Body composition changes in children living with HIV initiated on dolutegravir or protease inhibitors in the CHAPAS-4 trial

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Short title: Body composition changes in children with HIV

Abstract

Background:

Few studies have compared body composition changes in children living with HIV receiving integrase inhibitors or boosted protease inhibitors.

Methods:

Children switching to second-line antiretroviral therapy (ART)were randomized to dolutegravir (DTG), darunavir/ritonavir (DRV/r), atazanavir/ritonavir (ATV/r) or lopinavir/ritonavir (LPV/r), and to tenofovir alafenamide (TAF) or standard of care ([SOC]: abacavir or zidovudine) using a factorial design. Body composition was measured using bioelectric impedance analysis over 96 weeks. Associations between baseline characteristics and changes in fat mass, fat-free mass, muscle mass, and body fat percentage were estimated using robust regression with multivariable fractional polynomial selection (exit p=0.05).

Results:

Eight hundred forty-one participants were included in the analysis. Females compared to males had greater fat accrual (+4.66% body fat, +1.32kg fat mass; both p<0.001). Compared to LPV/r, ATV/r and DTG exposures were associated with higher fat-free mass (+0.85kg [95% CI 0.43,1.27] and +0.79kg [0.37,1.21] respectively) and muscle mass (+0.82kg [0.41,1.23], +0.82kg [0.42,1.22] respectively) (all p<0.001). TAF and DRV/r exposures were associated with higher fat mass (+0.32kg [0.12,0.52] p=0.002; +0.33kg [0.04,0.61] p=0.025] respectively). Prior nevirapine exposure was also

associated with greater fat accrual (+0.36kg [0.13,0.58] vs efavirenz, p=0.002). Baseline CD4 and viral load, time on first-line ART, and site were also associated with composition changes.

Conclusion:

DTG and ATV/r were associated with greater gains in fat-free mass and muscle mass than LPV/r while DRV/r, TAF and prior nevirapine exposure were associated with fat mass accrual. Fat gain may initially reflect return to health but sustained increases may have metabolic implications. These findings suggest the need to monitor fat compartments with long-term exposure.

Clinical trial registration. ISRCTN22964075

Key words

Body composition, children, antiretroviral therapy, HIV

Introduction

People living with HIV(PLWH) are now surviving longer because of effective anti-retroviral therapy (ART), but they are prone to non-communicable diseases among which cardiovascular disease (CVD) is a concern in adults.[1] For example studies among adults have demonstrated that PLWH are at a higher risk of myocardial infarction compared with their counterparts without HIV and this has been linked to central fat accumulation. Risk factors include age, obesity and exposure to some ART.[2]

Boosted protease inhibitors (bPIs) and dolutegravir (DTG) are associated with central fat accumulation among adults with DTG linked to development of hypertension, cardiovascular events and diabetes.[3] Central fat accumulation is one of the traditional predictors of CVD among adults.[4]

DTG is the preferred anchor drug for PLWH and is associated with global fat-mass gain without lean mass gain among adults. [5] For example, in the ACTG A5260 sub-study, adults randomized to receive atazanavir/ritonavir (ATV/r], darunavir/ritonavir (DRV/r), or raltegravir (RAL) (an integrase strand transfer inhibitor [INSTI) in the same class as DTG) underwent dual-energy X-ray absorptiometry (DXA) scanning over 96 weeks. The study reported comparable increases in both fat mass and lean mass across all treatment arms.[6] Anthropometric measurements offer simple, low-cost, and scalable tools to assess both fat distribution and muscle growth that may be valuable in pediatric HIV care in low-income settings, given that circumference measures have been shown to correlate with metabolic risk in adults.[2] For example consistent with DXA results, in the ACTG A5257 trial, adults randomized to RAL experienced significantly greater

increases in waist circumference over 96 weeks compared to those on DRV/r (p = 0.013). Increases in the ATV/r arm were intermediate, falling between those observed with RAL and DRV/r. The effect of RAL was pronounced among women and Black participants.[7] In the AFRICOS cohort study, adults switching to DTG-based ART had higher waist-to-hip ratio gains compared to those maintained on non-DTG regimens.[8] Similarly, in an observational cohort from Uganda and South Africa, adults on DTG-based TLD (tenofovir/lamivudine/dolutegravir) experienced greater increases in waist circumference: 2.3 cm in South Africa and 0.8 cm in Uganda within 48 weeks.[9]

However, there is very limited information about the effect of DTG compared with bPIs on body composition among children living with HIV (CLWH). For example, a small single-arm study reported marked increase in trunk fat and trunk/body fat ratio after 12 months among adolescent participants on DTG, with a parallel decrease in low-density lipoproteins(LDL).[10] We found that increases in body mass index (BMI) were similar across DTG-based, DRV/r-based and ATV/r-based treatment arms in the CHAPAS-4 trial that evaluated children initiating second-line ART but were smaller in the lopinavir/ritonavir (LPV/r) arm,[11] BMI cannot differentiate between fat mass and lean mass**,** such as muscle and bone. In HIV care, where changes in fat and lean mass distribution such as lipodystrophy, lipoatrophy, and fat accumulation are common, relying solely on BMI may fail to identify important alterations in body fat composition or distribution or both which are associated with CVD. No published studies have directly compared the effects of DTG, LPV/r, DRV/r, and ATV/r on regional body circumferences in CLWH.

In this sub-study of the CHAPAS-4 trial randomized trial, we therefore compared longitudinal changes in body composition and regional anthropometric measures over 96 weeks among CLWH failing first-line non-nucleoside reverse transcriptase inhibitor(NNRTI)-based ART and initiating tenofovir alafenamide/emtricitabine (TAF/FTC) or standard of care (SOC) (zidovudine/lamivudine (ZDV/3TC) or abacavir/lamivudine (ABC/3TC), randomized) with DTG or ATV/r or DRV/r or LPV/r (also randomized using a factorial design). We also sought to identify clinical and demographic factors associated with these changes.

Materials and Methods

Study design and population

This was a secondary analysis within the CHAPAS- 4 open-label randomized trial, evaluating the virologic response (primary endpoint) to alternative second-line ART in CLWH (ISRCTN22964075).

In CHAPAS-4, 919 children aged 3-15 years on a failing first-line ART regimen of 2 nucleotide reverse transcriptase inhibitors(NRTI) + NNRTI (with a viral load of 400 copies/mL or more) were randomized to receive TAF/FTC or SOC, depending on their first-line regimen.[11]Children were also randomized in a factorial design to replace their NNRTI with DTG or DRV/r or ATV/r or LPV/r.[11]

This secondary analysis included 841(92%) children from all six sites who had bioelectrical impedance analysis (BIA) results available to assess changes in body composition from baseline to 96 weeks (i.e., had non-missing values at baseline and 96 weeks). Of these, 444 children from three sites — one in Zimbabwe (University of

Zimbabwe Clinical Research Centre, Harare) and two in Uganda (Joint Clinical Research Centre, Kampala, and Joint Clinical Research Centre, Mbarara) also underwent skinfold thickness and body circumference assessments to evaluate the effects of trial drugs on body fat distribution. Participants were enrolled between January 2019 and March 2021 and were followed for a minimum of 96 weeks.

Body circumference and skinfold thickness measurements were taken at enrolment and weeks 48 and 96, and recorded in the case report forms. Mid upper arm (MUAC), waist, hip, mid-thigh, and calf circumference were taken using a tape measure; the means of three measurements for each child were used for analysis to reduce measurement error. Skinfold thickness was also measured in millimeters in triplicate at six body sites (biceps, triceps, subscapular, suprailiac, midthigh, and calf) using Holtain caliper and recorded on a case report form. The mean of the three readings at each body site was used for analysis.

Body composition was measured using the Tanita DC-430MA bio impedance analysis (BIA) device. Age in years, sex, height, and weight were entered, and fat mass, fat-free mass, muscle mass in kilograms, and body-fat percentage were obtained directly from the machine output. Measurements were standardized (morning, barefoot, fasted) and the analyzer was regularly calibrated.

Ethical approval

The CHAPAS-4 trial received approval from the institutional review boards in each participating country. Written informed consent was obtained from the legal guardians or parents of the enrolled children before trial and sub-study participation. According to

specific participating country guidelines, children provided age -appropriate written informed assent.

Statistical analysis

Data were exported to STATA 15 (StataCorp, College Station Texas, USA) for analysis. Normality of continuous variables was assessed using the Shapiro–Wilk test and by visual inspection of histograms (50 bins). Where necessary, variables were log-transformed or analyzed using Kruskal-Wallis and other non-parametric methods.

The outcome variables were changes in body composition, skinfold thickness and body circumferences from week 0 to week 96. Waist-to-height ratio (WHtR) was calculated as waist circumference (cm) divided by standing height (cm). Age- and sex-specific Z-scores for WHtR were generated using reference values from the National Health and Nutrition Examination Survey (NHANES).[12] We did not use WHO norms because these are not available for those over age 10 years and the trial included a substantial minority of children older than this.

To examine associations between patient characteristics and changes in body fat percentage, fat mass, fat-free mass, and muscle mass, we applied multivariable fractional polynomial (MFP) regression with robust estimation, analyzing each outcome separately. The baseline value of the outcome, randomized anchor drug, NRTI backbone, and study site were forced into all models. Other covariates entered as candidate predictors included sex, age at baseline, WHO clinical stage, first-line NNRTI (efavirenz (EFV) vs nevirapine (NVP)), time on first-line ART, waist circumference, baseline CD4 cell count, baseline log transformed viral load, and baseline lipid values

(high density lipoproteins (HDL) cholesterol, total cholesterol, and triglycerides). Candidate variables were retained in the final model if selected by the MFP procedure at α=0.05 based on a log-likelihood test. Regression results are presented as coefficients (β) with 95% confidence intervals and Wald p-values: where likelihoods are not completely normally distributed. Wald p-values will differ and therefore interpretation focused on factors with Wald p<0.05. For categorical variables, coefficients represent the mean difference in body composition change compared with the reference group; for continuous variables, coefficients represent the change in body composition per unit higher unless otherwise shown. Spearman correlation coefficients were computed to assess the relationship between changes in anthropometric measures and changes in body composition.

Results

Baseline characteristics of the 841 children with body composition change results (Table 1) (of whom 444 also had anthropometric data) were similar to those previously reported for the complete CHAPAS-4.[11]Children were enrolled from six sites**:** 184 (21.9%) from JCRC Kampala, 156 (18.6%) from JCRC Mbarara, 215 (25.6%) from UZCRC Harare, 101 (12.0%) from Bulawayo, 115 (13.7%) from Lusaka, and 70 (8.3%) from Ndola**.** Overall, 447 (53.2%) were male**.** The median age at enrollment was 10.8 years (IQR 8.6–13.1) (range 5-15)**,** with a largely normal baseline BMI-for-age z-score (median 0.93). The median baseline viral load was 4.2 log10 copies/mL (IQR 3.7–4.7) and the median CD4 cell count was 657 cells/µl (IQR 408-954).711 (84.5%) classified as WHO stage 1 or 2 disease (worst pre-baseline clinical stage). Baseline

characteristics were balanced across all treatment groups as expected from the randomization.

Table 2:

Body Fat (%)

In multivariate models (Table 2), females had a larger increase in body fat percentage than males. Larger increases were also observed with ATV/r, DRV/r than LPV/r, with a weaker trend for DTG and among children from Lusaka and Harare compared with those from Kampala. Lower baseline CD4 cell count was also associated with greater increases in body fat percentage, while higher baseline body fat was associated with smaller body fat increases.

Fat Mass (kg)

Females had a larger increase in fat mass than males. Larger increases were also seen with DRV/r (with weaker trends for ATV/r and DTG), TAF (vs SOC), and having received first-line NVP (vs EFV), and among children in Lusaka, Harare, and Bulawayo compared with those in Kampala. Higher baseline viral load and lower CD4 cell count were associated with greater increases in fat mass, while higher baseline fat mass was associated with smaller increases.

Fat-Free Mass (kg)

Larger increases in fat-free mass were observed with ATV/r and DTG than LPV/r. Children with advanced WHO stage and those older at baseline had greater increases,

while longer duration on first-line ART and lower baseline fat-free mass or CD4 cell count were associated with smaller increases. Children in Lusaka and Ndola had smaller increases in fat-free mass compared to those from Kampala.

Muscle Mass (kg)

Children on ATV/r and DTG had larger increases in muscle mass compared to LPV/r with a weaker trend for DRV/r. Greater increases were also seen in older children, while smaller increases were associated with longer duration on first-line ART and lower baseline muscle mass. Higher baseline viral load and lower CD4 cell count were associated with greater increases in muscle mass. Children in Lusaka and Ndola had smaller increases in muscle mass than those in Kampala.

Table 3 presents the correlations between changes in anthropometric measures and BIA-derived body composition changes over 96 weeks. Skinfold changes showed small but statistically significant correlations with changes in fat mass and body fat percentage, and no meaningful correlations with fat-free mass or muscle mass. In contrast, circumference measures demonstrated moderate correlations with all body composition outcomes ($r \approx 0.30–0.48$, $p < 0.001$), with waist, MUAC, mid-thigh, calf, and hip circumferences showing the strongest associations.

Table 4 shows comparisons of body circumferences in the subset of 394 children with these measurements. Children on DTG showed greater median increases in MUAC, waist, midthigh, calf, and hip circumferences over 96 weeks compared to those on bPIs (LPV/r, ATV/r, and DRV/r) with the smallest increases in children on LPV/r, then DRV/r

then ATV/r. In contrast, there was no evidence of differences in WHtR Z-score changes among the four drugs.

Table 5 presents comparisons of skinfold thicknesses. Baseline values were comparable for both peripheral (biceps, triceps, calf) and central (subscapular, suprailiac, midthigh) sites. By week 96, small increases were observed in all skinfolds. However, there were no significant differences in skinfold change across the anchor drug groups, and the overall pattern of change was similar regardless of anchor drug

Table 2 and Figure 1 show comparisons of body composition measures

Figure 1. Mean changes in body composition measures from baseline to week 96 across anchor drug regimens. Gains in fat-free mass and muscle mass differed significantly between drugs (both $p<0.001$). Mean fat-free mass increased by 4.37 kg with LPV/r and 5.5 kg with DTG, while mean muscle mass increased by 4.1 kg with LPV/r and 5.4 kg with DTG.

Discussion

Our study aimed to examine the changes in body composition and associated factors among CLWH who were failing first-line ART and initiated on second-line treatment. Specifically, we sought to determine how different ART anchor drugs and other clinical and demographic factors were associated with changes in body composition over time.

The main findings of this study are threefold. First, children receiving newer ART anchor drugs namely DTG, ATV/r, and DRV/r experienced greater gains in both fat and lean body compartments compared to those on LPV/r. These differences were observed in

direct body composition measurements as well as regional anthropometric indicators. Secondly, sex and age were independently associated with body composition outcomes**,** with females and older children showing higher fat accumulation and lean mass respectively, consistent with physiological and pubertal development patterns.[13]Thirdly, higher baseline CD4 cell count and viral load (at the point of first-line failure and switch to second-line ART) were associated with differential patterns of fat and lean mass accrual, emphasizing the influence of immunological and virologic status on growth and nutritional recovery.

The observed differences in body composition between ART anchor drugs align with growing evidence that newer ART drugs for example, INSTIs like DTG, are associated with greater increases in body mass compared to older regimens such as LPV/r in children as well as adults.[14] This amplifies our findings in the main CHAPAS-4 trial, where we reported higher BMI gains among children randomized to DTG compared to those on LPV/r.[11] This analysis extends these observations by providing detailed body composition outcomes beyond BMI, demonstrating that DTG-based regimens lead to greater increases in fat-free mass and muscle mass in children with trends towards greater changes in body fat percentage and fat mass. This deeper assessment reveals that the weight changes observed in the main CHAPAS-4 trial analysis reflect changes in tissue compartments, rather than simply generalized weight increase. However, importantly, after adjusting for other factors (Table 4), the magnitude of changes in body fat percentage and fat mass were similar across ATV/r, DRV/r and DTG; in contrast, increases in fat-free and muscle mass were greatest with DTG and ATV/r, and intermediate with DRV/r.

The greater muscle mass and fat-free mass gains observed with ATV/r and DTG compared to LPV/r suggest that LPV/r may suppress physical growth and tissue recovery more than newer bPIs. Several studies have reported suboptimal growth and weight recovery in children exposed to LPV/r,[15] possibly due to LPV/r's higher inclination to induce mitochondrial toxicity, insulin resistance, and low-grade inflammation that may disrupt muscle protein metabolism.[16] DTG and ATV/r-based regimens led to greater increases in fat-free mass and muscle mass compared to LPV/r, suggesting a more favorable lean mass profile for these agents. Importantly, increases in fat-free mass are clinically meaningful, as lean tissue accrual during childhood and adolescence is linked to improved physical function and long-term health[17], with early growth patterns predictive of higher adult fat-free mass[18]. In adult cohorts, DTG has shown mixed effects, with some studies reporting gains in total body weight, particularly in fat mass[19] while others found stable lean mass with improved metabolic profiles.[4] Our findings in children suggest that DTG may support lean mass accrual without significantly increasing fat mass, although the relatively short follow-up and baseline characteristics could influence these effects.

These results are partly consistent with the ODYSSEY trial, where children randomized to DTG had modestly greater gains in weight and mid-upper arm circumference compared with those receiving SOC by then (EFV or LPV/r), but no excess increase in body fat percentage or central adiposity.[20] Unlike ODYSSEY, which compared DTG with EFV and LPV/r, our analysis extended the comparison to additional second-line anchor drugs (ATV/r and DRV/r) after failure of first-line NNRTI regimens, thereby providing broader evidence of differential effects on body composition in the switch setting.

TAF use, relative to SOC, was independently associated with greater increases in fat mass, a finding consistent with adult studies where TAF has been linked to weight gain largely driven by increases in fat rather than lean mass.[5] Our data suggest that in children, TAF contributes to increased fat accumulation following virologic failure. In undernourished pediatric populations, this effect may have mixed implications, potentially supporting catch-up growth but also raising concerns about long-term metabolic health.

Pediatric studies directly comparing fat mass accrual in children switching from EFV versus NVP are scarce, with most available data focusing on BMI rather than body composition outcomes.[21, 22] In our study, NVP was associated with larger gains in fat mass than EFV with a weaker trend towards similar effects with body fat percentage. This pattern contrasts with reports from adult West African cohorts where greater weight gain after switching to DTG was observed among those previously on EFV, and to a lesser extent NVP.[23, 24] These divergent patterns may reflect underlying differences in the regimens from which patients were switching, as adults commonly transitioned from tenofovir(TDF)–based first-line therapy, whereas in our study children switched from ABC or ZDV–based backbones. EFV has also been associated with mitochondrial dysfunction and lipoatrophy in adipose tissue.[25] This effect may reduce fat accrual compared with NVP, which is considered less toxic to adipose tissue among children.

Longer exposure to first-line ART before switch may reflect prolonged virologic failure, nutritional compromise, and cumulative toxicities, which can blunt lean tissue recovery

after initiation of second-line therapy. Similar observations have been reported where a delayed switch was linked to poorer growth outcomes.[26]

The positive association between age and increases in fat-free mass and muscle mass reflects the relationship between chronological growth and ART-mediated recovery. Older children may experience more pronounced gains due to catch-up growth or because they are entering adolescence, when natural increases in fat and lean mass occur.

Absolute CD4 cell count showed divergent associations: negatively linked to all body fat percentage and lean compartments (fat-free and muscle mass). This pattern contrasts with much of the existing literature, where higher CD4 cell counts are typically associated with greater improvements in both fat and lean compartments. For example, the Nutrition for Healthy Living Study in HIV-positive adults demonstrated that greater CD4 cell counts were associated with larger gains in trunk and extremity fat as well as lean mass.[27] Similarly, a pediatric study of children initiating ART generally showed positive associations between baseline CD4 percentages and subsequent lean mass accrual.[26] Several factors may explain this difference. Our cohort was composed of CLWH experiencing first-line ART failure and transitioning to second-line therapy during the pubertal developmental window. In addition, differences in ART regimens, duration of HIV exposure, or environmental factors compared to prior studies may contribute to these contrasting associations.

The association of viral load with greater fat mass and muscle mass gain likely reflects that children with elevated viral loads may have been more immunocompromised and

nutritionally compromised at study entry, and therefore more prone to substantial catch-up growth once viral suppression was achieved. This is consistent with the well-described return-to-health effect, in which effective ART reduces inflammation, improves appetite and nutrient absorption hence supporting lean tissue recovery. Comparable trends have been reported in both pediatric and adult studies of ART initiation, where improvements in nutritional status were accompanied by increases in lean mass.[26, 28] In addition, in our study, children with a history of advanced HIV disease (worst-ever WHO stage 3/4) had greater gains in fat-free mass but not fat mass. A study in African adolescents similarly found that non-suppressed HIV was associated with lower lean but not fat mass, together suggesting that lean compartments may be particularly sensitive to HIV disease burden.[29]

There were also differences in body composition changes between trial sites- most notably that children in Lusaka had greater increases in body fat percentage and fat mass and smaller increases in fat-free mass and muscle mass, with similar trends in other sites. These are likely to reflect contextual factors such as nutritional diversity, food security, and socioeconomic environment, which shape recovery during ART. Variability in cultural feeding practices and the timing of pubertal development across regions may also contribute to the differences observed. Similar site differences in growth outcomes have been previously reported in African pediatric HIV cohorts.[30]

Body circumference measures showed moderate correlation with fat and lean mass changes, supporting their value where BIA is unavailable.

Together, these findings indicate that ART regimens, host and environmental factors contribute to changes in body composition in CLWH, with DTG and ATV/r showing relatively favorable profiles.

A major strength of this study is its comprehensive assessment of body composition using both direct measures (fat mass, fat-free mass, muscle mass, body fat percentage) and regional anthropometric data**,** which provided a detailed understanding of ART-related changes. The inclusion of multiple ART regimens, especially newer agents like DTG, DRV/r, and TAF, enhances the relevance of our findings for current and future HIV treatment options. The use of longitudinal data allowed for the evaluation of change over time. Lastly, this was a multisite study which enhanced generalizability of results and randomization to minimize bias in drug comparisons.

Study limitations include the use of BIA, which provides only indirect estimates of fat distribution and can be influenced by hydration status. Direct measures of visceral fats such as MRI or DXA, provide more accurate assessments but are more expensive and DXA exposes children to radiation.[31] BIA was therefore the only practical method across all sites and results from a smaller DXA sub-study in CHAPAS-4 are consistent with our findings.[11] Secondly, the study was conducted among children on failing first-line ART, and findings may not generalize to ART-naïve populations. Thirdly, while we adjusted for several confounders, estimates of the effect of other non-randomized factors could be affected by residual confounding from, for example diet, physical activity, or most importantly, pubertal stage, which were not captured. These factors, particularly Tanner stage, were not collected within the trial. While randomization

reduces the likelihood of systematic imbalance between treatment groups, residual confounding by unmeasured factors such as pubertal stage cannot be excluded. However, analyses stratified using age as a proxy for Tanner staging (classifying females/males as pre-pubertal if<11/13 years) showed similar results (data not shown). Lastly, the follow-up period may not have been long enough to detect long-term body composition changes, as children will be on these drugs for many years.

Conclusion

In this cohort of ART-experienced children randomized to second-line ART, female sex, age, duration of first-line ART, CD4 cell count, viral load at switch to second-line and specific ART regimens influenced body composition changes 96 weeks after initiating second-line ART. Use of DTG and ATV/r were most strongly associated with greater increases in fat-free mass and muscle mass, while TAF, DRV/r and prior NVP exposure were most strongly associated with higher increases in fat mass. Longitudinal studies are needed to assess the longer-term implications of these body composition changes as CLWH grow into adulthood.

Conflict of interest

The authors have no conflicts of interest.

Acknowledgements

This work was done as part of the CHAPAS- 4 trial. The authors would like to thank the children and their caretakers who volunteered to participate in this study.

We thank the data collection team at the Joint Clinical Research Centre, Kampala and Mbarara, University of Zimbabwe Clinical Research Centre, Harare, Zimbabwe, University of Zambia, School of Medicine Zambia, Mpilo Central Hospital Bulawayo, Zimbabwe, Arthur Davison Children's Hospital Ndola, Zambia

Funding

The CHAPAS-4 trial was funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) as part of the EDCTP program, which is supported by the European Union through a grant (TRIA2015-1078). Gilead Sciences, CIPLA, ViiV Healthcare and Janssen provided the trial drugs and Gilead Sciences and Janssen also provided funding to support the study, AJS, DMG and ASW were supported by core support to the MRC Clinical Trials Unit at UCL (MC UU 00004/03). ASW is an NIHR Senior Investigator.

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Figure legend

Figure 1. Body composition change from baseline to week 48 and 96 for body fat (%)

(A) fat mass (kg)(B), fat-free mass(kg) (C) and muscle mass(kg) (D) (N=841)

DTG=dolutegravir, ATV/r=Atazanavir/ritonavir, DRV/r=darunavir/ritonavir, LPV/r=Lopinavir/ritonavir

Table 1: Baseline characteristics of 841 children randomized to dolutegravir, atazanavir/ritonavir, darunavir/ritonavir and lopinavir/ritonavir-based ART in the CHAPAS-4 trial with body composition measures

Characteristic	LPV/r (n=202)	ATV/r (n=208)	DRV/r (n=218)	DTG (n=213)	Total (N=841)
Median (IQR)					
Age (years)	10.6 (8.1,12.9)	10.8 (8.4,13.2)	10.7 (8.8,13.1)	11.3 (8.9,13.3)	10.8 (8.6,13.1)
Absolute CD4 (cells/μL)	681 (408,977)	659 (446,934)	671 (410,997)	622 (350,880)	657 (408,954)
CD4%	28.2 (19.2,35.7)	27.9 (20.7,34.4)	28.0 (18.2,37.0)	27.0 (18.0,35.9)	27.8 (19.1,35.7)
HIV RNA log10 copies/mL	4.2 (3.8,4.8)	4.2 (3.7,4.7)	4.3 (3.8,4.7)	4.2 (3.7,4.8)	4.2 (3.7,4.7)
BMI z-score	-0.80 (-1.63,-0.31)	-0.87 (-1.62,-0.39)	-0.98 (-1.68,-0.43)	-0.95 (-1.66,-0.34)	-0.93 (-1.66, -0.36)
WAZ	-1.46(-2.30, -0.87)	-1.69(-2.45, -1.02)	-1.73(-2.42, -0.94)	-1.62(-2.47, -0.94)	-1.54(-2.48, -0.93)
HAZ	-1.48(-2.28, -0.70)	-1.69(-2.30, -1.06)	-1.65(-2.35, -0.85)	-1.54(-2.48, -0.93)	-1.58(-2.35, -0.91)
MUAC (cm)	18.0 (16.5,20.0)	18.2 (16.3,20.1)	18.1 (16.5,19.6)	18.5 (17.0,20.1)	18.2 (16.5,20.0)
Waist circumference (cm)	59 (55,62.7)	59.5 (55.1,63.0)	59 (55.6,62.0)	59.3 (56,63.5)	59 (55.5,62.8)
Body fat %	14.9 (11.5,18.0)	14.3 (10.3,17.5)	14.3 (10.9,17.2)	14.3 (10.7,18.2)	14.4 (10.8,17.7)
Fat mass (kg)	3.6 (2.8,4.8)	3.6 (2.8,4.6)	3.4 (2.7,4.9)	3.6 (2.8,5.0)	3.5 (2.7,4.8)
Fat-free mass (kg)	21.8 (17.8,28.9)	22.4 (17.6,28.1)	22.7 (18.1,28.0)	23.9 (18.9,30.2)	22.8 (18.1,28.5)
Muscle mass (kg)	20.7 (16.7,27.3)	21.1 (16.6,26.5)	21.4 (17.0,26.5)	22.6 (17.9,28.6)	21.5 (17.0,27.0)
Lipid fractions(mmol/L)					
LDL	1.9(1.5,2.3)	2.1(1.7,2.5)	2.0(1.5,2.4)	2.0(1.5,2.40)	2.0(1.6,2.40)
HDL	1.1(0.9,1.3)	1.1(1.0,1.40)	1.2(0.9,1.30)	1.1(1.0,1.4)	1.1(0.9,1.4)
TC	3.4(3.0,3.8)	3.6(3.1,4.2)	3.4(2.9,4.0)	3.5(3.0,4.0)	3.4(3.0,4.0)
Trig	0.9(0.7,1.4)	1.0(0.7,1.4)	1.0(0.7,1.4)	1.0(0.8,1.3)	1.0(0.7,1.4)
Sex, n (%)					
Male	102 (50.5)	116 (55.8)	115 (52.8)	114 (53.5)	447 (53.2)
Female	100 (49.5)	92 (44.2)	103 (47.2)	99 (46.5)	394 (46.9)
First-line regimen, n (%)					

Characteristic	LPV/r (n=202)	ATV/r (n=208)	DRV/r (n=218)	DTG (n=213)	Total (N=841)
EFV	118 (58.4)	117 (56.8)	119 (54.8)	120 (56.3)	474 (56.6)
NVP	84 (41.6)	89 (43.2)	98 (45.2)	93 (43.7)	364 (43.4)
WHO stage, n (%)					
Stage 1,2	170 (84.2)	176 (84.6)	183 (83.9)	182 (85.5)	711 (84.5)
Stage 3,4	32 (15.8)	32 (15.4)	35 (16.1)	31 (14.6)	130 (15.5)
NRTI backbone, n (%)					
ABC/ZDV	100 (49.5)	101 (48.6)	108 (49.5)	111 (52.1)	420 (49.9)
TAF	102 (50.5)	107 (51.4)	110 (50.5)	102 (47.9)	421 (50.1)
Site, n (%)					
Kampala	43 (21.3)	45 (21.6)	47 (21.6)	49 (23.0)	184 (21.9)
Mbarara	35 (17.3)	37 (17.8)	41 (18.8)	43 (20.2)	156 (18.6)
Lusaka	29 (14.4)	29 (13.9)	29 (13.3)	28 (13.1)	115 (13.7)
Ndola	17 (8.4)	18 (8.7)	18 (8.3)	17 (8.0)	70 (8.3)
Harare	52 (25.7)	53 (25.5)	56 (25.7)	54 (25.4)	215 (25.6)
Bulawayo	26 (12.9)	26 (12.5)	27 (12.4)	22 (10.3)	101 (12.0)

ABC=Abacavir, EFV=Efavirenz, NVP=Nevirapine, TAF=Tenofovir alafenamide, BMI=Body mass index, MUAC=Mid upper arm circumference, LDL=Low density lipoproteins, HDL=High density lipoproteins, TC=Total cholesterol, Trig=Triglycerides, IQR=Interquartile range, HAZ=Height for age Z-score, WAZ=Weight for age Z-score

Table 2: Variables associated with change in body composition measures at 96 weeks in multivariable models(N=841)

Variable	Change in body fat (%)	Change in fat mass (kg)	Change in fat-free mass (kg)	Change in muscle mass (kg)
Sex				
Male (ref)	0	0		
Female vs male	4.66 [4.08, 5.25]; p<0.001	1.32 [1.10, 1.54]; p<0.001		
Anchor drug				
LPV/r (ref)	0	0	0	0
ATV/r	0.78 [0.02, 1.54]; p=0.044	0.28 [-0.01, 0.57]; p=0.055	0.85 [0.43, 1.27]; p<0.001	0.82 [0.41, 1.23]; p<0.001
DRV/r	0.84 [0.09, 1.59]; p=0.028	0.33 [0.04, 0.61]; p=0.025	0.32 [-0.09, 0.73]; p=0.130	0.36 [-0.04, 0.76]; p=0.079
DTG	0.75 [-0.01, 1.50]; p=0.053	0.26 [-0.03, 0.55]; p=0.078	0.79 [0.37, 1.21]; p<0.001	0.82 [0.42, 1.22]; p<0.001
NRTI				
SOC (ref)	0	0		
TAF	0.45 [-0.08, 0.98]; p=0.096	0.32 [0.12, 0.52]; p=0.002		
First line ART				
EFV (ref)	0	0		
NVP	0.56 [-0.02, 1.15]; p=0.060	0.36 [0.13, 0.58]; p=0.002		
WHO stage				
WHO stage 1/2 (ref)			0	0
WHO stage 3/4			0.45 [0.02, 0.87]; p=0.038	–
Age at baseline	–	–	0.37 [0.26, 0.47]; p<0.001	0.36 [0.26, 0.46]; p<0.001

Variable	Change in body fat (%)	Change in fat mass (kg)	Change in fat-free mass (kg)	Change in muscle mass (kg)
Time on first line ART	–	–	-0.07 [-0.12, -0.01]; p=0.012	-0.06 [-0.11, -0.01]; p=0.030
Baseline value	-0.28 [-0.33, -0.23]; p<0.001	0.11 [0.05, 0.16]; p<0.001	0.04 [0.00, 0.09]; p=0.036	0.04[-0.00,0.08]; p=0.082
Waist circumference(cm)	–	0.01 [-0.01, 0.04]; p=0.275	–	–
Baseline CD4 count*	-0.06 [-0.11, -0.01; p=0.029	-0.02 [-0.04, 0.00]; p=0.067	-0.04 [-0.07, -0.01]; p=0.012	-0.04 [-0.07, -0.00]; p=0.028
Baseline log10 VL		0.07 [-0.08, 0.21]; p=0.357		0.27 [0.06, 0.47]; p=0.011
Site				
Kampala (ref)	0	0	0	0
Mbarara	0.79 [-0.12, 1.71]; p=0.089	0.31 [-0.04, 0.65]; p=0.079	-0.35 [-0.84, 0.14]; p=0.164	-0.39 [-0.86, 0.09]; p=0.108
Lusaka	1.56 [0.61, 2.51]; p=0.001	0.68 [0.32, 1.04]; p<0.001	-0.73 [-1.24, -0.22]; p=0.005	-0.75 [-1.25, -0.26]; p=0.003
Ndola	0.96 [-0.18, 2.10]; p=0.100	0.25 [-0.18, 0.69]; p=0.249	-0.67 [-1.29, -0.05]; p=0.035	-0.72 [-1.32, -0.12]; p=0.019
Harare	1.16 [0.39, 1.92]; p=0.003	0.57 [0.28, 0.86]; p<0.001	-0.34 [-0.77, 0.09]; p=0.122	-0.32 [-0.73, 0.09]; p=0.130
Bulawayo	0.69 [-0.24, 1.63]; p=0.146	0.56 [0.20, 0.91]; p=0.002	-0.25 [-0.79, 0.28]; p=0.354	-0.12 [-0.62, 0.38]; p=0.628

* effect per 100 cells/mm^3 higher

DTG=Dolutegravir, ATV/r=Atazanavir/ritonavir, DRV/r=Darunavir/ritonavir, LPV/r=Lopinavir/ritonavir, NVP=Nevirapine, EFV=Efavirenz. Note: based on backwards elimination using exit p=0.05 based on a log-likelihood test, forcing site, randomized anchor drug and baseline value into the model regardless of significance. Wald p-values shown in the table do not correspond exactly to the log-likelihood p-values used for model selection.

Table 3: Correlations Between Changes in Anthropometric Measures and BIA-Derived Body Composition Changes.

Anthropometric Measure change	Change in Fat Mass r (p-value)	Change in Fat-Free Mass r (p-value)	Change in Body Fat % r (p-value)	Change in Muscle Mass r(p-value)
Skin folds				
Biceps skinfold	0.104 (0.043)	-0.012 (0.823)	0.119 (0.021)	-0.020 (0.695)
Subscapular skinfold	0.164 (< 0.001)	-0.014 (0.788)	0.140 (0.006)	-0.017 (0.742)
Suprailiac skinfold	0.206 (< 0.001)	0.064 (0.211)	0.151 (0.003)	0.058 (0.263)
Midthigh skinfold	0.199 (< 0.001)	-0.042 (0.420)	0.193 (< 0.001)	-0.044 (0.394)
Calf skinfold	0.186 (< 0.001)	-0.033 (0.523)	0.171 (< 0.001)	-0.036 (0.489)
Triceps skinfold	0.095 (0.063)	-0.027 (0.598)	0.099 (0.054)	-0.031 (0.546)
Body circumference				
Waist circumference	0.392 (< 0.001)	0.376 (< 0.001)	0.384 (< 0.001)	0.365 (< 0.001)
Mid-thigh circumference	0.337 (<0.001)	0.417 (<0.001)	0.302 (<0.001)	0.402 (<0.001)
Calf circumference	0.252 (<0.001)	0.429 (<0.001)	0.226 (<0.001)	0.419 (<0.001)
Hip circumference	0.363 (<0.001)	0.342 (<0.001)	0.320(<0.001)	0.331 (<0.001)
MUAC	0.355 (<0.001)	0.480 (<0.001)	0.358 (<0.001)	0.465 (<0.001)

MUAC=Mid upper arm circumference, r=correlation coefficient

Table 4: Body Circumference at baseline and change at 96 weeks(N=394)

Body Region	ART Regimen	N	Baseline	IQR (cm)	Median Change (cm)	IQR (cm)	Kruskal-Wallis *p*-value
MUAC	LPV/r	99	18.05	16.50, 20.10	2.08	1.15, 2.85	0.0004
	ATV/r	103	18.20	15.75, 20.45	2.50	1.70, 3.78	
	DRV/r	95	18.10	16.50, 20.10	2.40	1.67, 3.50	
	DTG	97	18.50	16.80, 20.40	2.77	1.93, 4.00	
Waist Circumference	LPV/r	99	58.00	54.70, 62.00	3.00	0.33, 5.10	0.0028
	ATV/r	103	59.40	53.60, 61.80	4.63	2.02, 6.53	
	DRV/r	95	57.80	54.80, 61.80	3.93	1.70, 6.57	
	DTG	97	60.10	55.50, 63.80	4.67	2.13, 6.73	
Midthigh Circumference	LPV/r	99	34.35	31.00, 38.10	3.07	1.57, 4.70	0.0003
	ATV/r	103	33.80	29.90, 37.50	4.47	2.62, 5.80	
	DRV/r	95	34.50	30.50, 38.20	3.90	2.30, 5.70	
	DTG	97	34.80	31.50, 38.00	4.40	2.90, 6.20	
Calf Circumference	LPV/r	99	25.05	22.50, 28.10	2.20	1.27, 3.03	0.0001
	ATV/r	103	24.55	21.35, 27.55	3.00	1.85, 3.90	
	DRV/r	95	25.20	22.40, 28.00	2.67	1.93, 3.50	
	DTG	97	25.22	23.00, 27.40	3.20	2.07, 4.33	

Body Region	ART Regimen	N	Baseline	IQR (cm)	Median Change (cm)	IQR (cm)	Kruskal-Wallis *p*-value
Body Region	**ART Regimen**	**N**	**Baseline**	**IQR (cm)**	**Median Change (cm)**	**IQR (cm)**	**Kruskal-Wallis *p*-value**
Hip Circumference	LPV/r	99	62.15	56.80, 70.00	5.30	3.27, 7.70	0.0019
	ATV/r	103	61.50	54.30, 70.10	7.10	4.73, 9.28	
	DRV/r	95	62.40	56.60, 70.00	6.40	4.47, 8.53	
	DTG	97	63.60	58.90, 70.10	7.57	4.60, 9.90	
WHtR Z-scores	**ART Regimen**		**Baseline**	**IQR(Z-score)**	**Median change (Z-score)**	**IQR(Z-score)**	**Kruskal-Wallis *p*-value**
	LPV/r	91	-0.28	-0.76, 0.11	-0.04	-0.48, 0.22	0.2924
	ATV/r	96	-0.23	-0.58, 0.19	0.001	-0.33, 0.30	
	DRV/r	97	-0.27	-0.58, 0.67	-0.02	-0.41, 0.40	
	DTG	104	-0.27	-0.58, 0.07	0.05	-0.27, 0.43	

DTG=dolutegravir, ATV/r=Atazanavir/ritonavir, DRV/r=darunavir/ritonavir, LPV/r=Lopinavir/ritonavir, WHtR=Waist-to-height ratio, MUAC=Mid-upper arm circumference

Table 5: Skin fold thickness at baseline and change at 96 weeks(n=441)

Body region	Anchor drug	N	Baseline (mm) (IQR)	Median Change (mm) (IQR)	Kruskal, Wallis p-value (change)
Biceps	LPV/r	110	2.7 (1.7, 3.3)	0.3 (0.0, 1.2)	0.7005
	ATV/r	109	2.0 (1.3, 3.0)	0.7 (0.0, 2.0)	
	DRV/r	107	2.0 (1.5, 3.2)	0.8 (0.0, 1.3)	
	DTG	106	2.0 (1.3, 3.0)	0.7 (0.0, 1.5)	
Triceps	LPV/r	110	3.0 (1.0, 5.0)	0.5 (0.0, 1.8)	0.9868
	ATV/r	109	2.7 (1.0, 5.0)	0.7 (0.0, 1.3)	
	DRV/r	107	3.0 (1.0, 5.0)	0.7 (0.0, 2.0)	
	DTG	106	2.7 (1.3, 4.3)	0.3 (0.0, 1.8)	
Subscapular	LPV/r	110	3.3 (1.8, 4.8)	0.2 (0.0, 1.5)	0.2839
	ATV/r	109	3.0 (1.8, 4.8)	0.7 (0.0, 1.7)	
	DRV/r	107	3.3 (2.0, 5.0)	0.3 (0.0, 1.7)	
	DTG	106	3.0 (2.0, 4.7)	0.8 (0.0, 1.5)	
Suprailiac	LPV/r	110	3.0 (1.7, 4.7)	0.3 (0.0, 2.0)	0.5186
	ATV/r	109	2.7 (1.3, 4.7)	0.7 (0.0, 2.0)	
	DRV/r	107	3.0 (2.0, 5.3)	0.7 (0.0, 2.3)	
	DTG	106	2.8 (2.0, 4.8)	0.8 (0.0, 2.0)	

Midthigh	LPV/r	110	3.2 (0.7, 6.3)	0.7 (0.0, 2.7)	0.3489
	ATV/r	109	3.0 (1.0, 6.0)	0.8 (0.0, 2.0)	
	DRV/r	107	3.0 (1.0, 7.0)	0.7 (0.0, 3.0)	
	DTG	106	3.0 (1.0, 5.0)	1.0 (0.0, 3.7)	
Calf	LPV/r	110	3.0 (0.7, 6.3)	0.2 (0.0, 2.0)	0.6817
	ATV/r	109	3.0 (0.7, 6.3)	0.7 (0.0, 2.2)	
	DRV/r	106	3.0 (0.7, 6.7)	0.7 (0.0, 1.7)	
	DTG	106	2.7 (0.7, 5.7)	0.7 (0.0, 2.3)	

DTG=Dolutegravir, ATV/r=Atazanavir/ritonavir, DRV/r=darunavir/ritonavir, LPV/r=Lopinavir/ritonavir. Note: only measured at 3 sites