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# Efavirenz is associated with higher bone mass in South African children with HIV

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## Abstract

**Background—**We investigate if switching from a ritonavir-boosted lopinavir (LPV/r)-based to an efavirenz-based antiretroviral therapy (ART) regimen is associated with beneficial bone development.

**Methods—**The CHANGES Bone Study follows HIV-infected children who participated in a non-inferiority randomized trial in Johannesburg, South Africa evaluating the safety and efficacy of pre-emptive switching to efavirenz (N=106) compared to remaining on LPV/r (N=113). HIV-uninfected children were also recruited. Whole body (WB) and lumbar spine bone mineral content (BMC) were assessed by dual-energy X-ray absorptiometry (DXA) at a cross-sectional visit. BMC Z-scores adjusted for sex, age, and height were generated. Physical activity (PA) and dietary intake were assessed. CD4 percentage and viral load were measured. We compared bone indices of HIV-infected to HIV-uninfected children and LPV/r to efavirenz by intent-to-treat.

**Results—**The 219 HIV-infected (52% male) and 219 HIV-uninfected (55% male) children were 6.4 and 7.0 years of age, respectively. Mean ART duration for HIV-infected children was 5.7 years. WB BMC Z-score was 0.17 lower for HIV-infected children compared to HIV-uninfected children after adjustment for PA, dietary vitamin D and calcium (p=0.03). WB BMC Z-score was 0.55 higher for HIV-infected children switched to efavirenz compared to those remaining on

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LPV/r after adjustment for PA, dietary vitamin D and calcium, CD4 percentage and viral load ($p<0.0001$).

**Conclusion—**South African HIV-infected children receiving ART have lower bone mass compared to HIV-uninfected controls. Accrued bone mass is positively associated with switching to efavirenz-based ART compared to remaining on LPV/r, providing additional rationale for limiting LPV/r exposure once viral suppression has been achieved.

### Keywords

bone; antiretroviral therapy; efavirenz; children; pediatrics

## Introduction

Advances in antiretroviral therapy (ART) have altered the disease course for the estimated 2.6 million children in the world living with HIV [1]. For those with perinatally-acquired HIV, initiation of ART early in life has resulted in declines in mortality and survival well into adulthood [2–4]. Developing management approaches that optimize long-term outcomes for those with perinatally-acquired HIV has emerged as an important area of clinical and public health research.

Among HIV-infected adults, the incidence of a number of chronic conditions, such as cardiovascular disease and osteoporosis, is increased [5]. The increased risk of osteoporosis and bone fractures in HIV-infected adults compared to the general population [6, 7] is likely due to multiple factors, including effects of HIV-1 viral proteins, inflammatory cytokines and ART on bone cells and bone turnover [8–13]. Lower bone mass accrual is also reported in HIV-infected children and adolescents [14–24]. While manifest later in life, osteoporosis has its origins in patterns of bone growth and turnover in childhood and adolescence when 85–90% of adult peak bone mass is attained [25]. Impaired skeletal growth during these critical periods may compromise bone microarchitecture and peak bone mass that are important determinants of bone strength and fracture risk in later life [26–28]. Few prior studies conducted in children, however, reflect current standards of care that emphasize initiation of ART early in life regardless of clinical or immunologic status. In addition, little is known about bone development among HIV-infected children in sub-Saharan Africa where >90% of HIV-infected youth live [1].

Ritonavir-boosted lopinavir (LPV/r) is recommended by the World Health Organization and widely used as part of the first line regimen for HIV-infected children. While ART regimens containing LPV/r are potent inhibitors of HIV replication and provide a high genetic barrier to emergence of drug resistance, there are a number of limitations for long-term use including poor palatability, dyslipidemias and lipodystrophy [29]. Our group has demonstrated the safety and efficacy of pre-emptive switching to non-nucleoside reverse transcriptase inhibitors in children on LPV/r who have well-suppressed virus [30–32]. Specifically, we recently reported the non-inferiority in virological control through 48 weeks of switching to EFV-based therapy compared to remaining on LPV/r [32]. The objective of the current study was to first to compare bone mass of South African HIV-infected children initiated on ART early in life to an HIV-uninfected control group and secondly, as follow-up

of the children enrolled in the non-inferiority trial, to investigate whether a switch from LPV/r to efavirenz for HIV-infected children well-controlled on ART is associated with improved bone development.

## Methods

### Study population

We present a cross-sectional analysis of 219 HIV-infected and 219 HIV-uninfected children enrolled in the CHANGES Bone Study in Johannesburg, South Africa. The 219 HIV-infected children were enrolled into the study after completion of a non-inferiority randomized clinical trial evaluating the safety and efficacy of pre-emptive switching to efavirenz compared to remaining on LPV/r [32]. All children had been exposed to nevirapine used for prevention of mother-to-child transmission (PMTCT) and initiated on a protease inhibitor-based regimen, mostly LPV/r, at a mean age of 9 months. To be eligible for the clinical trial, children had to be virally suppressed on LPV/r at 3–5 years of age before being randomized to either remain on LPV/r or switch to efavirenz. A group of 219 healthy HIV-uninfected children were recruited for the present study from among eligible siblings or household members of HIV-infected study subjects or those attending the study site for routine outpatient health services. HIV-uninfected children with known chronic medical conditions, including known bone, renal, or liver disease, malabsorption syndrome, or inflammatory bowel disease, were excluded from enrollment.

### Measurements and procedures

At the study visit, demographic data were collected and all participants underwent physical examinations to obtain anthropometric measures and to assess pubertal development. Weight was measured to the nearest 0.1 kg using a digital scale and standing height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by height ($m^2$). Weight- (WAZ), height- (HAZ), and BMI-for-age (BAZ) z-scores were calculated using World Health Organization standards [33]. Underweight was defined as WAZ <-2 and stunted was defined as HAZ<-2. Pubertal status was assessed and graded by trained study physicians according the method of Tanner [34, 35]. Females were staged using the highest score of either breast or pubic hair development. At the visit, blood was drawn and CD4 percentages and HIV RNA levels for HIV-infected children were measured (Roche COBAS TaqMan HIV-1 test).

Bone area (BA) in $cm^2$, bone mineral content (BMC) in grams, and areal bone mineral density (BMD) in grams/$cm^2$ of the whole body (WB) (sub-total excluding the head) and lumbar spine (LS) (L1-4) were determined by dual-energy X-ray absorptiometry (DXA) using a Hologic Discovery Wi bone densitometer with Apex software version 3.4 (Hologic Inc, Bedford, MA, USA). Standard operational procedures for obtaining DXA images, data transfer, image reading, quality assurance, and data management were established involving the Department of Radiology of Rahima Moosa Mother and Child Hospital (Johannesburg, South Africa) and Image Reading Center (New York, NY). All scans were analyzed by a single technician blinded to the HIV status and treatments of the participants. LS scans performed in fast array mode were used for this analysis. DXA provides a measure of areal

BMD, not volumetric BMD, that systematically underestimates bone mass-for-age in small-for-age children and the International Society for Clinical Densitometry recommends adjusting DXA results for short stature [36]; therefore, we calculated WB and LS BMC Z-scores adjusted for sex, age, race, and height-age Z-score based on reference norms from the United States Bone Mineral Density in Childhood Study [37]. This method accounts for considerable size deficits for children with perinatally-acquired HIV-infection, and correlates well with volumetric BMD determined by quantitative computed tomography [38, 39].

The frequency and duration of physical activities and sedentary behaviors were obtained with a validated interviewer-administered recall questionnaire that detailed all physical activity and inactivity over the past 7 days [40, 41]. The number of minutes of vigorous physical activity per week was calculated as previously described and the proportion of children meeting World Health Organization recommendations for physical activity was determined [42, 43]. Dietary intake was collected by an interviewer-administered 24 hour recall of the previous day's intake. Total calcium (mg) and vitamin D (IU) intake per day was calculated by the FoodFinder3, software program which includes the South African Food Composition Database [44].

Signed informed consent was provided by each child's parent or guardian. Children provided assent if they were at least 7 years old and able to understand. The study was approved by the Institutional Review Boards of Columbia University (New York, New York) and the University of the Witwatersrand (Johannesburg, South Africa).

## Statistical analysis

We compared characteristics as well as WB and LS BMC, BMD, and BMC Z-scores between 1) HIV-infected and HIV-uninfected children and 2) HIV-infected children randomized to remain on LPV/r and HIV-infected children randomized to switch to efavirenz by intent-to-treat analysis. Linear regression was used to adjust comparisons of Z-scores between the HIV-infected and HIV-uninfected groups for physical activity and dietary vitamin D and calcium, as well to adjust comparisons of Z-scores between children on LPV/r and children on efavirenz for physical activity and dietary vitamin D and calcium, as well as viral load and CD4 percentage and current NRTI backbone (abacavir + lamivudine, stavudine + lamivudine, or zidovudine + lamivudine). All analyses were stratified by sex. Sensitivity analyses were conducted excluding the 12 children who were Tanner Stage 2 at the time of assessment. We also repeated all analyses "as-treated", comparing bone outcomes for the HIV-infected children based on their current treatment groups (LPV/r vs. efavirenz). In addition, current duration on efavirenz as both a categorical (currently not on efavirenz, on efavirenz 0–24 months, on efavirenz 24 months or greater) and as a continuous variable was assessed. Where applicable, a chi-squared or Fisher's exact test was used to compare proportions, a t-test was used to compare means, and a Wilcoxon rank sum test was used to compare medians. All $p$-values are 2-tailed and $p$-values $<0.05$ were considered statistically significant. All statistical calculations were performed using SAS version 9.4 (Cary, North Carolina, USA).

## Results

Demographic and anthropometric characteristics of the 219 HIV-infected children (49% male) and 219 HIV-uninfected children (55% male) are presented in Table 1. HIV-infected children were younger than controls (mean 6.4 vs. 7.0 years). As expected, WAZ was lower in the HIV-infected group and 11% of the children were underweight compared to 3% in the HIV-uninfected group. Similarly, HAZ was lower in the HIV-infected group and 28% of the children were stunted compared to 9% in the HIV-uninfected group. HIV-infected children engaged in approximately 2 hours fewer of vigorous activity compared to HIV-uninfected children. Mean reported dietary intake of vitamin D (IU/day) and calcium (mg/day) was low in both groups.

Characteristics of the HIV-infected children grouped according to original randomization are presented in Table 2. The children were enrolled into the present study 1–4 years (mean 2.1 years) after randomization in the clinical trial. All HIV-infected children were on a three drug ART regimen. In addition to either LPV/r or efavirenz, all children were receiving two nucleoside reverse transcriptase inhibitors (NRTIs). All were receiving lamivudine and either abacavir, zidovudine, or stavudine. None had any past or current use of tenofovir. None were receiving corticosteroids or antiepileptic medications. The mean (SD) duration on treatment for HIV-infected children was 5.7 (1.1) years (range 2.8–8.7). At the time of evaluation, 93.6% of children had an HIV-1 RNA quantity <400 copies/mL and a mean (SD) CD4 percentage 37.3 (7.1).

DXA results for HIV-infected and uninfected children are presented in Table 3. HIV-infected children had significantly lower WB mean BMC (415 vs. 490 g, $p<0.0001$) and BMD (0.51 vs. 0.55 g/cm$^2$, $p<0.001$) compared to the HIV-uninfected group. The BMC Z-score was 0.15 lower in the HIV-infected group compared to the HIV-uninfected group (−0.95 vs. −0.80, $p=0.046$). The mean LS BMC and BMD were also significantly lower in the HIV-infected groups (14.4 vs 16.1 g, $p<0.0001$ and 0.46 vs. 0.49 g/cm$^2$, $p<0.0001$, respectively) but no differences in LS BMC Z-score were observed. Differences in BMC and BMC Z-score at the WB and LS were similar when we excluded the children who were Tanner Stage 2 from the analysis.

Children randomized to switch to efavirenz had a higher WB mean BMC (425 vs. 406 g, $p=0.14$) and BMD (0.52 vs. 0.50 g/cm$^2$, $p=0.016$) compared to children randomized to remain on LPV/r. The mean LS BMC and BMD were also higher for children in the efavirenz vs. LPV/r group (14.8 vs. 14.1 g, $p=0.098$ and 0.47 vs. 0.45 g/cm$^2$, $p=0.009$, respectively). The BMC Z-score for children in the LPV/r group was 0.52 lower than the children in the efavirenz group (−1.20 vs. −0.68, $p<0.001$).

After adjustment for physical activity and dietary vitamin D and calcium with linear regression, WB BMC Z-score remained 0.17 lower for HIV-infected children compared to HIV-uninfected children ($p=0.03$). WB BMC Z-score remained approximately 0.55 higher for HIV-infected children in the efavirenz compared to LPV/r group after adjustment for physical activity, dietary vitamin D and calcium, CD4 percentage and viral load ($p<0.0001$). LS BMC Z-score remained approximately 0.50 higher for HIV-infected children in the

efavirenz compared to LPV/r group after adjustment for physical activity, dietary vitamin D and calcium, CD4 percentage and viral load (p=0.0001). WB and LS BMC Z-score differences between the LPV/r and efavirenz groups were similar after further adjustment for current NRTI backbone.

Additional analyses were performed stratified by sex. HIV-infected boys had lower WB BMC Z-score (−0.84 vs. −0.61, p=0.027) compared to HIV-uninfected boys but LS BMC Z-scores were not significantly different (−0.12 vs. −0.19, p=0.53). WB BMC Z-scores were significantly lower in boys on LPV/r compared to boys on efavirenz (−1.02 vs. −0.67, p=0.03). LS BMC Z-score was lower in boys on LPV/r compared to boys on efavirenz albeit not significant (−0.23 vs. −0.01, p=0.15). No statistically significant differences were observed between HIV-infected girls and HIV-uninfected girls in WB BMC Z-score (−1.05 vs. −1.02, p=0.79) or LS BMC Z-score (−0.33 vs −0.47, p=0.26). Girls on LPV/r had lower WB BMC Z-score (−1.37 vs. −0.69, p<0.001) and LS BMC Z-score compared to girls on efavirenz (−0.64 vs. 0.03, p=0.0002).

The treatment regimen differences were similar between the intent-to-treat analysis reported above and in as-treated analyses. Mean WB BMC Z-score of HIV-infected children currently on LPV/r, on efavirenz for 0–24 months, and on efavirenz for 24 months or greater are presented in Figure 1. There was a trend towards a greater mean WB BMC Z-score with increased duration on efavirenz (p<0.0001), although there was no significant difference in WB BMC Z-score between children on efavirenz for 0–24 months and 24 months or greater. In an additional regression analysis treating current time on efavirenz as a continuous variable, for every one month increase in current duration on efavirenz use, WB BMC Z-score increased by 0.02 (p=0.0002).

## Discussion

Deficits in bone mass accrual are detectable in HIV-infected children who initiated ART early and have well-controlled disease. Furthermore, HIV-infected children maintained on a LPV/r-containing regimen ART regimen had lower accrued bone mass compared to those switched to an efavirenz-containing regimen. To our knowledge, this is the first assessment of bone mass in a population of HIV-infected children living in sub-Saharan Africa, the region where >90% of HIV-infected children reside [1].

The finding that bone mass is better among those switched from a LPV/r-based regimen to an efavirenz-based regimen suggests that some of the reduction in attained BMC observed in HIV-infected children compared to uninfected children may be related to LPV/r treatment. Lower bone mass associated with LPV/r has been previously reported [14, 23]. In addition, studies conducted in HIV-infected adults report bone loss in association with many but not all protease inhibitors. A meta-analysis of cross-sectional studies by Brown and Qaqish found an odds ratio for osteoporosis of 1.57 (95% CI 1.05–2.34) in HIV-infected persons treated with protease inhibitors compared with those on non-protease inhibitor-containing ART regimens [6]. The putative mechanisms for disruption of bone homeostasis by protease inhibitors are through direct toxicity to bone cells or bone cell precursors but may vary by specific drug agents [45]. *In vitro* and *in vivo* studies have demonstrated that a number of

protease inhibitor agents (including ritonavir) inhibit osteoclastogenesis by impairing RANKL-induced signaling [11, 46]. Increased differentiation of peripheral blood mononuclear cells into osteoclasts by upregulation of growth factors and suppression of antagonist transcripts *in vitro* is also reported with ritonavir [47–49]. Other potential pathways involve drug-induced reductions in mesenchymal stem cell differentiation to osteoblasts as well as alterations in osteoblast gene expression and decreased bone formation [9, 50]. Protease inhibitors may also inhibit conversion of 25-hydroxyvitamin D to the bioactive metabolite 1,25-dihydroxyvitamin D by suppression of 25- and 1a-hydroxylase and thus impair bone formation via disruption of calcium homeostasis [51].

LPV/r, when used in combination with other agents, is a potent inhibitor of HIV replication and is widely used in young children. It was recommended initially as first-line ART for children because drugs used for PMTCT select NNRTI-resistant virus in the majority of infants with vertically-acquired HIV [52]. Furthermore, LPV/r was shown in randomized trials to have superior virological efficacy among both PMTCT-exposed and unexposed infants and young children [53]. For these reasons, LPV/r is recommended as part of first line ART for infants and young children (<3 years) by the World Health Organization [54]. However, LPV/r has a number of limitations of long-term use including poor palatability, dyslipidemia and lipodystrophy [29]. The greater BMC among children who switched to efavirenz from LPV/r we observed may provide additional rationale for limiting LPV/r exposure once viral suppression has been achieved [30, 31, 55].

In addition to ART, HIV-1 viral proteins may also have direct and indirect adverse effects on bone cells. *In vitro* studies demonstrate that exposure of osteoblast precursors to HIV proteins results in decreased osteogenesis [13], and exposure of osteoclast precursors to HIV proteins results increased osteoclast activation and differentiation [8]. HIV viral proteins have also been shown to induce T cell activation and elaboration of TNFα and RANKL, which induce osteoclastic bone resorption[8]. In our study, bone mass was reduced in HIV-infected children despite viral suppression. Residual low grade viral replication and immune activation are known to persist despite effective ART [56, 57]; therefore, the decreased BMD accrual in our HIV-infected children may be due to the effects of ART exposure as well as the direct effects of HIV viral replication and indirect effects of immune activation on bone cells.

Multiple studies report reduced bone mass accrual among children and adolescents with HIV compared to HIV-uninfected children [14, 21, 58]. These studies have assessed bone mass accrual largely by DXA. Whether these reductions in bone mass largely measured by DXA are solely due to smaller body size has not been established satisfactorily due mainly to inconsistencies in adjusting for smaller body size and selection of comparison group or reference norms. In this study, we observed differences between HIV infected and HIV-uninfected children in BMC Z-scores adjusted for age, sex, race, and HAZ, which account for body size difference, suggesting that decrements in bone mass are out of proportion to reductions in size. Neither do the decreases in bone accrual appear to be due to dietary intake of vitamin D and calcium or physical activity differences.

Although DXA does not distinguish between cortical (or compact) and trabecular bone, we found the differences between HIV-infected and uninfected subjects more consistently in WB BMC and BMD rather than LS similar to a report by Jacobson *et al.* [59]. Skeletal bone mass is comprised of 80% cortical bone which provides much of the mechanical strength and 20% trabecular bone, whereas the spine is approximately 20% cortical bone and 80% trabecular bone [60] and the distal ends of long bones (e.g. distal radius) is also comprised largely of trabecular bone. Although caution is warranted in interpretation, these findings suggest that during childhood, cortical bone accrual may be more vulnerable to effects of LPV/r. Studies that apply imaging methods such as quantitative computed tomography which provide measures of cortical and trabecular bone are needed to better understand and the importance of these findings to mechanical bone properties and strength and potential for increasing fracture risk.

In this sample the HIV-infected boys appear to have worse measures of bone mass compared to HIV-uninfected boys. This pattern of sex differences in bone outcomes with more unfavorable findings among boys has been reported by others especially after puberty. Jacobson *et al.* in a U.S. study of 48 perinatally HIV-infected males and females reported sex differences in post-pubertal bone measures, but not at earlier stages of biologic maturation [59]. Post-pubertal HIV-infected males had lower adjusted WB BMC, as well as adjusted WB and LS BMD than controls. Another study conducted in Brazil found no sex differences in patterns of bone measures between HIV-infected boys and girls [61]. Determining whether the sex differences we observed persist throughout the period of skeletal maturation is an important area of future research.

The inclusion of an HIV-uninfected comparison group is a strength. We chose to use population norms drawn from a large study in the United States as there are none available for children in this age group in South Africa or another African country which would have been preferable. Thus, our main outcomes cannot be used for identifying individual study subjects with low bone or estimating the prevalence of low bone mass (e.g. Z-score <-2) as there are important population differences in bone mass characteristics [37]. In addition, although we were able to measure other potential confounders including physical activity, and dietary vitamin D and calcium, these were based on self-report and are subject to non-differential misclassification. Although we were unable to assess independent effects of NRTI on bone, exposure to stavudine vs. abacavir vs. zidovudine did not attenuate the differences between LPV/r and efavirenz. Finally, we are limited by the cross-sectional nature of the study, as we did not have a measure of bone mass available at randomization in the trial.

Bone mass accrual during childhood and adolescence is a major determinant of adult peak bone mass, which in turn is an important determinant of osteoporosis later in life and lifetime fracture risk. Maximizing bone accumulation during childhood may have immediate benefit by reducing fractures in adolescence [62]; however potential deferred benefits of decreasing osteoporosis and fracture in older age are far more important [63]. Mathematical models indicate that relatively small increases (10%) in peak bone mass acquisition in healthy females could delay onset of osteoporosis by as many as 13 years [64], underscoring the importance of identifying strategies to optimize bone acquisition in HIV.

In conclusion, accrued bone mass is positively associated with switching to efavirenz-based ART compared to remaining on LPV/r and switching may help children achieve better peak bone mass. Use of “bone friendly” drugs may be beneficial for bone health in children with HIV.

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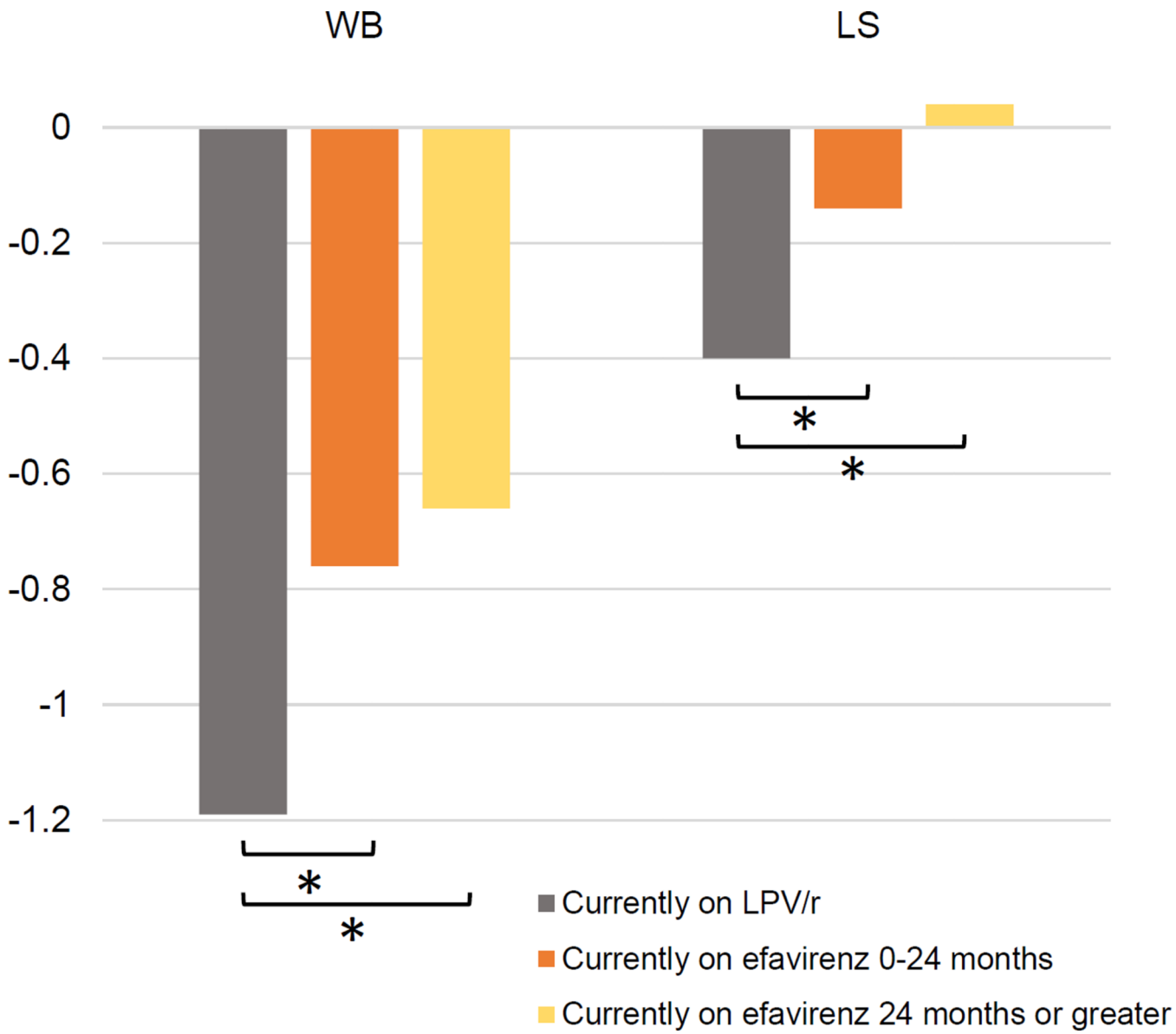


**Figure 1.**

Mean BMC-Z-score of the whole body (WB) and lumbar spine (LS) of HIV-infected infected children currently on LPV/r, on efavirenz for 0–24 months, and on efavirenz for 24 months or greater (*indicates $p<0.05$)

## Table 1

Characteristics of 219 HIV-infected and 219 HIV-uninfected children in Johannesburg, South Africa

| Characteristic | HIV-infected (N=219) | HIV-uninfected (N=219) | P |
|---|---|---|---|
| Male, N (%) | 107 (48.9) | 120 (54.8) | 0.21 |
| Age in years, Mean (SD) | 6.4 (1.2) | 7.0 (1.5) | <0.0001 |
| Weight in kg, Mean (SD) | 19.2 (3.9) | 22.4 (5.4) | <0.0001 |
| WAZ, Mean (SD) | −0.83 (0.9) | −0.30 (1.1) | <0.0001 |
| Underweight, N (%) | 24 (11.0) | 6 (2.7) | 0.0007 |
| Height in cm, Mean (SD) | 110 (8.3) | 117 (9.6) | <0.0001 |
| HAZ, Mean (SD) | −1.40 (0.9) | −0.82 (0.9) | <0.0001 |
| Stunted, N (%) | 61 (27.9) | 19 (8.7) | <0.0001 |
| BMI, Mean (SD) | 15.7 (1.6) | 16.2 (2.1) | 0.002 |
| BAZ, Mean (SD) | 0.08 (1.0) | 0.27 (1.1) | 0.047 |
| Tanner Stage 1, N (%) | 215 (98.2) | 210 (95.9) | 0.16 |
| Vigorous physical activity in minutes per week, Median (IQR) | 480 (228, 900) | 630 (255, 1095) | 0.05 |
| Meets WHO physical activity guidelines, N (%) | 182 (83.5) | 183 (83.6) | 0.98 |
| Vitamin D in IU, Median (IQR) | 42 (14, 177) | 59 (25, 202) | 0.017 |
| Calcium in mg, Median (IQR) | 276 (155, 459) | 244 (154, 421) | 0.19 |

Abbreviations: WAZ – weight-for-age Z-score; HAZ – height-for-age Z-score; BMI – body mass index; BAZ – BMI-for-age Z-score

## Table 2

Characteristics of 219 HIV-infected children randomized to remain on a ritonavir-boosted lopinavir (LPV/r)-based regimen (N=113) or switch to an efavirenz-based regimen (N=106)

| Characteristic | LPV/r (N=113) | Efavirenz (N=106) | P |
|---|---|---|---|
| Male, N (%) | 53 (46.9) | 54 (50.9) | 0.55 |
| Age in years, Mean (SD) | 6.4 (1.3) | 6.3 (1.2) | 0.74 |
| Weight in kg, Mean (SD) | 19.0 (3.6) | 19.4 (4.1) | 0.49 |
| WAZ, Mean (SD) | −0.90 (0.9) | −0.76 (0.9) | 0.25 |
| Underweight, N (%) | 15 (13.3) | 9 (8.5) | 0.26 |
| Height in cm, Mean (SD) | 111 (8.6) | 110 (8.0) | 0.51 |
| HAZ, Mean (SD) | −1.36 (0.9) | −1.45 (0.9) | 0.48 |
| Stunted, N (%) | 30 (26.6) | 31 (29.3) | 0.66 |
| BMI, Mean (SD) | 15.4 (1.4) | 15.9 (1.7) | 0.018 |
| BAZ, Mean (SD) | −0.05 (0.9) | 0.21 (1.0) | 0.046 |
| Tanner Stage 1, N (%) | 113 (100.0) | 102 (96.2) | 0.053 |
| Vigorous physical activity in minutes per week, Median (IQR) | 455 (230, 900) | 505 (225, 870) | 0.99 |
| Meets WHO physical activity guidelines, N (%) | 92 (82.1) | 90 (84.9) | 0.58 |
| Vitamin D in IU, Median (IQR) | 39 (13, 168) | 43 (18, 183) | 0.78 |
| Calcium in mg, Median (IQR) | 290 (162, 504) | 252 (143, 455) | 0.13 |
| Age at ART start in months, Mean (SD) | 9.2 (6.7) | 8.5 (6.8) | 0.49 |
| Age at ART start in months, N (%)<br><6<br>6–12<br>12–24<br>>24 | 48 (42.5)<br>33 (29.2)<br>28 (24.8)<br>4 (3.5) | 58 (54.7)<br>23 (21.7)<br>23 (21.7)<br>2 (1.9) | 0.30 |
| Treatment duration in years, Mean (SD) | 5.7 (1.1) | 5.7 (1.1) | 0.98 |
| Time since randomization in years, Mean (SD) | 2.2 (0.6) | 2.1 (0.6) | 0.54 |
| Remained on randomized regimen at time of bone assessment, N (%) | 102 (90.3) | 99 (93.4) | 0.40 |
| Current NRTI backbone, N (%)<br>Lamivudine, abacavir<br>Lamivudine, zidovudine<br>Lamivudine, stavudine | 82 (72.6)<br>4 (3.5)<br>27 (23.9) | 81 (76.4)<br>1 (0.9)<br>24 (22.6) | 0.50 |
| Plasma HIV-1 RNA <400 copies/mL, N (%) | 92.9 | 94.3 | 0.67 |
| CD4 percentage, Mean (SD) | 35.7 (6.6) | 39.0 (7.2) | 0.0006 |

Abbreviations: WAZ – weight-for-age Z-score; HAZ – height-for-age Z-score; BMI – body mass index; BAZ – BMI-for-age Z-score; ART – antiretroviral therapy

**Table 3**

Bone parameters by dual x-ray absorptiometry of 219 HIV-infected children (including 113 randomized to remain on LPV/r and 106 randomized to switch to efavirenz) and 219 HIV-uninfected children in Johannesburg, South Africa, Mean (SD)

| Measurement | HIV-infected (N=219) | HIV-uninfected (N=219) | P | LPV/r (N=113) | Efavirenz (N=106) | P |
|---|---|---|---|---|---|---|
| **Total Body** | | | | | | |
| BMC, g | 415 (97) | 490 (119) | <0.001 | 406 (98) | 425 (97) | 0.14 |
| BMC Z-score[1] | −0.95 (0.83) | −0.80 (0.77) | 0.046 | −1.20 (0.82) | −0.68 (0.76) | <0.001 |
| BMD, g/cm$^2$ | 0.51 (0.06) | 0.55 (0.07) | <0.001 | 0.50 (0.06) | 0.52 (0.06) | 0.016 |
| **Lumbar Spine** | | | | | | |
| BMC, g | 14.4 (3.1) | 16.1 (3.5) | <0.001 | 14.1 (3.0) | 14.8 (3.1) | 0.098 |
| BMC Z-score[1] | −0.23 (0.89) | −0.32 (0.85) | 0.28 | −0.45 (0.89) | 0.01 (0.84) | 0.0001 |
| BMD, g/cm$^2$ | 0.46 (0.06) | 0.49 (0.07) | <0.001 | 0.45 (0.06) | 0.47 (0.07) | 0.009 |

Note:

[1]Z-scores from Bone Mineral Density in Childhood Study (adjusted for age, sex, race, and height-for-age Z-score)

Abbreviations: BMC – bone mineral content; BMD – bone mineral density