0.001$). Also, with significant variation by region, particularly lower zBMI values in West Africa with a median baseline zBMI of -1.1 (IQR: -1.9, -0.2), followed by East africa with -0.8 (IQR: -1.6, 0.0). The region with the highest median baseline zBMI was the CCASAnet with -0.4 (IQR: -1.0, 0.5). Severe underweight and underweight status were more common among males (5.3% and 9.7%, respectively) than females (2.5% and 6.1%, $p<0.001$) and the median follow-up duration prior to DTG initiation was 57 weeks (IQR: 13–103) (Appendix-Table 4).

Regarding treatment history, approximately 17.4% of participants were ART-naive at DTG initiation, with a higher proportion of naive individuals among females (21.4%) than males (12.6%, $p<0.001$). The majority transitioned from NNRTI/NRTI-based regimens (55.4%), followed by PI-based regimens (21.3%). And 6% had an unknown prior ART regimen, though they were not treatment naïve. At DTG initiation, 66.3% of participants were on

regimens that included TDF, ZDV or ABC, and 4.3% were on TAF+DTG regimens; 100% of these patients came from the Southern Africa region (Table 1).

Viral suppression (<50 copies/mL) was observed in 45.4% at DTG initiation, with males slightly more likely to be suppressed than females (47.6% vs. 43.5%, p<0.001). CDC immunological staging was available for a subset (15.3%), with most classified as Stage 1 (8.8%) or Stage 2 (4.1%). Stage distribution differed by sex (p<0.001), with slightly more males in Stage 1. However, CD4 counts at DTG start were comparable between sexes, with a median of 588 cells/mm³ (IQR: 325, 853).

Table 1. Demographic characteristics by sex

Characteristics	Overall N = 29,663[1]	Male N = 13,671[1]	Female N = 15,992[1]	p-value[2]
Age at DTG start	12.9 (9.2, 15.9)	12.4 (8.9, 15.3)	13.3 (9.5, 16.5)	<0.001
Age groups at DTG start				<0.001
< 2 years	692 (2.3%)	323 (2.4%)	369 (2.3%)	
2 to 5 years	2,390 (8.1%)	1,162 (8.5%)	1,228 (7.7%)	
6 to 11 years	9,772 (32.9%)	4,852 (35.5%)	4,920 (30.8%)	
>= 12 years	16,809 (56.7%)	7,334 (53.6%)	9,475 (59.2%)	
Duration on ART at DTG Start (Months)	57 (13, 103)	64 (23, 108)	49 (4, 96)	<0.001
BMI z-score at DTG start	-0.62 (-1.47, 0.16)	-0.84 (-1.69, -0.03)	-0.45 (-1.26, 0.30)	<0.001
BMI Z-score Category at DTG Start				<0.001
Severe underweight	1,112 (3.7%)	720 (5.3%)	392 (2.5%)	
Underweight	2,309 (7.8%)	1,328 (9.7%)	981 (6.1%)	
Normal weight	20,327 (68.5%)	8,972 (65.6%)	11,355 (71.0%)	
Overweight/Obesity	440 (1.5%)	201 (1.5%)	239 (1.5%)	
Not available	5,475 (18.5%)	2,450 (17.9%)	3,025 (18.9%)	
Region				<0.001
Asia-Pacific	980 (3.3%)	531 (3.9%)	449 (2.8%)	
Caribbean, Central and South America	330 (1.1%)	138 (1.0%)	192 (1.2%)	

Central Africa	1,564 (5.3%)	782 (5.7%)	782 (4.9%)	
East Africa	9,921 (33.4%)	4,645 (34.0%)	5,276 (33.0%)	
Southern Africa	14,685 (49.5%)	6,395 (46.8%)	8,290 (51.8%)	
West Africa	2,183 (7.4%)	1,180 (8.6%)	1,003 (6.3%)	
Rurality				<0.001
Urban/Mostly Urban	22,316 (75.2%)	10,606 (77.6%)	11,710 (73.2%)	
Rural/Mostly Rural	7,210 (24.3%)	3,011 (22.0%)	4,199 (26.3%)	
Unknown	137 (0.5%)	54 (0.4%)	83 (0.5%)	
Previous ART Regimen				<0.001
Naive	5,148 (17.4%)	1,727 (12.6%)	3,421 (21.4%)	
NNRTI or NRTI based	16,440 (55.4%)	7,874 (57.6%)	8,566 (53.6%)	
PI based	6,306 (21.3%)	3,245 (23.7%)	3,061 (19.1%)	
Prior regimen unknown	1,769 (6.0%)	825 (6.0%)	944 (5.9%)	
ART Regimen Associated with DTG				0.7
DTG+others	8,714 (29.4%)	3,995 (29.2%)	4,719 (29.5%)	
DTG+TAF	1,284 (4.3%)	606 (4.4%)	678 (4.2%)	
DTG+TDF|ZDV|ABC	19,665 (66.3%)	9,070 (66.3%)	10,595 (66.3%)	
Viral Load at DTG Start				<0.001
<50 copies/ml	13,466 (45.4%)	6,507 (47.6%)	6,959 (43.5%)	
50–999 copies/ml	3,437 (11.6%)	1,716 (12.6%)	1,721 (10.8%)	
>=1000 copies/ml	3,318 (11.2%)	1,628 (11.9%)	1,690 (10.6%)	
Not available	9,442 (31.8%)	3,820 (27.9%)	5,622 (35.2%)	
CD4 Count (cells/mm³)	588 (325, 853)	599 (342, 859)	578 (315, 850)	0.2
Unknown	25,134	11,546	13,588	
CDC immunological stage for age at DTG start				<0.001
Stage 1	2,610 (8.8%)	1,308 (9.6%)	1,302 (8.1%)	
Stage 2	1,216 (4.1%)	532 (3.9%)	684 (4.3%)	
Stage 3	721 (2.4%)	351 (2.6%)	370 (2.3%)	

Not available	25,116 (84.7%)	11,480 (84.0%)	13,636 (85.3%)

[1]Median (Q1, Q3); n (%), [2]Wilcoxon rank sum test; Pearson's Chi-squared test, DTG = Dolutegravir, NRTI, = Nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine, ABC = abacavir, zBMI = BMI-for-age z score, CDC = center for disease control and prevention, ART = antiretroviral therapy.

A total of 6,198 patients were excluded from the main analysis due to missing values in height and/or weight (Appendix-Table 5). Compared to the included group, a slightly higher proportion were female (56.8%), and they tended to be older, with a median age of 14.8 years (IQR: 10.7–17.3). The majority (68.6%) were in the ≥12 years age group. Regionally, most were also from Southern Africa (55.8%), followed by East Africa (21.7%) and Central Africa (12.5%) and differently to patients included in analysis there was a lower prevalence of patients from Asia-pacific region (1.1%).

Data on CD4 count and viral load at DTG start were entirely missing in this group. A larger proportion were ART-naïve (27.7%), and 72.3% had unknown prior ART regimens. Patients in this group were also more likely to reside in rural or mostly rural areas (46.5%), The median time since ART started was 53 months (IQR: 0–107).

Compared to those included in the analysis, patients with missing height and/or weight data were generally older, more likely to be female, and had higher rates of missing laboratory data. They were also more likely to be ART-naïve or to have an unknown prior regimen and were more frequently from rural areas and despite the statistical significance, the regional distribution was comparable (Appendix-Table 5). These differences suggest that the excluded group may represent patients that were recently included in the IeDEA cohort and that were probably more geographically marginalized.

Longitudinal analyses (knot at time 0):

A total of 29,663 patients were included in the adjusted analysis of long-term changes in BMI-for-age Z-score (zBMI) before and after the initiation of dolutegravir (DTG). The predicted baseline mean zBMI at the time of DTG initiation was −0.54 (95% CI: −0.62 to −0.48).

In adjusted models, the annual rate of zBMI change was 0.06 (95% CI: −0.01 to 0.13) in the period prior to DTG initiation, and 0.15 (95% CI: 0.07 to 0.22) after DTG initiation, indicating

a trend toward faster zBMI gain following DTG-based therapy. However, this acceleration was not statistically significant (p = 0.09).

The rate of zBMI change differed significantly by sex (p = 0.01). At baseline, females had a higher mean zBMI compared to males (−0.37 vs. −0.73) and showed greater annual increases in zBMI both before DTG initiation (0.08 vs. 0.03) and after DTG initiation (0.18 vs. 0.11). (Table 2). When examined within each sex, the difference in zBMI slope before and after DTG was not statistically significant for males (p = 0.16), but showed a borderline significance for females with an annual increase of 0.08 (95% CI: 0.01 to 0.16) pre DTG to 0.18 (95% CI: 0.11 to 0.26) (p = 0.06), suggesting a possible sex-specific response to DTG in terms of weight gain trajectory.

zBMI trajectories also varied significantly by age group (p < 0.001). Children aged 2 to 5 years had the highest baseline zBMI (−0.24; 95% CI: −0.33 to −0.16), whereas adolescents aged ≥12 years had the lowest baseline zBMI (−0.79; 95% CI: −0.86 to −0.72). While most age groups did not show significant changes in zBMI slope before versus after DTG initiation (Table 2), adolescents ≥12 years exhibited a borderline significant acceleration in zBMI gain post-DTG, with the rate increasing from 0.04 (95% CI: −0.03 to 0.11) pre-DTG to 0.14 (95% CI: 0.07 to 0.22) post-DTG (p = 0.04).

Regional differences in baseline zBMI and zBMI trajectories were also observed. West Africa had the lowest baseline zBMI (−1.02; 95% CI: −1.10 to −0.94) and a significant increase in the yearly zBMI slope post-DTG (0.23; 95% CI: 0.15 to 0.31), compared to a slightly negative slope pre-DTG (−0.02; 95% CI: −0.10 to 0.06; p < 0.001). In East Africa, baseline zBMI was also low (−0.77; 95% CI: −0.84 to −0.70), but the increase in zBMI from 0.06 (95% CI: −0.02 to 0.13) pre-DTG to 0.10 (95% CI: 0.02 to 0.17) post-DTG did not reach statistical significance. In Southern Africa, baseline zBMI was moderately low (−0.46; 95% CI: −0.53 to −0.40), and the annual zBMI increased significantly from 0.04 (95% CI: −0.04 to 0.11) pre-DTG to 0.16 (95% CI: 0.09 to 0.23) post-DTG (p = 0.019). Notably, this region is unique in that it includes the only cohort of patients receiving DTG in combination with TAF-based regimens, which may partly explain the observed differences. Other regions showed no statistically significant changes in zBMI trajectories between the pre- and post-DTG periods (Table 2).

zBMI changes also differed significantly by prior ART regimen (p < 0.001). Patients previously on NRTI/NNRTI-based regimens experienced a significant increase in the rate of zBMI change, from −0.03 (95% CI: −0.08 to 0.02) pre-DTG to 0.11 (95% CI: 0.04 to 0.19) post-DTG (p < 0.01). Similarly, those transitioning from PI-based regimens showed a

significant increase from −0.03 (95% CI: −0.08 to 0.02) to 0.17 (95% CI: 0.09 to 0.24) post-DTG ($p < 0.01$). In contrast, ART-naive patients and those with unknown prior regimens showed no significant change in zBMI slopes between the pre- and post-DTG periods.

The most pronounced increase in zBMI was observed among patients who initiated DTG in combination with TAF, with the rate rising from 0.06 (95% CI: −0.02 to 0.14) pre-DTG to 0.22 (95% CI: 0.14 to 0.30) post-DTG. In comparison, patients on DTG with TDF, ZDV, or other regimens showed smaller and more stable rates of zBMI gain across both periods (Table 3). These findings reinforce growing concerns about excess weight gain associated with TAF, consistent with previous reports in both adult and pediatric populations.

No substantial differences in zBMI change were observed across rurality classifications ($p = 0.007$). Within each category, there was no statistically significant change in zBMI slope before and after DTG initiation. However, a borderline significant increase was noted among patients residing in Rural/Mostly Rural settings, with zBMI increasing from 0.09 (95% CI: 0.03 to 0.16) pre-DTG to 0.16 (95% CI: 0.13 to 0.19) post-DTG ($p = 0.05$).

Viral load and CD4 count data at DTG initiation were missing for 35% and 85% of participants, respectively, limiting comprehensive assessment of immunologic status as a modifier of zBMI trajectories. However, a sensitivity analysis restricted to participants with available viral load and CD4 data—adjusted for demographic covariates—suggested minimal differences in zBMI trends by virologic or clinical stage status.

Among participants with suppressed viral load (<50 copies/mL), the annual zBMI gain was 0.12 (95% CI: 0.05 to 0.19) before DTG initiation and slightly decreased to 0.09 (95% CI: 0.06 to 0.11) after DTG initiation, though the change was not statistically significant. Similar non-significant trends were observed in participants with unsuppressed viral loads.

More pronounced differences were observed by clinical stage. In participants classified as Stage 1 at DTG initiation, the annual zBMI increase dropped significantly from 0.40 (95% CI: 0.27 to 0.52) pre-DTG to 0.02 (95% CI: –0.04 to 0.08) post-DTG ($p < 0.001$). Conversely, in participants at Stage 3, the rate of zBMI increase remained relatively stable: 0.38 (95% CI: 0.25 to 0.50) pre-DTG and 0.37 (95% CI: 0.30 to 0.43) post-DTG ($p = 0.88$) (table 2).

In summary, the greatest increases in zBMI following DTG initiation were observed among females, adolescents aged ≥12 years, individuals in the West and Southern Africa regions, and those previously treated with PI-based regimens or initiating DTG+TAF. While most groups showed some degree of weight gain acceleration post-DTG, these subpopulations demonstrated the most pronounced changes, suggesting that both demographic and

treatment-related factors may influence the weight trajectory of CALHIV transitioning to DTG-based ART.

Table 2. Baseline characteristics of patients at initiation of a dolutegravir-based regimen by age group

	Before DTG start			After DTG start			
Characteristics	Mean annual zBMI change	95% CI		Mean annual zBMI change	95% CI		p value[1]
All	**0.06**	**-0.01**	**0.13**	**0.15**	**0.07**	**0.22**	**0.09**
Sex							(0.003)
Male	0.03	-0.04	0.11	0.110	0.03	0.19	0.156
Female	0.08	0.01	0.16	0.184	0.11	0.26	0.061
Age groups							(<0.001)
< 2 years	0.34	0.21	0.47	0.46	0.37	0.56	0.134
2 to 5 years	-0.12	-0.20	-0.05	-0.03	-0.11	0.05	0.084
6 to 11 years	-0.02	-0.09	0.05	0.01	-0.06	0.09	0.490
>= 12 years	0.04	-0.03	0.11	0.14	0.07	0.22	0.044
Region							(<0.001)
Asia-Pacific	0.07	-0.01	0.15	0.12	0.04	0.20	0.385
Caribbean, Central and South America	0.08	-0.01	0.18	0.13	0.02	0.23	0.565
Central Africa	0.13	0.05	0.20	0.16	0.07	0.24	0.593
East Africa	0.06	-0.02	0.13	0.10	0.02	0.17	0.476
Southern Africa	0.04	-0.04	0.11	0.16	0.09	0.23	0.019
West Africa	-0.02	-0.10	0.06	0.23	0.15	0.31	<0.001
Previous ART Regimen							(<0.001)
Naive	0.13	-0.09	0.34	0.28	0.20	0.36	0.178
NNRTI or NRTI based	-0.03	-0.08	0.02	0.11	0.04	0.19	0.002
PI based	-0.03	-0.08	0.02	0.17	0.09	0.24	<0.001
Prior regimen unknown	0.17	0.07	0.28	0.03	-0.06	0.11	0.035
ART Regimen Associated with DTG							(<0.001)
DTG+others	0.06	-0.01	0.14	0.12	0.04	0.20	0.309
DTG+TAF	0.06	-0.02	0.14	0.22	0.14	0.30	0.007
DTG+TDF|ZDV|ABC	0.05	-0.02	0.12	0.10	0.03	0.18	0.297
Rurality							0.007

Table 2. Baseline characteristics of patients at initiation of a dolutegravir-based regimen by age group							
	Before DTG start			After DTG start			
Characteristics	Mean annual zBMI change	95% CI		Mean annual zBMI change	95% CI		p value[1]
Urban/Mostly Urban	0.12	0.06	0.19	0.16	0.13	0.19	0.310
Rural/Mostly Rural	0.09	0.03	0.16	0.16	0.13	0.19	0.056
Unknown	-0.04	-0.16	0.08	0.12	-0.09	0.34	0.206
Viral Load at DTG Start							(<0.001)
<50 copies/ml	0.12	0.05	0.19	0.09	0.06	0.11	0.340
50-999 copies/ml	0.13	0.06	0.21	0.06	0.03	0.09	0.071
>=1000 copies/ml	0.08	0.01	0.16	0.07	0.04	0.10	0.752
Disease Stage at DTG start							(<0.001)
Stage 1	0.40	0.27	0.52	0.02	-0.04	0.08	<0.001
Stage 2	0.39	0.26	0.51	0.00	-0.07	0.06	<0.001
Stage 3	0.38	0.25	0.50	0.37	0.30	0.43	0.885
BMI Z-score Category at DTG Start							(<0.001)
Severe underweight	-0.22	-0.30	-0.15	1.00	0.96	1.05	<0.001
Underweight	-0.03	-0.10	0.04	0.57	0.53	0.60	<0.001
Normal weight	0.16	0.09	0.23	0.11	0.08	0.13	0.153
Overweight/Obesity	0.43	0.35	0.52	-0.73	-0.80	-0.67	<0.001

[1]P wald test. Mean BMI-for-age score was estimated using mixed effects models with linear splines at DTG start (week 0). Adjusting for sex, age group, region, history of ART regimen, viral load (different model only for those with available data (n=20,221)), and CDC immunological stage for age at DTG start (different model only for those with available data (n=4,547), with time interactions for said variables. P-values in brackets (across subgroups) represent the significance level for the interaction term. P-values by subgroup compare the slope of change in zBMI before and after DTG start. DTG = Dolutegravir, NRTI, = Nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine, ABC = abacavir, zBMI = BMI-for-age z score, ART= antiretroviral therapy, CDC = center for disease control and prevention.

Longitudinal analyses (Knots at -48, 0, 48 weeks)

To better characterize temporal patterns in zBMI change, a secondary analysis was performed using the same study population but with a modified model incorporating distinct knots at 0 and 48 weeks. This allowed estimation of three separate annual zBMI slopes corresponding to the pre-DTG period (–48 to 0 weeks), early post-DTG (0 to 48 weeks), and late post-DTG (48 to 96 weeks), Table 6 with mean zBMI estimates can be found in the list of appendices.

Overall, the annual rate of zBMI gain was 0.13 (95% CI: 0.02 to 0.24) in the pre-DTG period, increasing slightly in the first year after DTG initiation to 0.19 (95% CI: 0.09 to 0.30), though the difference was not statistically significant (p = 0.70). In contrast, the second year on DTG showed a flattening of the trajectory, with a slight downward trend in zBMI change estimated at –0.02 (95% CI: –0.25 to 0.21, p = 0.80), indicating potential plateauing of the initial weight gain.

Sex-stratified analyses revealed consistent trends. Among females, the pre-DTG annual increase was 0.15 (95% CI: 0.04 to 0.26), rising to 0.22 (95% CI: 0.12 to 0.33) in the first year post-DTG, before stabilizing at 0.03 (95% CI: –0.20 to 0.26) in the second year. Males had a pre-DTG annual increase of 0.11 (95% CI: 0.01 to 0.23), which increased modestly to 0.16 (95% CI: 0.06 to 0.26) in the first year post-DTG and declined to –0.06 (95% CI: –0.29 to 0.16) in the second year. However, none of these within-sex changes across the time periods reached statistical significance (Figure 1).

These findings suggest a modest short-term increase in zBMI following DTG initiation, particularly in the first year, followed by a trend toward stabilization or deceleration in the second year. While sex differences in zBMI trajectories persist, the short- vs long-term dynamics appear broadly similar between males and females.

When stratified by age group, children under 2 years of age showed the most pronounced change in zBMI trajectory. In this group, the annual rate of zBMI gain increased significantly from 0.29 (95% CI: 0.12 to 0.46) in the pre-DTG period to 0.64 (95% CI: 0.51 to 0.77) during the first year post-DTG. However, this acceleration was not sustained, with the rate halving in the second year to 0.08 (95% CI: –0.17 to 0.33). This pattern may reflect age-related developmental changes, such as the transition from maternal milk to complementary feeding during this period.

In contrast to the <2-year and adolescent groups, children aged 2–5 and 6–11 years showed minimal or no meaningful zBMI changes in the short- and long-term periods surrounding DTG initiation. For 2–5-year-olds, zBMI trends were slightly negative across all intervals: –0.05 pre-DTG, –0.03 in the first year post-DTG, and –0.10 in the second year post-DTG. Similarly, among 6–11-year-olds, a modest zBMI increase was observed pre-DTG (0.12), which plateaued to 0.00 in the first year post-DTG, followed by a slight decline (–0.07) in the second year. These patterns suggest relatively stable or even slightly declining zBMI trajectories in these intermediate age groups, with no evidence of significant acceleration in weight gain post-DTG (Figure 1).

However, among adolescents (≥12 years), earlier indications of increased zBMI post-DTG were not confirmed in this short-term model. The annual zBMI change was 0.17 (95% CI: 0.07 to 0.28) pre-DTG, and 0.15 (95% CI: 0.05 to 0.26) in the first year post-DTG (p = 0.90), with a near-neutral trajectory in the second year (0.02, 95% CI: –0.21 to 0.24). Across the other age categories (2–<5, 5–<10, and 10–<12 years), no statistically significant differences were observed between pre-DTG, early post-DTG, and late post-DTG periods (Figure 1).

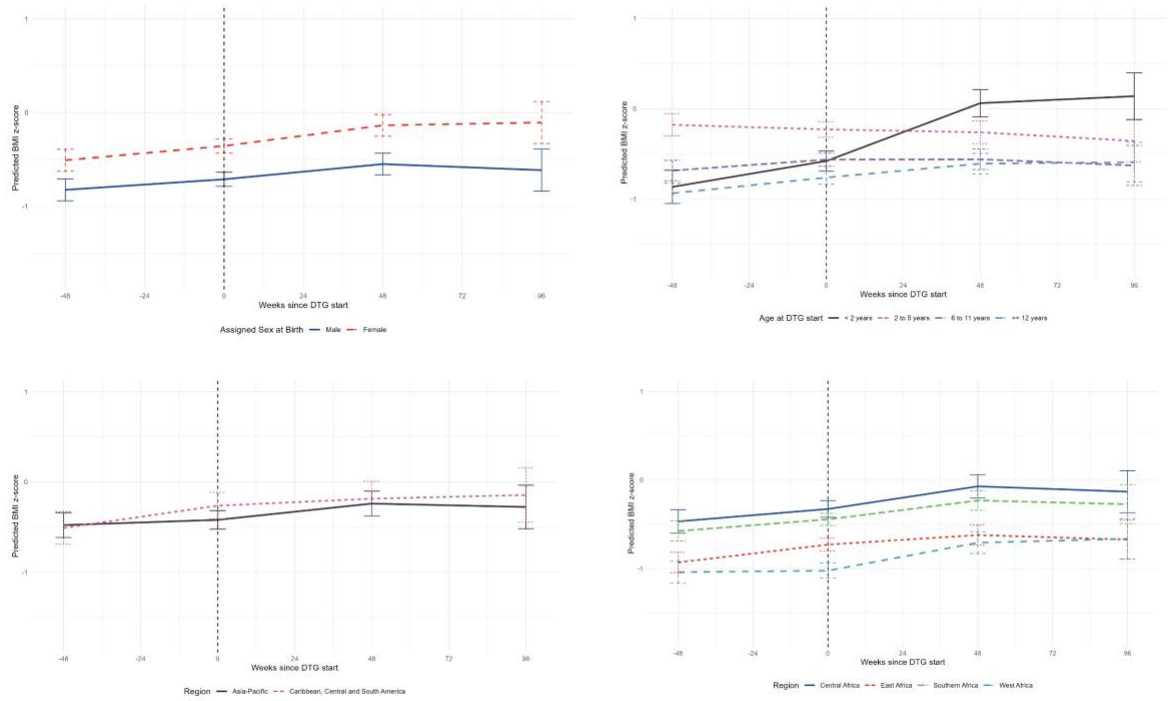

Figure 1. Mean BMI z-score estimated using mixed effects models with linear splines for time since DTG start with a knot at 0 and 48 weeks, adjusted for sex, age groups, region, immunological state, and prior and actual ART regimen composition with time interaction terms for each variable.

Regional trends in zBMI change revealed continued variation in response to DTG initiation. The most pronounced increase was observed in West Africa, where zBMI rose from 0.02 (95% CI: -0.10 to 0.13) pre-DTG to 0.32 in the first year post-DTG (95% CI: 0.21 to 0.42, p < 0.01), before stabilizing at 0.04 (95% CI: -0.19 to 0.27) in the second year. A similar, though less marked, pattern was seen in Southern and Central Africa, where zBMI increased in the first post-DTG year (0.21 and 0.26, respectively), followed by a small decline in the second year (–0.04 and –0.06, respectively).

In contrast, East Africa showed a moderate increase pre-DTG (0.20), but a smaller gain in the first year (0.11) (p =0.5) and a slight decline afterward (–0.05). Asia-Pacific and Caribbean, Central and South America (CCASAnet) regions displayed minimal post-DTG

zBMI increases in year one (0.18 and 0.08, respectively), with a plateau or mild reversal in the second year (–0.04 and 0.04) (Figure 1). These findings underscore the heterogeneous regional responses, with more pronounced short-term gains in zBMI in West and Southern Africa, that continue to stabilize with time.

zBMI change by prior ART regimen demonstrated distinct patterns across treatment histories. Among ARV-naïve individuals, the zBMI increased substantially during the first year on DTG, from a pre-DTG slope of 0.19 (95% CI: –0.11 to 0.50) to 0.45 (95% CI: 0.34 to 0.55), followed by a notable decline in the second year post-DTG (–0.11, 95% CI: –0.34 to 0.12). Although the pre-DTG estimate had wide confidence intervals, the sharp early post-DTG gain may reflect catch-up growth (Figure 1 – Table 6).

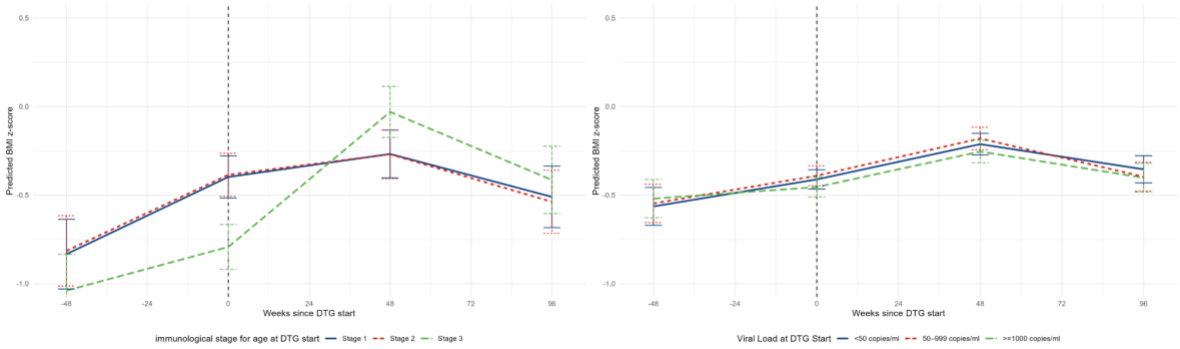

Figure 2. Mean BMI z-score estimated using mixed effects models with linear splines for time since DTG start, with a knot at 0 and 48 weeks, adjusted for sex, age groups, region, immunological state, and prior and actual ART regimen composition with time interaction for each variable. Immunological stage for age at DTG start = CD4 cell count categorized to age-specific thresholds (based on the CDC Pediatric HIV CD4 Cell Count Categorization).

For those on NNRTI or NRTI-based regimens, pre-DTG zBMI change was modest at 0.05 (95% CI: –0.03 to 0.12), rising slightly to 0.13 (95% CI: 0.03 to 0.24) in the first post-DTG year, and stabilizing in the second year (0.00, 95% CI: –0.22 to 0.23). A similar trend was observed in PI-based regimen users, with a gradual increase from 0.08 pre-DTG (95% CI: 0.00 to 0.16) to 0.18 in the first year post-DTG (95% CI: 0.07 to 0.28), then plateauing in the second year (0.04, 95% CI: –0.18 to 0.27) (Table 6).

When stratified by backbone ARV combinations revealed that zBMI changes over time varied across regimens (p<0.001). For participants receiving **DTG in combination with TAF**, the largest short-term increase in zBMI was observed in the first year post-DTG, with an annual change of **0.30** (95% CI: 0.18 to 0.42) (Table 6). This was preceded by a pre-DTG change of **0.21** (95% CI: 0.09 to 0.33) and followed by a decrease in the second year post-DTG to **-0.08** (95% CI: -0.32 to 0.16) (p=0.03), suggesting a possible short-term weight gain associated with TAF that plateaus in the longer term (Figure 3).

For those on **DTG with TDF, ZDV, or ABC**, zBMI increased more modestly across all three time points: **0.09** (95% CI: -0.02 to 0.20) pre-DTG, **0.11** (95% CI: 0.01 to 0.21) in the first year post-DTG, and **0.03** (95% CI: -0.19 to 0.26) in the second year. suggesting a slower, steadier trend without major fluctuations.

Participants on **DTG with other backbones** showed no significant change on pre vs post DTG zBMI change but also stabilized at **0.00** (95% CI: -0.23 to 0.22) in the second year, indicating a leveling off after an initial rise.

When stratifying Previous ART regimen by Current ART regimen, ART-naïve children, who initiated **DTG+TAF** experienced the largest zBMI increase in the first year (0.56; 95% CI: 0.44 to 0.68), followed by those on **DTG+TDF/ZDV/ABC** (0.37; 95% CI: 0.26 to 0.47). However, this early gain was not sustained into the second year, where negative or plateauing trends were observed (e.g., –0.17 for DTG+TAF, p<0.001) (Table 6). Overall, regimens containing **TAF** were associated with higher early gains in BMI z-scores across most prior ART groups (Figure 3).

These findings reinforce earlier results suggesting **DTG+TAF is associated with the highest initial zBMI gains**, although this effect appears to **diminish over time**. In contrast, other backbone regimens showed more **stable** changes in zBMI over the entire period studied.

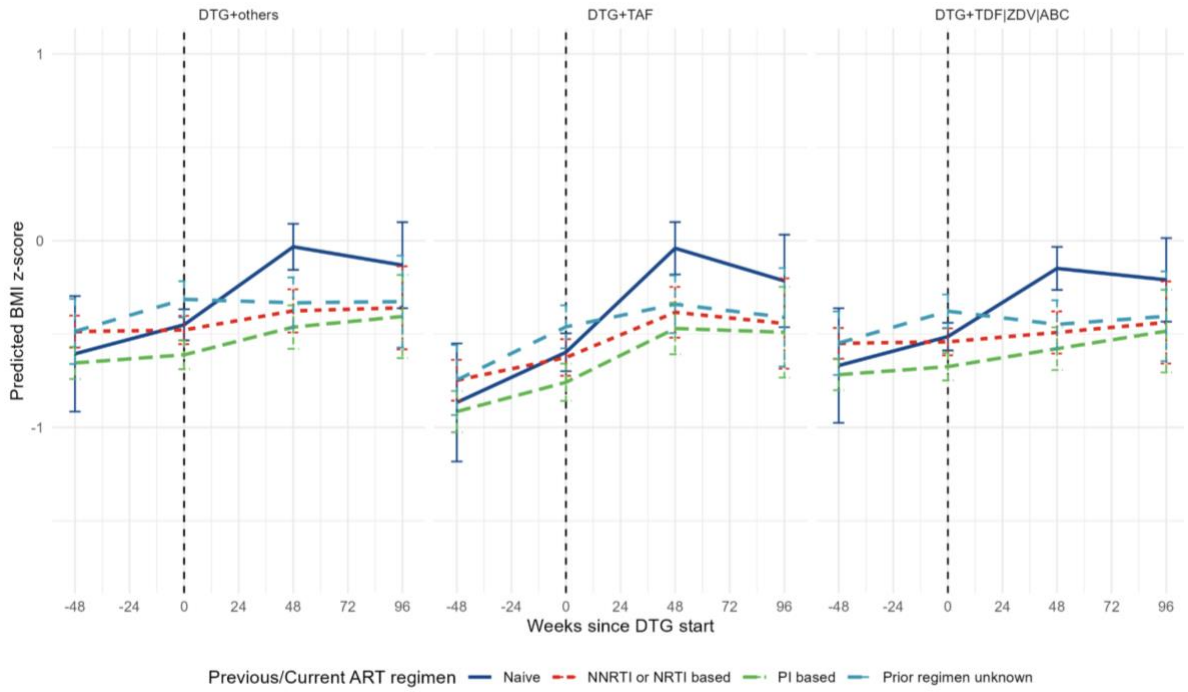

Figure 3. Mean BMI z-score estimated using mixed effects models with linear splines for time since DTG start, with a knot at 0 and 48 weeks, adjusted for sex, age groups, region, immunological state and prior and actual ART regimen composition with time interactinteractions for each variable. NRTI =

Nucleoside/Nucleotide Reverse Transcriptase Inhibitors , NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitors, PI= Protease Inhibitors (PIs), DTG = dolutegravir, TAF = Tenofovir Alafenamide, TDF = Tenofovir disoproxil fumarate, ZDV = Zidovudine, ABC = Abacavir

Sensitivity analyses:

Sensitivity analyses were consistent with the primary results, confirming that the direction and magnitude of zBMI changes before and after DTG initiation remained stable across varying analytic cohorts. With females consistently showing a slightly greater increase than males, though the difference was not statistically significant in either analysis (Table 7: p = 0.250; Table 8: p = 0.565). Among adolescents aged ≥12 years, zBMI gains were more pronounced after DTG initiation in both samples, with a significant difference in Table 7 (p = 0.020) and a borderline trend in Table 8 (p = 0.068). Patterns were regionally consistent, including the significance level of the West Africa region, in Table 7 and Table 8, post-DTG zBMI change was significantly greater (p = 0.001). Participants on DTG+TAF had larger zBMI increases post-DTG in both analyses, though statistical significance was only reached in participants with at least two observations before or after DTG start (p = 0.016).

Discussion:

In this large, multicenter cohort study drawing on data from diverse regions, primarily across the Global South, we contribute meaningfully to the growing understanding of the metabolic effects of ART in pediatric and adolescent populations. This work represents a significant advancement in the field, as existing studies on this topic have generally been limited by small sample sizes (often fewer than 1,000 participants) and have predominantly focused on cohorts from high-income settings in the Global North. (41–45) By contrast, our study includes nearly 30,000 children and adolescents from multiple countries, offering a more globally representative picture of ART-related growth and metabolic changes in low- and middle-income settings where the burden of pediatric HIV is highest.

This expanded scale not only strengthens the statistical power of the findings but also enhances their generalizability to real-world clinical settings. Importantly, the inclusion of a wide age range, varied geographic locations, and diverse ART histories allowed an examination of subgroup-specific patterns that are often overlooked in smaller, homogeneous cohorts. As such, our results reveal novel insights that are uniquely relevant to the global pediatric HIV population.

Overall, we observed a modest and statistically non-significant increase in zBMI following DTG initiation, a pattern that remained consistent across multiple stratified subgroups. After adjusting for relevant covariates, the mean annual rate of zBMI gain rose from 0.06 pre-DTG to 0.15 post-DTG (95% CI: 0.07–0.22), a change that did not reach statistical significance (p

= 0.09). These findings are consistent with some adult and pediatric cohorts and trials, like the French pediatric cohort, which reported a comparable annual zBMI change of 0.08 (95% CI: –0.07 to 0.22)(41), but contrast with some other studies such as the DC cohort study, where a more pronounced annual zBMI increase of +0.21 units (95% CI: 0.08 to 0.35) was observed (23). Notably, that population had a higher baseline prevalence of overweight and obesity, which may have influenced the degree of observed change. Similarly, a study in Eswatini reported significant mean BMI increase of 1.2 kg/m² post DTG (34), although the cohort was composed exclusively of adolescents older than 14 years, likely undergoing significant pubertal development, an important factor influencing weight and body composition during this life stage.

In adult cohorts, INSTIs (especially DTG) have been consistently associated with weight gain (24,26,46,50). However, pediatric trials such as ODYSSEY found no significant difference in weight gain between DTG and non-DTG arms over 96 weeks (51). The SMILE trial, while identifying excess weight gain in the DTG+DRV/r group, noted the overall increase was modest, with very few children reaching obesity thresholds.

Importantly, dividing follow-up into the first and second years of DTG exposure provided more nuanced insights into the trajectory of weight changes among CALHIV. While the first year post-DTG initiation showed a modest increase in zBMI, the second year was characterized by a stabilization of growth patterns, with a mean annual zBMI change of –0.02 (95% CI: –0.25 to 0.21). This result closely mirrors findings from the French pediatric cohort, where the second-year change was similarly negligible at +0.03 (95% CI: –0.08 to 0.13)

This temporal breakdown is essential because initial weight changes following ART switches may reflect transient physiological responses, including improved clinical condition, immune reconstitution, or changes in appetite and absorption, what is often referred to as a "return-to-health" effect (21,46). By looking beyond, the first year, we can better differentiate between short-term adaptation and long-term growth alterations. The observed plateau effect after the first year suggests a self-limiting phenomenon, and it supports the notion that weight changes post DTG may not translate into clinical consequences.

Notably, zBMI trajectories varied substantially by sex, with females experiencing greater increases post-DTG, this pattern likely reflects a combination of biological and developmental factors, particularly as the association was more pronounced among females aged 12 years and older (p=0.02). At this stage of life, several physiological and social transitions typically begin, including the onset of menstruation, pubertal hormonal shifts,

initiation of sexual activity, and considerations around contraception, all of which may influence weight and metabolic regulation.

Age also shaped growth trends, with adolescents over 12 years old exhibiting greater zBMI gains following DTG initiation. Although the overall increase remained modest ($p = 0.04$), stratification by sex revealed that this effect was more pronounced among females. Interestingly, this association was not evident in short-term analyses ($p = 0.9$) and in long term it supported the observed plateau effect in the second year post-DTG, as described earlier in the overall cohort analysis. These findings are relatively in line with previous work such as the study by Thivalapalli et al., which focused on adolescents with a median age of 14 years (IQR: 12–14), and similarly documented increased weight gain during this developmental stage. The limited statistical significance of some of our subgroup comparisons may reflect both the heterogeneity of growth patterns during adolescence and the multifactorial influences on weight gain, including hormonal changes, puberty onset, and behavioral factors such as dietary shifts and maybe physical activity. This pattern underscores the importance of close monitoring for adolescents, particularly females.

The geographic region emerged as a significant factor affecting growth trajectories. The West African cohort, which includes Benin, Burkina Faso, Côte d'Ivoire, Ghana, Mali, Nigeria, and Togo, recorded the highest prevalence of severe underweight (7.3%) and underweight (11.4%) among all regions studied. However, other Sub-Saharan African countries also displayed similarly high levels of malnutrition (Table 3), underscoring the widespread nutritional challenges faced across the region.

Before DTG initiation, predicted growth trends in West Africa were generally flat or negative, for instance, the mean annual change in zBMI was –0.02 (95% CI: –0.10 to 0.06). These trends likely reflect the broader context of food insecurity, poverty, and limited access to healthcare that disproportionately affect CALHIV. Despite this, West Africa demonstrated the most significant improvement in zBMI post-DTG, with a mean annual increase of 0.23 (95% CI: 0.15 to 0.31). Nevertheless, overall zBMI values remained low, and the plateau effect was observed in the second year, consistent with findings in other regions. This pattern supports the "return to health" hypothesis, whereby children experiencing severe HIV- and malnutrition-related health burdens show early gains in weight and growth upon initiation of more effective ART and supportive care (46,47). These findings warrant continued investigation, but overall, they demonstrate how improved clinical management and treatment adherence, especially in vulnerable populations, can lead to measurable improvements in child growth and development.

Similarly, Southern Africa stood out in this cohort as the only region where patients were receiving DTG + TAF-containing regimens, a factor that may help explain the observed patterns of increased zBMI in this group. While randomized clinical trials have consistently shown that TDF is associated with lower lipid levels compared to TAF(23), direct clinical or laboratory evidence on how TAF may affect hormonal pathways or adipose tissue remains limited. Nonetheless, emerging observational studies suggest that TDF, and potentially other non-TAF NRTIs, may exert a weight-suppressive effect (48,49). In our study, the most pronounced zBMI increases were observed among children and adolescents who initiated DTG in combination with TAF, regardless of their prior ART regimen. This trend was not mirrored in those on DTG combined with other NRTIs or NNRTIs, further strengthening the association between TAF use and accelerated weight gain. These findings contribute to the growing body of evidence suggesting that TAF may play a role in promoting weight gain, particularly when used alongside DTG, and underscore the need for careful consideration of NRTI backbone choice in pediatric ART regimens.

Among children with available CD4 (15.3%) and viral load data (68.2%), zBMI trajectories varied by immunological status at the time of DTG initiation. Children classified as being in WHO clinical stages 1 and 2 exhibited stable zBMI trends post-DTG, likely reflecting adequate ART adherence and clinical stability prior to switching. In contrast, those in stage 3—the most advanced disease category—began with the lowest mean zBMI but showed a notable increase during the first year following DTG initiation. This pattern likely reflects a degree of immunologic recovery and improved clinical condition. On the other hand, no significant differences in zBMI change were observed across viral load subgroups at DTG initiation (Figure 2), aligning with findings from Frange et al., who also reported no association between virologic suppression and zBMI changes (41). These results, while suggestive, should be interpreted cautiously given the limited availability of immunologic data in our cohort. Nonetheless, they raise important questions about the role of immune restoration in weight and growth recovery and highlight the need for further research on immunometabolic pathways during ART transitions in pediatric populations.

Several mechanisms may contribute to weight gain under DTG, including better gastrointestinal tolerability, rebound from previous weight suppressing ARVs (e.g., TDF, ZDV, EFV), hormonal shifts, or even alterations in adiponectin levels. However, distinguishing ART-specific effects from environmental, genetic, or lifestyle factors remains challenging. Environmental influences, such as nutrition quality, food availability, cultural practices, and economic conditions, may all contribute, particularly in low- and middle-income settings where obesity is an emerging rather than established public health concern.

Ethnicity has been proposed as a modifying factor, but SMILE and other studies suggest that racial or regional effects are not uniform, and that findings should not be generalized across populations. Notably, in our study, the prevalence of overweight/obesity at baseline was only 1.5%, significantly lower than in Eswatini (5.9%), ODYSSEY (6%), or U.S. cohorts (up to 37%). This reinforces the idea that environmental context, not just race, plays a critical role.

Our findings support the idea that early zBMI increases after ART switch are often transient and do not necessarily indicate long-term risk, they are also consistent with prior concerns about weight gain following DTG, particularly when combined with TAF and the higher zBMI increases in adolescent females, point to subgroups who may require closer metabolic monitoring. Regional differences are evident but are highly correlated with socioeconomic, cultural, political and overall environmental factors that would be necessary to analyse in future research, clearly, we could associate and increase in weight gain with pharmacological effects, however this present study raises the question of how well different populations are receiving a lifesaving treatment.

Finally, careful selection of ART regimens, particularly among adolescents and females, who appear more susceptible to weight gain following DTG initiation is essential. cautious use of DTG+TAF containing regimens is recommended until more evidence is available. Clinicians should consider individual risk factors such as age, sex, baseline nutritional status, and pubertal stage when choosing NRTI backbones, and where feasible, alternative regimens may be preferable for those at higher risk of adverse metabolic outcomes. These considerations are especially important in settings where obesity and metabolic disease are emerging/well established health concerns. Future studies should investigate longer term cardiometabolic consequences and whether these early changes persist into adulthood.

Strengths and Design Considerations

This study benefits from a large sample size, broad multi-regional representation, particularly from underrepresented areas, and detailed modeling of longitudinal zBMI trajectories. Analyses were conducted using age, sex, region, immunological state and backbone drugs-adjusted changes in BMI standard deviation scores, with data points spanning one year before, at the time of switch, and one year after transition to DTG. This information reveals real-world use across diverse health systems and socioeconomic contexts, and it might be key for informing targeted interventions in public health and clinical decision-making.

Limitations

Several important limitations must be acknowledged. A significant proportion of participants had missing viral load and CD4 count data at the time of DTG initiation, limiting our ability to explore immunologic correlates of weight change. Additionally, the study lacked standardized clinical visit schedules and rigorous monitoring procedures across sites. The observational nature of the study limits causal inference, and residual confounding due to unmeasured variables such as nutritional status, pubertal stage (sexual maturity), or socioeconomic context may persist.

Another key limitation is the absence of body composition data, making it impossible to distinguish between fat mass and lean mass gain. While BMI is a validated anthropometric marker with strong discriminatory power to detect excess adiposity in pediatric populations (52), it does not fully capture underlying physiological changes. Similarly, adherence data were not available, which could influence both virologic response and metabolic outcomes. Finally, the lack of a comparator group receiving non-INSTI-based regimens limits our ability to contextualize DTG-specific effects, though this was due to the limited number of non-INSTI initiators during the study period.

Continuous work:

While working at CERPOP, I actively participated in weekly group meetings focused on global health initiatives and ongoing collaborations with various organizations addressing HIV-related issues. I worked closely with epidemiologists and statisticians on impactful and scientifically rigorous projects. This study specifically investigates both growth outcomes and metabolic effects, as outlined in its original aims. Due to time constraints, the analysis of laboratory parameters such as glycemia, cholesterol, and renal function will be included in a second phase of the project. The strength and quality of the current findings already support their suitability for scientific publication, and the incoming metabolic analyses are expected to further enhance the impact and completeness of the study for a final submission.

Conclusions:

Overall, these analyses provide a nuanced understanding of the short- and long-term effects of dolutegravir (DTG) on BMI z-scores (zBMI) among children and adolescents living with HIV. By using spline modeling and harmonizing observation periods before and after DTG initiation, we minimized bias from uneven follow-up, enabling a more balanced and robust comparison across time points. Our findings reinforce previously observed trends:

adolescent females experienced the most substantial zBMI increases, and participants from West and Southern Africa showed more pronounced early weight changes. Notably, DTG regimens combined with tenofovir alafenamide (TAF) were associated with the greatest initial gains in zBMI. However, these increases generally stabilized after the first year, suggesting a limited long-term clinical impact for most individuals.

While average zBMI increases were mild, the variation across sex, region, and ART backbone highlights the importance of individualized monitoring. These results contribute to the growing body of evidence on DTG-associated weight changes in pediatric populations and underscore the need for continued research. Future work should aim to disentangle the metabolic effects of DTG and TAF from normal pubertal growth, assess long-term cardiometabolic outcomes as adolescents transition into adulthood, and explore the biological and social mechanisms underlying sex-specific patterns of weight gain.

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French Abstract:

Contexte :
Les directives mondiales privilégient désormais l'initiation précoce et universelle du traitement antirétroviral (TAR) chez les enfants et adolescents vivant avec le VIH (EAVVI), avec des schémas à base de dolutégravir (DTG), en raison de leur efficacité, sécurité et formulations adaptées aux enfants. Cependant, des données émergentes suggèrent que le DTG, notamment lorsqu'il est associé au ténofovir alafénamide (TAF), pourrait être lié à une prise de poids excessive et à des troubles métaboliques chez les populations plus âgées, soulignant la nécessité d'un choix de schéma thérapeutique attentif chez les EAVVI et d'une surveillance à long terme.

Objectif :
Cette étude vise à évaluer les trajectoires de croissance chez les EAVVI après l'initiation ou le passage à un TAR à base de DTG, en utilisant les données de la cohorte pédiatrique mondiale d'IeDEA. Elle examine spécifiquement les variations des scores z de l'indice de masse corporelle pour l'âge (zIMC).

Méthodes :
L'analyse inclut les EAVVI âgés de plus de 30 jours à moins de 19 ans, avec au moins une mesure anthropométrique valide dans les 24 mois suivant l'initiation du DTG, dans six régions d'IeDEA. Les tendances longitudinales du zIMC ont été modélisées à l'aide de modèles mixtes linéaires avec splines linéaires, en ajustant pour les covariables démographiques et cliniques.

Résultats :
Au total, 29 663 enfants et adolescents vivant avec le VIH ont été inclus dans l'analyse, dont 13 671 garçons (46,1 %) et 15 992 filles (53,9 %). À l'initiation du DTG, l'âge médian était de 12,9 ans (intervalle interquartile [IQR] : 9,2–15,9). La région d'Afrique australe représentait la plus grande proportion de participants (50 %), suivie de l'Afrique de l'Est (33 %), de l'Afrique de l'Ouest (7 %) et de l'Afrique centrale (5 %). Le zIMC de base médian était de –0,62 (IQR : –1,47 à 0,16), significativement plus bas chez les garçons que chez les filles (–0,84 vs –0,45, p<0,001). Dans les analyses longitudinales, la différence de pente du zIMC avant et après DTG montrait une tendance à la significativité chez les filles, avec une augmentation annuelle de 0,08 (IC 95 % : 0,01 à 0,16) avant DTG à 0,18 (IC 95 % : 0,11 à 0,26) après DTG (p = 0,06). Les adolescents ≥12 ans présentaient une accélération significative à la limite du zIMC après DTG (0,04 à 0,14, p = 0,04). La plus forte augmentation du zIMC a été observée chez les patients ayant initié un schéma DTG+TAF, passant de 0,06 (IC 95 % : –0,02 à 0,14) avant DTG à 0,22 (IC 95 % : 0,14 à 0,30) après DTG. Dans une analyse secondaire, le zIMC a augmenté modérément la première année suivant l'initiation du DTG (+0,19 IC 95 % : 0,09 à 0,30/an), suivi d'une stabilisation la deuxième année (–0,02 IC 95 % : –0,25 à 0,21), tendance observée dans tous les groupes d'âge et les deux sexes. Les adolescents ont présenté peu de changement (0.81). L'effet régional le plus marqué a été observé en Afrique de l'Ouest (p< 0.001). Les schémas DTG+TAF étaient associés à la plus forte augmentation initiale du zIMC (+0,30 IC 95 % : 0,18 à 0,49/an) (p = 0,319), suivie d'un déclin la deuxième année (-0.08 IC 95 % : -0,32 à 0,16/an).

Discussion :
Dans cette vaste cohorte multicentrique de près de 30 000 EAVVI issus majoritairement de pays à revenu faible ou intermédiaire, nous avons observé une augmentation modeste et non significative du zIMC après l'initiation du DTG, avec une tendance à une prise de poids précoce

qui se stabilise ensuite. Ce schéma était cohérent dans toutes les régions et sous-groupes, bien que plus prononcé chez les adolescentes et les patients recevant DTG+TAF. Ces résultats appuient l'hypothèse d'un effet de « retour à la santé » chez les populations sous-alimentées et suggèrent que la prise de poids associée au DTG pourrait être transitoire plutôt que progressive. Bien que les tendances globales de croissance soient rassurantes, nos résultats soulignent l'importance d'une surveillance continue dans certains sous-groupes et la nécessité de recherches supplémentaires sur les conséquences métaboliques à long terme.

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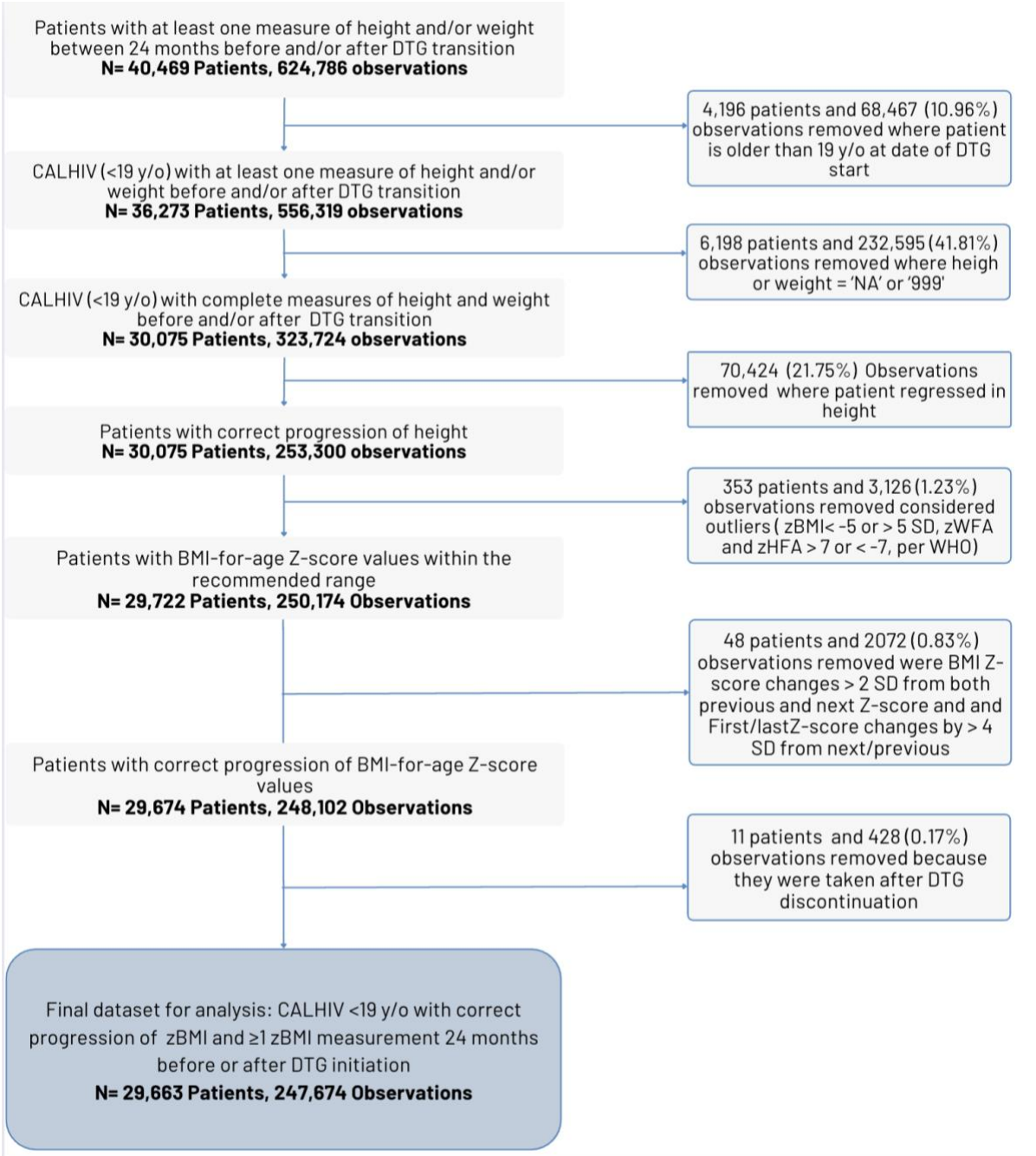


Figure 4. Flow diagram of children and adolescents living with HIV (CALHIV) included in analysis.

Figures 5-14. Represent mean BMI z-score estimated using mixed effects models with linear splines for time since DTG start, with a knot at 0 weeks, adjusted for sex, age groups, region, immunological state and prior and actual ART regimen composition with time interactions for each variable. Stratified by sex, age groups, region, prior ART regimen, actual regimen associated to DTG, rurality, immunological stage of disease for age at DTG start (different model, included only patients with available observations), viral load at DTG start (different model, included only patients with available observations) and finally z-BMI category at DTG start (different model, included only patients with available observations). P-values by subgroup compare the slope of change in zBMI before and after DTG start.

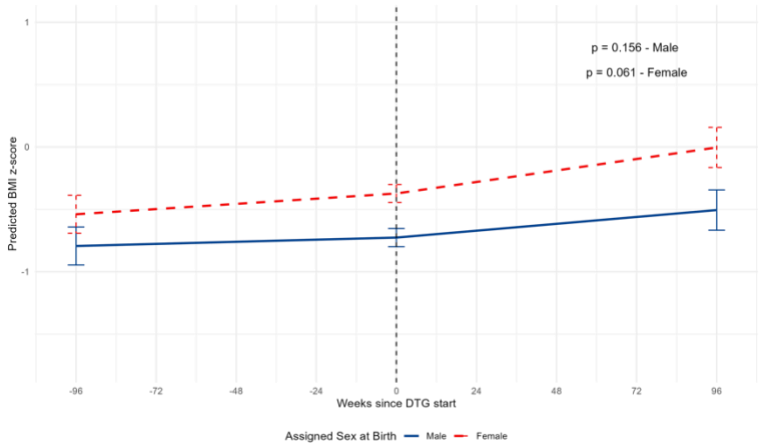


Figure 5.

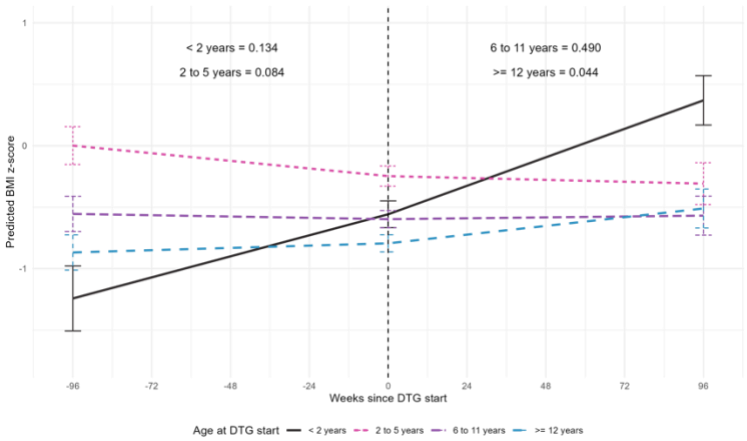
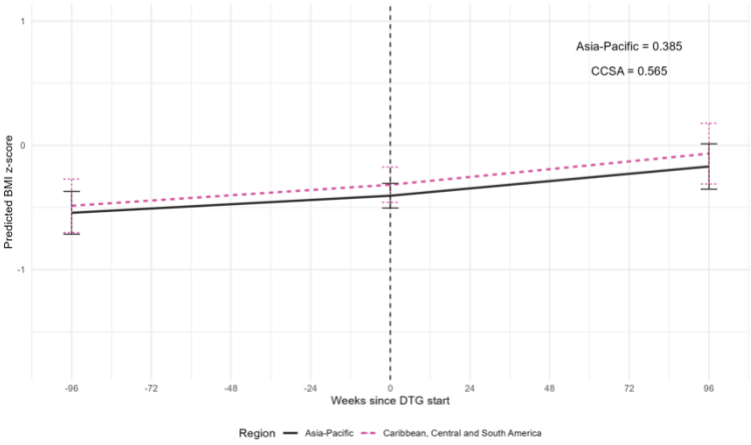


Figure 6.



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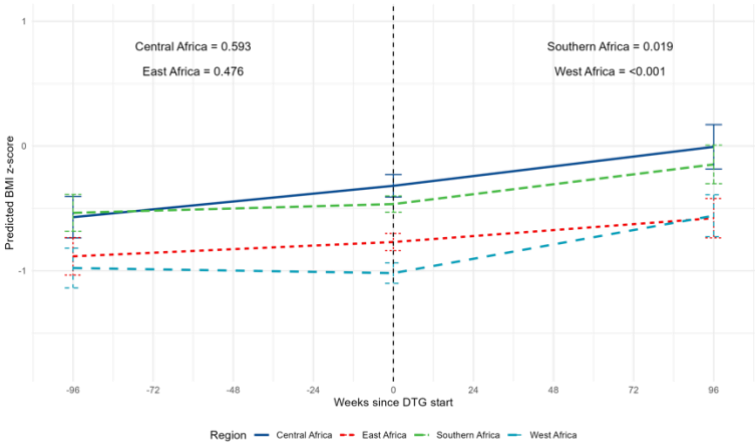

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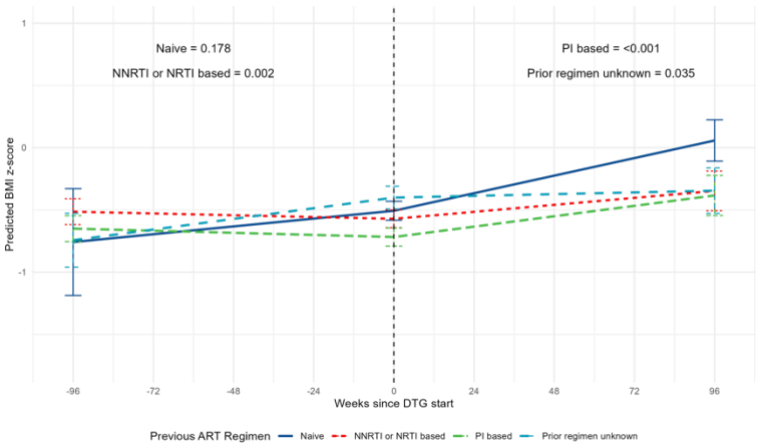


Figure 9.

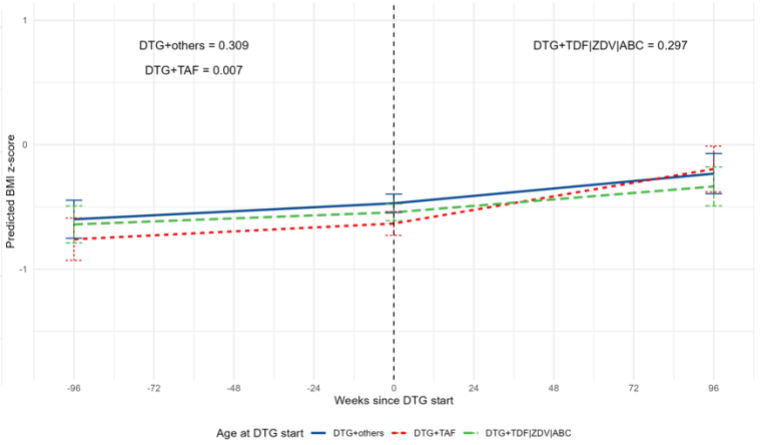


Figure 10.

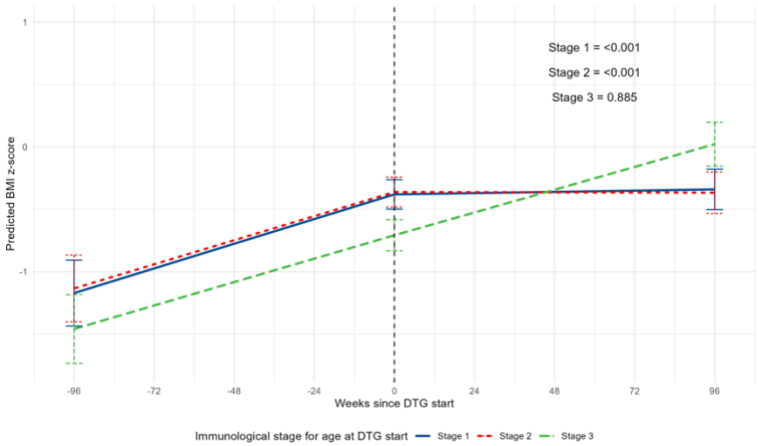
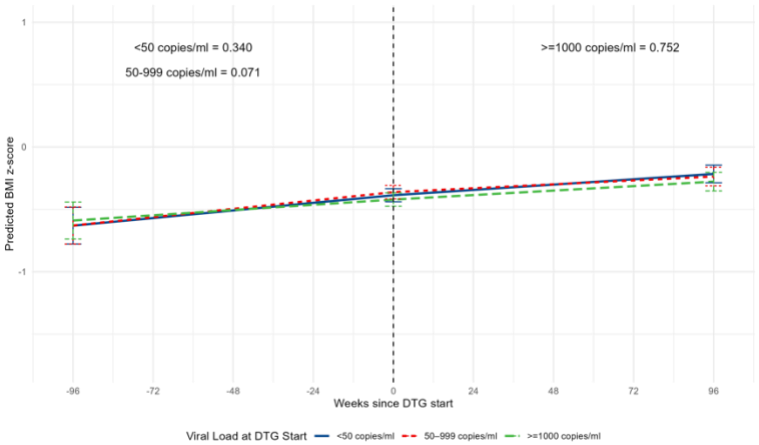


Figure 11.



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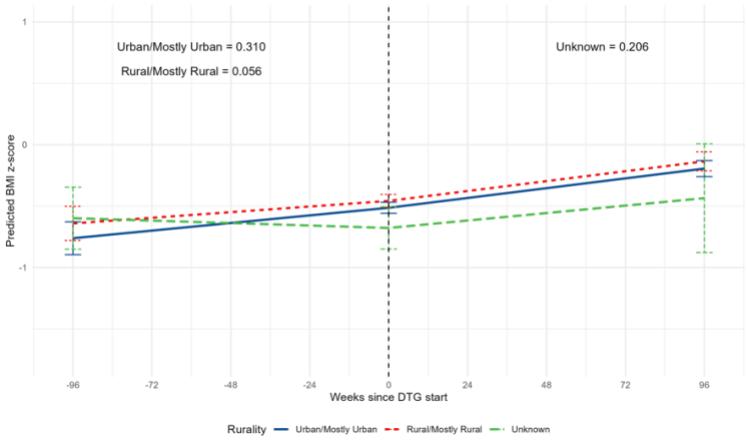

Figure 13.

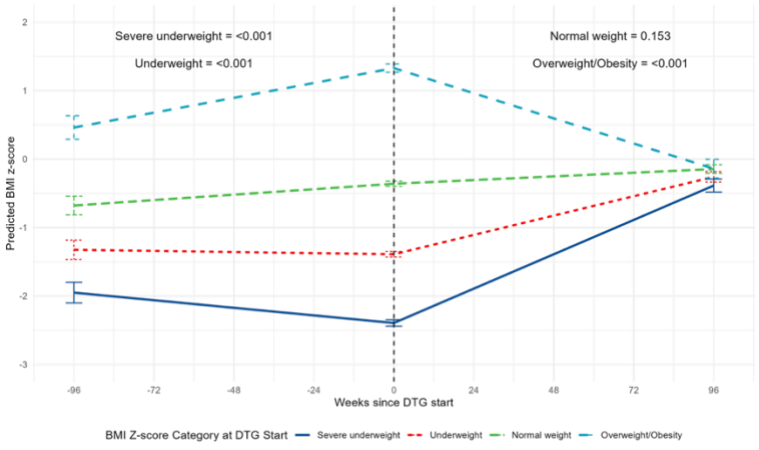

Figure 14.

Table 3. Baseline characteristics of patients at initiation of a dolutegravir-based regimen stratified by age group						
Characteristics	**Overall** N = 29,663[1]	**< 2 years** N = 692[1]	**2 to 5 years** N = 2,390[1]	**6 to 11 years** N = 9,772[1]	**>= 12 years** N = 16,809[1]	**p-value**[2]
Age at DTG start	13 (9, 16)	1 (1, 2)	4 (3, 5)	10 (8, 11)	16 (14, 17)	<0.001
Duration on ART at DTG Start (Months)	57 (13, 103)	0 (0, 4)	25 (5, 41)	59 (24, 86)	73 (14, 123)	<0.001
BMI z-score at DTG start	-0.6 (-1.5, 0.2)	-0.6 (-2.0, 0.6)	-0.3 (-1.2, 0.7)	-0.6 (-1.4, 0.2)	-0.7 (-1.5, 0.1)	<0.001
BMI Z-score Category at DTG Start						<0.001
Severe underweight	1,112 (3.7%)	66 (9.5%)	90 (3.8%)	310 (3.2%)	646 (3.8%)	
Underweight	2,309 (7.8%)	82 (11.8%)	146 (6.1%)	644 (6.6%)	1,437 (8.5%)	
Normal weight	20,327 (68.5%)	416 (60.1%)	1,626 (68.0%)	6,793 (69.5%)	11,492 (68.4%)	
Overweight/Obesity	440 (1.5%)	40 (5.8%)	112 (4.7%)	144 (1.5%)	144 (0.9%)	
Not available	5,475 (18.5%)	88 (12.7%)	416 (17.4%)	1,881 (19.2%)	3,090 (18.4%)	
Region						<0.001
Asia-Pacific	980 (3.3%)	22 (3.2%)	45 (1.9%)	246 (2.5%)	667 (4.0%)	
Caribbean, Central and South America	330 (1.1%)	26 (3.8%)	42 (1.8%)	128 (1.3%)	134 (0.8%)	
Central Africa	1,564 (5.3%)	34 (4.9%)	107 (4.5%)	504 (5.2%)	919 (5.5%)	
East Africa	9,921 (33.4%)	200 (28.9%)	844 (35.3%)	3,307 (33.8%)	5,570 (33.1%)	
Southern Africa	14,685 (49.5%)	324 (46.8%)	1,130 (47.3%)	4,827 (49.4%)	8,404 (50.0%)	
West Africa	2,183 (7.4%)	86 (12.4%)	222 (9.3%)	760 (7.8%)	1,115 (6.6%)	

Table 3. Baseline characteristics of patients at initiation of a dolutegravir-based regimen stratified by age group						
Characteristics	**Overall** N = 29,663[1]	**< 2 years** N = 692[1]	**2 to 5 years** N = 2,390[1]	**6 to 11 years** N = 9,772[1]	**>= 12 years** N = 16,809[1]	**p-value**[2]
Rurality						
Urban/Mostly Urban	22,316 (75.2%)	432 (62.4%)	1,680 (70.3%)	7,415 (75.9%)	12,789 (76.1%)	
Rural/Mostly Rural	7,210 (24.3%)	259 (37.4%)	705 (29.5%)	2,303 (23.6%)	3,943 (23.5%)	
Unknown	137 (0.5%)	1 (0.1%)	5 (0.2%)	54 (0.6%)	77 (0.5%)	
Previous ART Regimen						<0.001
Naive	5,148 (17.4%)	437 (63.2%)	463 (19.4%)	1,056 (10.8%)	3,192 (19.0%)	
NNRTI or NRTI based	16,440 (55.4%)	45 (6.5%)	500 (20.9%)	5,530 (56.6%)	10,365 (61.7%)	
PI based	6,306 (21.3%)	170 (24.6%)	1,325 (55.4%)	2,783 (28.5%)	2,028 (12.1%)	
Prior regimen unknown	1,769 (6.0%)	40 (5.8%)	102 (4.3%)	403 (4.1%)	1,224 (7.3%)	
ART Regimen Associated with DTG						<0.001
DTG+others	8,714 (29.4%)	126 (18.2%)	960 (40.2%)	3,366 (34.4%)	4,262 (25.4%)	
DTG+TAF	1,284 (4.3%)	0 (0.0%)	8 (0.3%)	762 (7.8%)	514 (3.1%)	
DTG+TDF|ZDV|ABC	19,665 (66.3%)	566 (81.8%)	1,422 (59.5%)	5,644 (57.8%)	12,033 (71.6%)	
Viral Load at DTG Start						<0.001
<50 copies/ml	13,466 (45.4%)	75 (10.8%)	897 (37.5%)	4,910 (50.2%)	7,584 (45.1%)	
50–999 copies/ml	3,437 (11.6%)	65 (9.4%)	286 (12.0%)	1,174 (12.0%)	1,912 (11.4%)	
>=1000 copies/ml	3,318 (11.2%)	129 (18.6%)	280 (11.7%)	1,031 (10.6%)	1,878 (11.2%)	

Table 3. Baseline characteristics of patients at initiation of a dolutegravir-based regimen stratified by age group

Characteristics	Overall N = 29,663[1]	< 2 years N = 692[1]	2 to 5 years N = 2,390[1]	6 to 11 years N = 9,772[1]	>= 12 years N = 16,809[1]	p-value[2]
Not available	9,442 (31.8%)	423 (61.1%)	927 (38.8%)	2,657 (27.2%)	5,435 (32.3%)	
CD4 Count (cells/mm³)	588 (325, 853)	1,011 (659, 1,582)	834 (453, 1,240)	680 (376, 953)	523 (295, 755)	<0.001
Disease Stage at DTG start						<0.001
Stage 1	2,610 (8.8%)	38 (5.5%)	132 (5.5%)	986 (10.1%)	1,454 (8.7%)	
Stage 2	1,216 (4.1%)	33 (4.8%)	115 (4.8%)	258 (2.6%)	810 (4.8%)	
Stage 3	721 (2.4%)	22 (3.2%)	85 (3.6%)	193 (2.0%)	421 (2.5%)	
Not available	25,116 (84.7%)	599 (86.6%)	2,058 (86.1%)	8,335 (85.3%)	14,124 (84.0%)	

[1]Median (Q1, Q3); n (%);[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test. DTG = Dolutegravir, NRTI, = Nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine, ABC = abacavir, zBMI = BMI-for-age z score,

Table 4. Baseline characteristics of patients at initiation of a dolutegravir-based regimen stratified by Region

Characteristics	Overall N = 29,663[1]	Asia-Pacific N = 980[1]	CCSA N = 330[1]	Central Africa N = 1,564[1]	East Africa N = 9,921[1]	Southern Africa N = 14,685[1]	West Africa N = 2,183[1]	p-value[2]
Age at DTG start	13 (9, 16)	13 (11, 15)	10 (7, 16)	13 (10, 16)	13 (9, 16)	13 (9, 16)	12 (9, 15)	<0.001
Age groups at DTG start								<0.001
< 2 years	692 (2.3%)	22 (2.2%)	26 (7.9%)	34 (2.2%)	200 (2.0%)	324 (2.2%)	86 (3.9%)	

Table 4. Baseline characteristics of patients at initiation of a dolutegravir-based regimen stratified by Region								
Characteristics	**Overall** N = 29,663[1]	**Asia-Pacific** N = 980[1]	**CCSA** N = 330[1]	**Central Africa** N = 1,564[1]	**East Africa** N = 9,921[1]	**Southern Africa** N = 14,685[1]	**West Africa** N = 2,183[1]	**p-value**[2]
2 to 5 years	2,390 (8.1%)	45 (4.6%)	42 (12.7%)	107 (6.8%)	844 (8.5%)	1,130 (7.7%)	222 (10.2%)	
6 to 11 years	9,772 (32.9%)	246 (25.1%)	128 (38.8%)	504 (32.2%)	3,307 (33.3%)	4,827 (32.9%)	760 (34.8%)	
>= 12 years	16,809 (56.7%)	667 (68.1%)	134 (40.6%)	919 (58.8%)	5,570 (56.1%)	8,404 (57.2%)	1,115 (51.1%)	
Duration on ART at DTG Start (Months)	57 (13, 103)	106 (56, 138)	42 (5, 91)	71 (32, 111)	68 (24, 107)	42 (4, 88)	76 (25, 119)	<0.001
BMI z-score at DTG start	-0.6 (-1.5, 0.2)	-0.6 (-1.5, 0.3)	-0.4 (-1.0, 0.5)	-0.5 (-1.5, 0.4)	-0.8 (-1.6, 0.0)	-0.5 (-1.3, 0.3)	-1.1 (-1.9, -0.2)	<0.001
BMI Z-score Category at DTG Start								
Severe underweight	1,112 (3.7%)	29 (3.0%)	8 (2.4%)	64 (4.1%)	417 (4.2%)	434 (3.0%)	160 (7.3%)	
Underweight	2,309 (7.8%)	78 (8.0%)	18 (5.5%)	113 (7.2%)	894 (9.0%)	957 (6.5%)	249 (11.4%)	
Normal weight	20,327 (68.5%)	648 (66.1%)	247 (74.8%)	900 (57.5%)	6,503 (65.5%)	10,739 (73.1%)	1,290 (59.1%)	
Overweight/Obesity	440 (1.5%)	21 (2.1%)	5 (1.5%)	74 (4.7%)	99 (1.0%)	220 (1.5%)	21 (1.0%)	
Not available	5,475 (18.5%)	204 (20.8%)	52 (15.8%)	413 (26.4%)	2,008 (20.2%)	2,335 (15.9%)	463 (21.2%)	

Table 4. Baseline characteristics of patients at initiation of a dolutegravir-based regimen stratified by Region

Characteristics	Overall N = 29,663[1]	Asia-Pacific N = 980[1]	CCSA N = 330[1]	Central Africa N = 1,564[1]	East Africa N = 9,921[1]	Southern Africa N = 14,685[1]	West Africa N = 2,183[1]	p-value[2]
Rurality								
Urban/Mostly Urban	22,316 (75.2%)	980 (100.0%)	330 (100.0%)	1,548 (99.0%)	5,817 (58.6%)	11,458 (78.0%)	2,183 (100.0%)	
Rural/Mostly Rural	7,210 (24.3%)	0 (0.0%)	0 (0.0%)	16 (1.0%)	4,104 (41.4%)	3,090 (21.0%)	0 (0.0%)	
Unknown	137 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	137 (0.9%)	0 (0.0%)	
Previous ART Regimen								<0.001
Naive	5,148 (17.4%)	67 (6.8%)	72 (21.8%)	234 (15.0%)	1,399 (14.1%)	3,009 (20.5%)	367 (16.8%)	
NNRTI or NRTI based	16,440 (55.4%)	737 (75.2%)	105 (31.8%)	1,021 (65.3%)	5,869 (59.2%)	7,381 (50.3%)	1,327 (60.8%)	
PI based	6,306 (21.3%)	176 (18.0%)	153 (46.4%)	290 (18.5%)	2,270 (22.9%)	2,928 (19.9%)	489 (22.4%)	
Prior regimen unknown	1,769 (6.0%)	0 (0.0%)	0 (0.0%)	19 (1.2%)	383 (3.9%)	1,367 (9.3%)	0 (0.0%)	
ART Regimen Associated with DTG								<0.001
DTG+others	8,714 (29.4%)	14 (1.4%)	5 (1.5%)	11 (0.7%)	5,547 (55.9%)	2,066 (14.1%)	1,071 (49.1%)	

Table 4. Baseline characteristics of patients at initiation of a dolutegravir-based regimen stratified by Region								
Characteristics	**Overall** N = 29,663[1]	**Asia-Pacific** N = 980[1]	**CCSA** N = 330[1]	**Central Africa** N = 1,564[1]	**East Africa** N = 9,921[1]	**Southern Africa** N = 14,685[1]	**West Africa** N = 2,183[1]	**p-value**[2]
DTG+TAF	1,284 (4.3%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1,283 (8.7%)	0 (0.0%)	
DTG+TDF|ZDV|ABC	19,665 (66.3%)	965 (98.5%)	325 (98.5%)	1,553 (99.3%)	4,374 (44.1%)	11,336 (77.2%)	1,112 (50.9%)	
Viral Load at DTG Start								<0.001
<50 copies/ml	13,466 (45.4%)	675 (68.9%)	173 (52.4%)	607 (38.8%)	5,346 (53.9%)	5,727 (39.0%)	938 (43.0%)	
50–999 copies/ml	3,437 (11.6%)	46 (4.7%)	12 (3.6%)	128 (8.2%)	1,409 (14.2%)	1,597 (10.9%)	245 (11.2%)	
>=1000 copies/ml	3,318 (11.2%)	104 (10.6%)	92 (27.9%)	239 (15.3%)	876 (8.8%)	1,629 (11.1%)	378 (17.3%)	
Not available	9,442 (31.8%)	155 (15.8%)	53 (16.1%)	590 (37.7%)	2,290 (23.1%)	5,732 (39.0%)	622 (28.5%)	
CD4 Count (cells/mm³)	588 (325, 853)	592 (230, 892)	613 (333, 921)	632 (370, 852)	509 (223, 839)	565 (342, 820)	704 (429, 980)	<0.001
Disease Stage at DTG start								<0.001
Stage 1	2,610 (8.8%)	120 (12.2%)	56 (17.0%)	20 (1.3%)	384 (3.9%)	1,506 (10.3%)	524 (24.0%)	
Stage 2	1,216 (4.1%)	48 (4.9%)	21 (6.4%)	17 (1.1%)	235 (2.4%)	765 (5.2%)	130 (6.0%)	

Table 4. Baseline characteristics of patients at initiation of a dolutegravir-based regimen stratified by Region

Characteristics	Overall N = 29,663[1]	Asia-Pacific N = 980[1]	CCSA N = 330[1]	Central Africa N = 1,564[1]	East Africa N = 9,921[1]	Southern Africa N = 14,685[1]	West Africa N = 2,183[1]	p-value[2]
Stage 3	721 (2.4%)	45 (4.6%)	11 (3.3%)	9 (0.6%)	211 (2.1%)	303 (2.1%)	142 (6.5%)	
Not available	25,116 (84.7%)	767 (78.3%)	242 (73.3%)	1,518 (97.1%)	9,091 (91.6%)	12,111 (82.5%)	1,387 (63.5%)	

[1]Median (Q1, Q3); n (%),[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test; DTG = Dolutegravir, NRTI, = Nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine, ABC = abacavir, zBMI = BMI-for-age z score, CCSA = Caribbean Central and South America.

Table 5. Comparison: Missing vs Complete Data			
Characteristics	**Complete** N = 29,663[1]	**Missing** N = 6,198[1]	**p-value**[2]
Age at DTG start	12.9 (9.2, 15.9)	14.8 (10.7, 17.3)	<0.001
Age groups at DTG start			<0.001
< 2 years	692 (2.3%)	216 (3.5%)	
2 to 5 years	2,390 (8.1%)	356 (5.7%)	
6 to 11 years	9,772 (32.9%)	1,373 (22.2%)	
>= 12 years	16,809 (56.7%)	4,253 (68.6%)	
Duration on ART at DTG Start (Months)	57 (13, 103)	53 (0, 107)	<0.001
Region			<0.001
Asia-Pacific	980 (3.3%)	67 (1.1%)	
Caribbean, Central and South America	330 (1.1%)	196 (3.2%)	
Central Africa	1,564 (5.3%)	777 (12.5%)	
East Africa	9,921 (33.4%)	1,347 (21.7%)	
Southern Africa	14,685 (49.5%)	3,458 (55.8%)	
West Africa	2,183 (7.4%)	353 (5.7%)	
Rurality			<0.001
Urban/Mostly Urban	22,316 (75.2%)	3,287 (53.0%)	
Rural/Mostly Rural	7,210 (24.3%)	2,882 (46.5%)	

Table 5. Comparison: Missing vs Complete Data			
Characteristics	**Complete** N = 29,663[1]	**Missing** N = 6,198[1]	**p-value**[2]
Unknown	137 (0.5%)	29 (0.5%)	
Previous ART Regimen			<0.001
Naive	5,148 (17.4%)	1,717 (27.7%)	
NNRTI or NRTI based	16,440 (55.4%)	0 (0.0%)	
PI based	6,306 (21.3%)	0 (0.0%)	
Prior regimen unknown	1,769 (6.0%)	4,481 (72.3%)	
ART Regimen Associated with DTG			<0.001
DTG+others	8,714 (29.4%)	6,198 (100.0%)	
DTG+TAF	1,284 (4.3%)	0 (0.0%)	
DTG+TDF|ZDV|ABC	19,665 (66.3%)	0 (0.0%)	
Viral Load at DTG Start			<0.001
<50 copies/ml	13,466 (45.4%)	0 (0.0%)	
50–999 copies/ml	3,437 (11.6%)	0 (0.0%)	
>=1000 copies/ml	3,318 (11.2%)	0 (0.0%)	
Not available	9,442 (31.8%)	6,198 (100.0%)	
Disease Stage at DTG start			<0.001
Stage 1	2,610 (8.8%)	0 (0.0%)	

Table 5. Comparison: Missing vs Complete Data			
Characteristics	**Complete** N = 29,663[1]	**Missing** N = 6,198[1]	**p-value**[2]
Stage 2	1,216 (4.1%)	0 (0.0%)	
Stage 3	721 (2.4%)	0 (0.0%)	
Not available	25,116 (84.7%)	6,198 (100.0%)	

[1]Median (Q1, Q3); n (%),[2]Wilcoxon rank sum test; Pearson's Chi-squared test; DTG = Dolutegravir, NRTI, = Nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine, ABC = abacavir, zBMI = BMI-for-age z score, CCSA = Caribbean Central and South America.

Table 6. Adjusted mean change in BMI z-score per year 48 weeks before and up to 96 weeks after dolutegravir exposure.

	Before DTG start			**1st year on DTG**			**p value[1]**	**2nd year on DTG**			**p value[1]**
Characteristics	**zBMI change**	**95% CI**		**zBMI change**	**95% CI**			**zBMI change**	**95% CI**		
All	0.13	0.02	0.24	0.19	0.09	0.30	0.483	-0.02	-0.25	0.21	0.148
Sex							**(0.307)**				**(0.073)**
Male	0.11	0.00	0.23	0.16	0.06	0.27	0.554	-0.06	-0.29	0.16	0.117
Female	0.15	0.04	0.26	0.22	0.12	0.33	0.422	0.03	-0.20	0.26	0.188
Age groups							**(<.001)**				**(<.001)**

Table 6. Adjusted mean change in BMI z-score per year 48 weeks before and up to 96 weeks after dolutegravir exposure.

	Before DTG start			1st year on DTG			p value[1]	2nd year on DTG			p value[1]
Characteristics	zBMI change	95% CI		zBMI change	95% CI			zBMI change	95% CI		
< 2 years	0.29	0.12	0.46	0.64	0.51	0.77	0.002	0.08	-0.17	0.33	<0.001
2 to 5 years	-0.05	-0.17	0.06	-0.03	-0.14	0.08	0.816	-0.10	-0.33	0.14	0.665
6 to 11 years	0.12	0.01	0.23	0.00	-0.10	0.11	0.152	-0.07	-0.30	0.16	0.620
>= 12 years	0.17	0.07	0.28	0.15	0.05	0.26	0.810	0.02	-0.21	0.24	0.339
Region							**(<.001)**				**(<.001)**
Asia-Pacific	0.06	-0.06	0.18	0.18	0.07	0.29	0.184	-0.04	-0.27	0.20	0.149
Caribbean, Central and South America	0.25	0.10	0.40	0.08	-0.08	0.24	0.166	0.04	-0.25	0.33	0.848
Central Africa	0.14	0.02	0.26	0.26	0.14	0.37	0.215	-0.06	-0.29	0.18	0.037
East Africa	0.20	0.09	0.31	0.11	0.00	0.21	0.263	-0.05	-0.28	0.18	0.268
Southern Africa	0.13	0.02	0.24	0.21	0.11	0.31	0.322	-0.04	-0.27	0.18	0.074
West Africa	0.02	-0.10	0.13	0.32	0.21	0.42	0.001	0.04	-0.19	0.27	0.062
Previous ART Regimen							**(0.002)**				**(<.001)**
Naive	0.19	-0.11	0.50	0.45	0.34	0.55	0.135	-0.11	-0.34	0.12	<0.001
NNRTI or NRTI based	0.05	-0.03	0.12	0.13	0.03	0.24	0.244	0.00	-0.22	0.23	0.374

Table 6. Adjusted mean change in BMI z-score per year 48 weeks before and up to 96 weeks after dolutegravir exposure.

	Before DTG start			1st year on DTG			p value[1]	2nd year on DTG			p value[1]
Characteristics	zBMI change	95% CI		zBMI change	95% CI			zBMI change	95% CI		
PI based	0.08	0.00	0.16	0.18	0.07	0.28	0.192	0.04	-0.18	0.27	0.355
Prior regimen unknown	0.21	0.04	0.37	0.01	-0.11	0.13	0.068	-0.01	-0.25	0.24	0.914
ART Regimen Associated with DTG							**(0.023)**				**(<.001)**
DTG+Others	0.09	-0.02	0.21	0.16	0.06	0.27	0.427	0.00	-0.23	0.22	0.250
DTG+TAF	0.21	0.09	0.33	0.30	0.18	0.42	0.319	-0.08	-0.32	0.16	0.012
DTG+TDF|ZDV|ABC	0.09	-0.02	0.20	0.11	0.01	0.21	0.849	0.03	-0.19	0.26	0.588
Previous/Current ART							**(<.001)**				**(<.001)**
Naïve/ DTG+Others	0.16	-0.15	0.46	0.42	0.31	0.53	0.124	-0.10	-0.33	0.13	0.001
Naïve/ DTG+TAF	0.27	-0.04	0.58	0.56	0.44	0.68	0.099	-0.17	-0.42	0.07	<0.001
Naïve/ DTG+TDF|ZDV|ABC	0.16	-0.15	0.46	0.37	0.26	0.47	0.213	-0.06	-0.29	0.17	0.003
NNRTI or NRTI based/ DTG+Others	0.01	-0.07	0.09	0.10	0.00	0.21	0.204	0.02	-0.21	0.24	0.552
NNRTI or NRTI based/ DTG+TAF	0.12	0.03	0.21	0.24	0.12	0.36	0.154	-0.06	-0.30	0.18	0.047
NNRTI or NRTI based/ DTG+TDF|ZDV|ABC	0.01	-0.07	0.08	0.05	-0.05	0.15	0.561	0.05	-0.17	0.28	0.981

Table 6. Adjusted mean change in BMI z-score per year 48 weeks before and up to 96 weeks after dolutegravir exposure.

	Before DTG start			1st year on DTG			p value[1]	2nd year on DTG			p value[1]
Characteristics	zBMI change	95% CI		zBMI change	95% CI			zBMI change	95% CI		
PI based/ DTG+Others	0.04	-0.03	0.12	0.15	0.04	0.25	0.157	0.06	-0.17	0.28	0.526
PI based/ DTG+TAF	0.16	0.06	0.25	0.29	0.17	0.41	0.123	-0.02	-0.26	0.22	0.044
PI based/ DTG+TDF|ZDV|ABC	0.04	-0.03	0.12	0.10	-0.01	0.20	0.468	0.09	-0.13	0.32	0.987
Prior regimen unknown/ DTG+Others	0.17	0.01	0.34	-0.02	-0.14	0.10	0.082	0.01	-0.24	0.25	0.870
Prior regimen unknown/ DTG+TAF	0.29	0.11	0.46	0.12	-0.01	0.25	0.161	-0.07	-0.32	0.18	0.242
Prior regimen unknown/ DTG+TDF|ZDV|ABC	0.17	0.01	0.33	-0.07	-0.18	0.04	0.024	0.04	-0.20	0.28	0.454
Viral Load at DTG Start							**(0.001)**				**(0.008)**
<50 copies/ml	0.15	0.05	0.25	0.20	0.16	0.24	0.411	-0.14	-0.20	-0.09	<0.001
50□999 copies/ml	0.16	0.06	0.26	0.21	0.16	0.26	0.369	-0.22	-0.28	-0.15	<0.001
>=1000 copies/ml	0.07	-0.03	0.16	0.20	0.15	0.25	0.022	-0.15	-0.21	-0.09	<0.001
CDC immunological stage for age at DTG start							**(<.001)**				**(<.001)**
Stage 1	0.44	0.27	0.60	0.13	0.05	0.21	0.002	-0.24	-0.37	-0.12	<0.001
Stage 2	0.43	0.26	0.60	0.12	0.03	0.20	0.002	-0.27	-0.40	-0.14	<0.001

Table 6. Adjusted mean change in BMI z-score per year 48 weeks before and up to 96 weeks after dolutegravir exposure.

	Before DTG start			1st year on DTG			p value[1]	2nd year on DTG			p value[1]
Characteristics	zBMI change	95% CI		zBMI change	95% CI			zBMI change	95% CI		
Stage 3	0.25	0.07	0.42	0.76	0.67	0.86	0.000	-0.38	-0.52	-0.24	<0.001

[1]P wald test. Mean BMI-for-age score was estimated using mixed effects models with linear splines for time 48 weeks before DTG start, at DTG start and 48 weeks after DTG start. Adjusting for sex, age group, region, history of ART regimen, viral load (different model only for those with available data (n=20,221)), and CDC immunological stage for age at DTG start (different model only for those with available data (n=4,547), with time interactions for said variables. P-values in brackets (across subgroups) represent the significance level for the interaction term. P-values by subgroup compare the slope of change in zBMI before and after DTG start. DTG = Dolutegravir, NRTI, = Nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine, ABC = abacavir, zBMI = BMI-for-age z score, ART= antiretroviral therapy, CDC = center for disease control and prevention.

Table 7. Comparison of adjusted mean change in BMI z-score per year, over 96 weeks before and after dolutegravir exposure, including patients with observation before AND after DTG start (N= 16,219).

Characteristics	Mean annual zBMI change pre DTG	95% CI		Mean annual zBMI Change post DTG	95% CI		p value[1]
All	0.29	0.16	0.43	0.24	0.17	0.32	**0.517**
Sex							**(<0.001)**
Male	0.10	0.03	0.17	0.12	0.09	0.15	0.250
Female	0.15	0.08	0.22	0.20	0.17	0.23	0.889
Age groups							**(<0.001)**
< 2 years	0.54	0.42	0.67	0.34	0.26	0.42	0.008
2 to 5 years	-0.07	-0.14	0.00	-0.05	-0.09	-0.01	0.568
6 to 11 years	0.03	-0.03	0.10	0.03	-0.01	0.07	0.931
= 12 years	0.08	0.02	0.15	0.17	0.13	0.20	0.020
Region							**(<0.001)**
Asia-Pacific	0.15	0.08	0.22	0.09	0.05	0.14	0.197
Caribbean, Central and South America	0.18	0.09	0.27	0.08	-0.01	0.16	0.091
Central Africa	0.21	0.14	0.28	0.12	0.07	0.16	0.026
East Africa	0.14	0.07	0.21	0.08	0.04	0.12	0.139
Southern Africa	0.13	0.07	0.20	0.15	0.12	0.19	0.626

Table 7. Comparison of adjusted mean change in BMI z-score per year, over 96 weeks before and after dolutegravir exposure, including patients with observation before AND after DTG start (N= 16,219).

Characteristics	Mean annual zBMI change pre DTG	95% CI		Mean annual zBMI Change post DTG	95% CI		p value[1]
West Africa	0.08	0.01	0.14	0.21	0.17	0.26	0.001
Previous ART Regimen							**(<0.001)**
Naive	0.17	-0.05	0.39	0.29	0.20	0.38	0.329
NNRTI or NRTI based	0.08	0.04	0.11	0.07	0.04	0.10	0.710
PI based	0.08	0.04	0.11	0.13	0.10	0.16	0.012
Prior regimen unknown	0.27	0.17	0.37	0.00	-0.08	0.08	0.000
ART Regimen Associated with DTG							**(<0.001)**
DTG+others	0.15	0.08	0.22	0.10	0.06	0.14	0.184
DTG+TAF	0.15	0.07	0.22	0.19	0.13	0.24	0.385
DTG+TDF|ZDV|ABC	0.14	0.08	0.21	0.08	0.05	0.12	0.104

[1]P wald test. Mean BMI-for-age score was estimated using mixed effects models with linear splines for time at DTG start (week 0). Adjusting for sex, age group, region, history of ART regimen, with time interactions for said variables. P-values in brackets (across subgroups) represent the significance level for the interaction term. P-values by subgroup compare the slope of change in zBMI before and after DTG start. DTG = Dolutegravir, NRTI, = Nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine, ABC = abacavir, zBMI = BMI-for-age z score, ART= antiretroviral therapy.

Table 8. Comparison of adjusted mean change in BMI z-score per year, over 96 weeks before and after dolutegravir exposure, including patients with at least to observations before OR after DTG initiation (N= 25,832).

Characteristics	Mean annual zBMI change pre DTG	95% CI		Mean annual zBMI Change post DTG	95% CI		p value[1]
All	0.29	0.16	0.43	0.24	0.17	0.32	**0.335**
Sex							**(<0.001)**
Male	0.10	0.03	0.17	0.12	0.09	0.15	0.565
Female	0.15	0.08	0.22	0.20	0.17	0.23	0.181
Age groups							**(<0.001)**
< 2 years	0.42	0.30	0.55	0.47	0.41	0.53	0.524
2 to 5 years	-0.06	-0.13	0.00	-0.02	-0.05	0.02	0.225
6 to 11 years	0.04	-0.02	0.10	0.03	0.00	0.05	0.737
>= 12 years	0.10	0.04	0.16	0.16	0.13	0.18	0.068
Region							**(<0.001)**
Asia-Pacific	0.14	0.07	0.21	0.13	0.09	0.17	0.839
Caribbean, Central and South America	0.16	0.07	0.25	0.14	0.06	0.22	0.796
Central Africa	0.19	0.12	0.27	0.17	0.13	0.21	0.530
East Africa	0.11	0.05	0.18	0.11	0.08	0.13	0.886
Southern Africa	0.10	0.03	0.16	0.17	0.15	0.19	0.039

Table 8. Comparison of adjusted mean change in BMI z-score per year, over 96 weeks before and after dolutegravir exposure, including patients with at least to observations before OR after DTG initiation (N= 25,832).

Characteristics	Mean annual zBMI change pre DTG	95% CI		Mean annual zBMI Change post DTG	95% CI		p value[1]
West Africa	0.05	-0.02	0.12	0.24	0.21	0.27	0.000
Previous ART Regimen							**(<0.001)**
Naive	0.20	-0.02	0.42	0.30	0.27	0.33	0.390
NNRTI or NRTI based	0.04	0.01	0.07	0.12	0.10	0.15	0.000
PI based	0.03	0.00	0.07	0.18	0.15	0.20	0.000
Prior regimen unknown	0.23	0.13	0.33	0.04	0.00	0.09	0.001
ART Regimen Associated with DTG							**(<0.001)**
DTG+others	0.13	0.06	0.19	0.13	0.10	0.16	0.928
DTG+TAF	0.13	0.06	0.21	0.23	0.19	0.28	0.016
DTG+TDF|ZDV|ABC	0.11	0.05	0.18	0.12	0.09	0.14	0.982

[1]P wald test. Mean BMI-for-age score was estimated using mixed effects models with linear splines for time at DTG start (week 0). Adjusting for sex, age group, region, history of ART regimen, with time interactions for said variables. P-values in brackets (across subgroups) represent the significance level for the interaction term. P-values by subgroup compare the slope of change in zBMI before and after DTG start. DTG = Dolutegravir, NRTI, = Nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, TAF = tenofovir alafenamide fumarate, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine, ABC = abacavir, zBMI = BMI-for-age z score, ART= antiretroviral therapy.