Weight and lean body mass change with antiretroviral initiation and impact on bone mineral density

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Objective: To compare the effect that initiating different antiretroviral therapy (ART) regimens has on weight, BMI, and lean body mass (LBM) and explore how changes in body composition are associated with bone mineral density (BMD).

Methods: A5224s was a sub-study of A5202, a prospective trial of 1857 ART-naive participants randomized to blinded abacavir–lamivudine (ABC/3TC) or tenofovir DF–emtricitabine (TDF/FTC) with open-label efavirenz (EFV) or atazanavir–ritonavir (ATV/r). All participants underwent dual-energy absorptiometry (DXA) and abdominal computed tomography for body composition. Analyses used two-sample *t*-tests and linear regression.

Results: A5224s included 269 participants: 85% men, 47% white non-Hispanic, median age 38 years, HIV-1 RNA 4.6 $\log_{10}$ copies/ml, and $CD4^+$ cell count 233 cells/μl. Overall, significant gains occurred in weight, BMI, and LBM at 96 weeks postrandomization (all $P < 0.001$). Assignment to ATV/r (vs. EFV) resulted in significantly greater weight (mean difference 3.35 kg) and BMI gain (0.88 kg/m^2; both $P = 0.02$), but not LBM (0.67 kg; $P = 0.15$), whereas ABC/3TC and TDF/FTC were not significantly different ($P \geq 0.10$). In multivariable analysis, only lower baseline $CD4^+$ cell count and higher HIV-1 RNA were associated with greater increase in weight, BMI, or LBM. In multivariable analyses, increased LBM was associated with an increased hip BMD.

Conclusion: ABC/3TC vs. TDF/FTC did not differ in change in weight, BMI, or LBM; ATV/r vs. EFV resulted in greater weight and BMI gain but not LBM. A positive association between increased LBM and increased hip BMD should be further investigated through prospective interventional studies to verify the impact of increased LBM on hip BMD.

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Introduction

Body weight is considered a key determinant of bone mineral density (BMD), however the body weight component among lean mass, peripheral fat mass or visceral adipose tissue with the greatest impact on bone mass is debated [1,2]. Lean body mass (LBM) augments BMD through mechanical load forces and LBM is associated with lower risk of bone fractures [3,4]. Fat mass can have a positive interaction on bone through skeletal

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loading and adipocyte hormone production, but inflammatory cytokines produced in visceral adipose tissue may exacerbate bone loss [5]. Furthermore, the impact of total fat mass and total LBM on BMD may differ by age, sex, race, and skeletal site [6].

Low BMD is reported across multiple cohorts of both men and women with HIV-infection, with a strong association between lower baseline weight and both lower baseline BMD [7,8] and a greater decline in BMD with antiretroviral therapy (ART) initiation [9–11]. Prior to initiating ART, individuals with HIV infection have lower BMD than the general population [12]. Lower weight appears to mediate a significant proportion of the BMD differences [13]. The initiation of ART is often characterized by weight gain [14–17], and it is hypothesized that these changes in weight help to stabilize BMD after the initial loss in BMD observed with ART initiation [13]. Changes in central and peripheral fat with ART initiation and ART regimens are also well described, however a gain in adiposity could be associated with a myriad of other health problems [18–20]. Despite a strong association between greater muscularity and lower mortality [21,22], comparisons of the role of individual ART on LBM and the contribution of body composition components on BMD have not been well defined.

We have previously presented data on changes after ART initiation in BMD, peripheral fat, and visceral adipose tissue from AIDS Clinical Trials Group A5224s, a substudy of A5202, in which HIV-infected treatment-naive participants were randomized in a double-blinded fashion to abacavir/lamivudine (ABC/3TC) or tenofovir DF/emtricitabine (TDF/FTC) with open-label efavirenz (EFV) or atazanavir–ritonavir (ATV/r) [20,23]. Briefly, randomization to TDF/FTC led to a greater decrease in spine and hip BMD, less gain in limb fat, and no significant difference in change in visceral fat compared with ABC/3TC [20,23]. Assignment to ATV/r led to greater losses in spine but not hip BMD, and was associated with significantly greater increase in limb fat and a trend towards greater increase in visceral fat compared with EFV. Here, we compare the changes in weight, BMI, and LBM between the nucleoside reverse transcriptase inhibitor (NRTI) components and the nonnucleoside reverse transcriptase inhibitor/protease inhibitor (NNRTI/PI) components from A5224s. We also explore the association of changes in BMI, LBM, and fat mass with changes in BMD.

Methods

A5224s was a sub-study of AIDS Clinical Trials Group A5202, in which ART-naive persons aged at least 16 years and with an HIV-1 RNA load greater than 1000 copies/ml received TDF/FTC or ABC/3TC, with EFV or ATV/r at standard doses. The primary analyses of both A5202 and A5224s have been presented previously [20,23–26]. Specific A5224s exclusion criteria were uncontrolled thyroid disease or hypogonadism; endocrine diseases, including Cushing's syndrome, diabetes mellitus, and the use of growth hormone, anabolic steroids, glucocorticoids, or osteoporosis medications (calcium and/or vitamin D were not included); or the intent to start these treatments known to influence BMD. The duration of the study was 96 weeks after the last A5202 participant enrolled.

Any participant enrolling in A5202 at one of the AIDS Clinical Trials Group sites participating in A5224s and meeting criteria for A5224s was eligible to enroll in the sub-study; A5202 randomization was stratified by willingness to enroll into the sub-study. Each participant signed a written informed consent before enrollment. The study was approved by the local institutional review board at each site.

At baseline, a complete history was obtained and participants underwent a physical examination, including standardized measurement of height and weight. Substudy evaluations, regardless of antiretroviral treatment status, included whole-body dual-energy absorptiometry (DXA) and site-specific (hip and lumbar spine) bone DXA at baseline and at weeks 24, 48, 96, and every 48 weeks until the end of follow-up, as well as a single-slice abdomen computed tomography (CT) scan at the L4-L5 level at baseline and week 96. LBM was defined as fat-free, bone-free mass as measured by DXA in the anteroposterior view (using Hologic or Lunar scanners). Hip BMD, lumbar spine BMD (from L1 to L4), and limb fat were measured by DXA. Technicians were instructed to scan the same hip of each participant for all BMD measurements and to use the same DXA machine on the same participant throughout the study. CT was used to quantify visceral adipose tissue. All DXAs and CT scans were standardized at the participating sites, then centrally read (Tufts) by blinded personnel.

On 18 February 2008, after a median follow-up of 97 weeks (range 0–124 weeks; Q1–Q3 58–108 weeks), the Data Safety and Monitoring Board recommended unblinding the NRTI component of the study for participants with screening HIV-1 RNA levels at least 100 000 copies/ml because of excess virological failures associated with ABC/3TC; participants receiving ABC/3TC were permitted to modify their NRTI regimen [24].

Statistical analysis

The current study was a posthoc, exploratory analysis to compare changes from baseline to week 96 in weight, BMI, and LBM between pooled, randomized NRTI components (ABC/3TC vs. TDF/FTC) and NNRTI/PI components (ATV/r vs. EFV). All analyses were initially performed using the intent-to-treat principle based on

randomized treatment assignment in which all available data were included and modifications to randomized treatment were ignored; no imputations were made for missing values. Supplemental as-treated analyses were performed in which values were censored after a change in the randomized NRTI component (when comparing NRTI components) or NNRTI/PI component (when comparing NNRTI/PI components). Comparisons used a factorial analysis approach in which, after assessing for treatment effect modification by the other component, the NRTI effect was analyzed by combining EFV and ATV/r arms and vice versa. The assessment of treatment effect modification (interaction) of each ART component with screening HIV-1 RNA stratum (<100 000 or ≥100 000 copies/ml) was prespecified.

Changes from baseline within study arm or regimen component used one-sample *t*-tests. Comparisons between regimen components used two-sample *t*-tests. There was no evidence of an interaction between the NRTI and NNRTI/PI components on 96 week change in weight, BMI, or LBM (all $P \geq 0.30$). Analyses that adjusted for baseline and postbaseline factors and explored associations with baseline and postbaseline factors used linear regression; all multivariable models were adjusted for both ART components. Univariate associations with a *P*-value less than 0.20 were included in a multivariable model which utilized backwards selection and only factors with a *P*-value less than 0.05 were retained. Analyses were performed using SAS, version 9.1.3 (SAS Institute, Cary, North Carolina, USA).

Results

Participant characteristics

A total of 271 participants from 37 AIDS Clinical Trials Group sites in the United States and Puerto Rico were randomized to receive ART; two participants were excluded from the analysis for eligibility violations. Sixty-nine participants were randomized to receive EFV and TDF/FTC, 70 to EFV and ABC/3TC, 65 to ATV/r and TDF/FTC, and 65 to ATV/r and ABC/3TC. Baseline characteristics are summarized in Table 1 and were balanced across study arms. The median age of the participants was 38 years, 85% were men, and 47% were white non-Hispanics. The mean weight was 78.0 kg,

Table 1. Baseline characteristics of study participants.

Characteristic	EFV + TDF/FTC *N* = 69	EFV + ABC/3TC *N* = 70	ATV/r + TDF/FTC *N* = 65	ATV/r + ABC/3TC *N* = 65	Total *N* = 269
Age (years)	39 (10)	39 (10)	38 (10)	37 (10)	38 (10)
	40 (33–44)	39 (31–46)	38 (30–44)	37 (29–43)	38 (31–44)
Sex					
Male	58 (84)	56 (80)	56 (86)	59 (91)	229 (85)
Female	11 (16)	14 (20)	9 (14)	6 (9)	40 (15)
Race/ethnicity					
White non-Hispanic	37 (54)	34 (49)	26 (40)	29 (45)	126 (47)
Black non-Hispanic	22 (32)	20 (29)	21 (32)	27 (42)	90 (33)
Hispanic	8 (12)	14 (20)	14 (22)	8 (12)	44 (16)
Other	2 (<1)	2 (<1)	4 (1)	1 (<1)	9 (<1)
$CD4^+$ T-cell count (cells/μl)	248 (160)	231 (167)	226 (142)	238 (189)	236 (165)
	250 (132–334)	213 (106–350)	247 (114–319)	222 (75–332)	233 (106–334)
HIV-1 RNA (log_{10} copies/ml)	4.6 (0.7)	4.6 (0.6)	4.6 (0.7)	4.7 (0.7)	4.6 (0.7)
	4.7 (4.2–4.9)	4.7 (4.2–4.9	4.5 (4.2–4.9)	4.6 (4.3–5.1)	4.6 (4.2–4.9)
HIV-1 RNA (copies/ml)					
<100 000 copies/ml	56 (81)	59 (84)	52 (80)	48 (74)	215 (80)
≥100 000 copies/ml	13 (19)	11 (16)	13 (20)	17 (26)	54 (20)
Hepatitis C antibody	5 (7)	8 (11)	3 (5)	7 (11)	23 (9)
BMI (kg/m^2)	24.7 (4.0)	25.5 (4.6)	26.2 (5.4)	25.7 (4.5)	25.5 (4.7)
	24.9 (21.6–27.1)	24.7 (22.6–28.3)	24.9 (21.8–28.8)	25.3 (21.8–28.9)	24.9 (21.8–28.2)
Weight (kg)	76.2 (15.7)	76.8 (14.3)	80.2 (17.1)	79.1 (15.0)	78.0 (15.5)
	72.6 (64.8–86.9)	77.6 (67.9–85.3)	77.0 (68.5–90.5)	75.7 (67.0–88.4)	76.2 (66.7–87.0)
Lean body mass (kg)	53.7 (9.8)	52.8 (9.1)	55.5 (9.9)	56.0 (8.1)	54.5 (9.3)
	53.1 (48.5–61.3)	54.0 (46.6–58.9)	55.0 (48.0–60.0)	56.6 (50.6–61.7)	54.6 (48.1–61.1)
Limb fat (kg)	7.7 (3.9)	8.8 (5.5)	8.8 (5.5)	8.1 (5.0)	8.3 (5.0)
	7.3 (4.7–9.4)	7.8 (4.9–10.5)	7.4 (5.0–11.6)	6.8 (4.3–10.5)	7.4 (4.7–10.1)
Visceral adipose tissue (cm^2)	94.0 (61.5)	94.5 (53.3)	93.0 (39.9)	88.6 (46.9)	92.6 (51.0)
	84.2 (52.0–110.3)	82.6 (62.8–111.6)	86.7 (60.2–121.9)	82.7 (55.2–116.1)	84.1 (57.2–115.9)
Lumbar spine BMD (g/cm^2)	1.12 (0.17)	1.10 (0.20)	1.15 (0.22)	1.14 (0.17)	1.13 (0.19)
	1.12 (1.00–1.23)	1.08 (0.97–1.23)	1.13 (1.03–1.24)	1.13 (1.04–1.23)	1.12 (0.99–1.23)
Hip BMD (g/cm^2)	1.00 (0.13)	1.03 (0.17)	1.07 (0.18)	1.06 (0.14)	1.04 (0.16)
	0.99 (0.92–1.07)	1.02 (0.93–1.11)	1.05 (0.98–1.18)	1.02 (0.97–1.13)	1.02 (0.94–1.11)
Prior bone fracture	22 (32)	24 (34)	18 (28)	22 (34)	86 (32)

Data are shown as mean (SD) and median (interquartile range) or number (frequency). ABC/3TC, abacavir-lamivudine; ATV/r, atazanavir-ritonavir; BMD, bone mineral density; EFV, efavirenz; TDF/FTC, tenofovir-emtricitabine.

BMI was 24.9 kg/m^2, CD4$^+$ cell count was 233 cells/μl, plasma HIV-1 RNA was 4.6 $\log_{10}$ copies/ml, and 80% had an HIV-1 RNA less than 100 000 copies/ml at study entry.

Sixty-six (25%) of A5224s participants prematurely discontinued study follow-up, four (1%) died, and 45% modified the randomized treatment regimen. These details have been previously published [20,23].

Change in weight

Among all participants, weight increased from baseline by a mean of 4.8 kg at week 96 ($P < 0.001$). The mean changes in weight for each study arm are shown in Fig. 1a. Although ABC/3TC had a trend towards greater weight gain compared with TDF/FTC by intent-to-treat analyses at week 96, this difference was not statistically significant (Fig. 1a). Results in the as-treated analysis were similar [$\Delta = 1.43$ kg; 95% confidence interval (CI) −0.97, 3.83 kg; $P = 0.24$]. ATV/r assignment resulted in significantly greater weight gain in both intent-to-treat (Fig. 1a) and as-treated analyses ($\Delta = 3.34$ kg; 95% CI 0.97, 5.71 kg; $P = 0.006$) compared with EFV.

Change in BMI

Among all participants, BMI increased by a mean of 1.5 kg/m^2 at week 96 ($P < 0.001$). The mean changes in BMI across study arms are shown in Fig. 1b. No significant differences in BMI were detected between ABC/3TC and TDF/FTC by intent-to-treat (Fig. 1b) or as-treated analyses ($\Delta = 0.53$ kg/m^2; 95% CI −0.25, 1.31 kg/m^2; $P = 0.18$). Participants randomized to ATV/r experienced a 0.88 kg/m^2 greater increase in BMI compared with EFV in the intent-to-treat analysis (Fig. 1b). BMI increase was also higher in the ATV/r compared with EFV by as-treated analysis ($\Delta = 1.08$; 95% CI 0.31, 1.86 kg/m^2; $P = 0.007$).

Change in lean body mass

Across all treatment arms, LBM increased significantly by a mean 1.4 kg at week 96 ($P < 0.001$). Mean changes in LBM across study arms are shown in Fig. 1c. No significant differences in LBM gain were seen between ABC/3TC and TDF/FTC by intent-to-treat (Fig. 1c) or as-treated analyses ($\Delta = -0.20$ kg; 95% CI −0.80, 1.20 kg; $P = 0.70$). In comparison to those receiving EFV, participants randomized to ATV/r did not have a significantly different LBM change by intent-to-treat analysis (Fig. 1c) but the difference did approach statistical significance by as-treated analysis ($\Delta = 1.03$ kg; 95% CI −0.03, 1.96 kg; $P = 0.056$).

A prespecified intent-to-treat subgroup analysis detected a significant interaction between the NNRTI/PI components and screening HIV-1 RNA stratum ($P = 0.053$), indicating that the treatment effect differed by RNA level. Participants with screening HIV-1 RNA at least 100 000 copies/ml had a significantly greater mean gain in LBM with ATV/r ($n = 38$) compared with EFV ($n = 43$; $\Delta = 1.75$ kg; 95% CI 0.18, 3.33; $P = 0.029$). Differences between ATV/r ($n = 56$) and EFV ($n = 66$) in LBM gain were not seen among participants with HIV-1 RNA less than 100 000 copies/ml ($\Delta = -0.06$ kg; 95% CI −1.15, 1.03 kg; $P = 0.91$).

Baseline associations with change in total body mass, BMI, and lean body mass

In both univariate and multivariable analyses of variables associated with body composition change, higher baseline HIV-1 RNA level and lower CD4$^+$ cell count were associated with a greater gain in total body mass, BMI, and LBM at week 96 after adjusting for treatment arm (Table 2).

Multivariable linear regression analyses

Univariate and multivariable analyses assessed baseline and postbaseline factors associated with week 96 change in hip and lumbar spine BMD. Compared with TDF/FTC, assignment to ABC/3TC was associated with less percentage loss in hip BMD from week 0 to week 96 (mean Δ 1.35; 95% CI 0.18, 2.53; $P = 0.02$; results previously presented [23]). The change in hip BMD between ATV/r and EFV arms was not statistically significant (mean Δ −0.31; 95% CI −1.50, 0.89; $P = 0.61$). For hip BMD, in addition to the significant TDF/FTC effect, lower baseline weight, higher increase in CD4$^+$ cell count over 96 weeks, lesser increase in LBM at 96 weeks, and history of fracture were independently and significantly associated with less increase in hip BMD at 96 weeks after adjusting for treatment arm.

Compared with TDF/FTC, assignment to ABC/3TC was associated with less percentage loss in lumbar spine BMD from week 0 to 96 (mean Δ 2.00; 95% CI 0.66, 3.33; $P = 0.004$) while ATV/r was associated with significantly greater percentage loss in lumbar spine BMD compared with EFV (mean Δ −1.46; −2.82, −0.10; $P = 0.035$; results previously presented [23]). In multivariable analyses, higher baseline HIV-1 RNA, lower baseline CD4$^+$ cell count, and lack of HIV-1 RNA suppression less than 50 copies/ml at week 96 were independently and significantly associated with less increase in lumbar spine BMD at 96 weeks after adjusting for treatment arm (Table 3).

Discussion

Our study presents the first longitudinal assessment of changes in LBM after the initiation of ART and the first longitudinal assessment of body fat, visceral fat, and LBM on the change on bone density with current first-line ART initiation. In the setting of a large, randomized trial of antiretroviral initiation among treatment-naive participants, we demonstrated an increase in body weight and

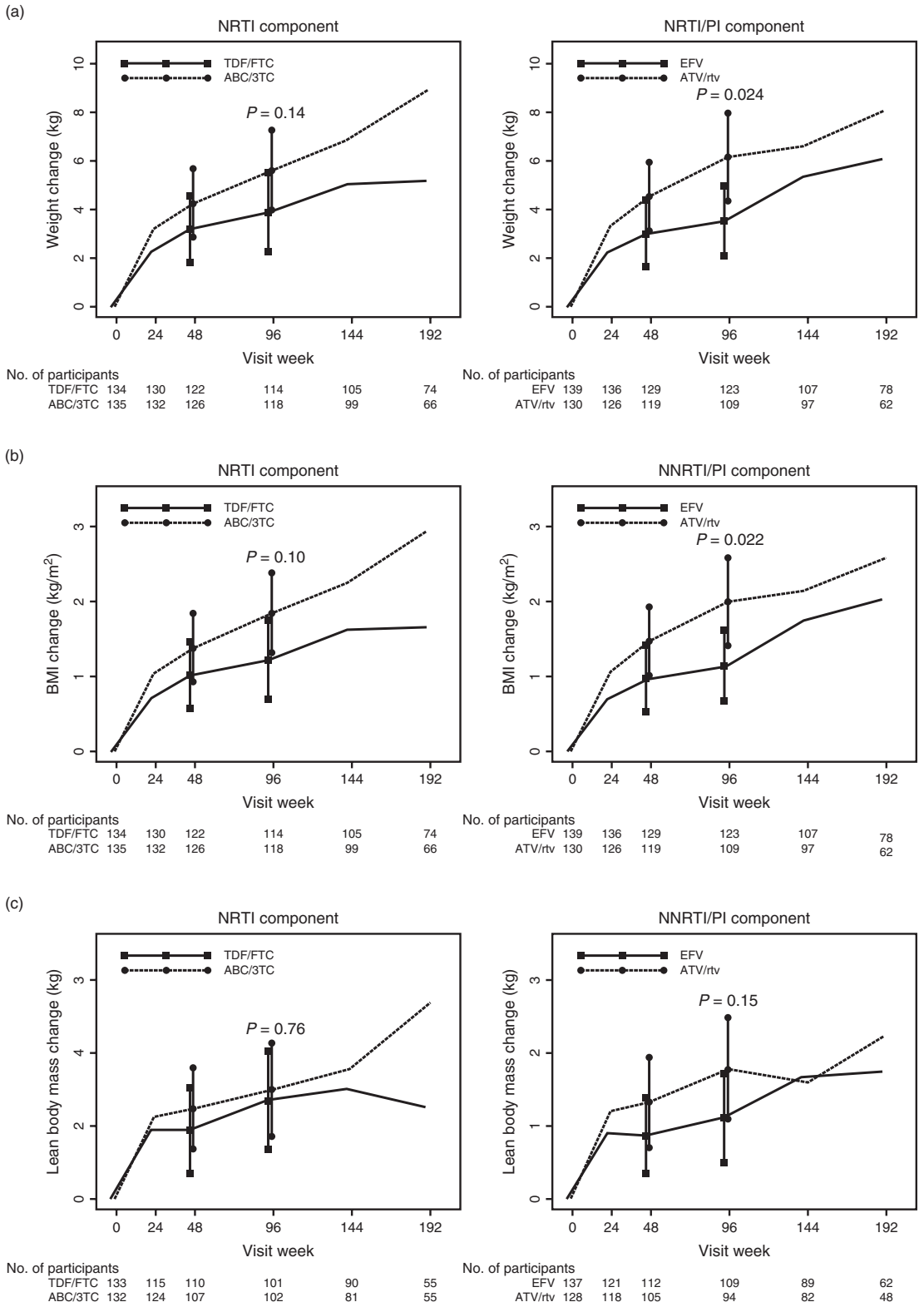

Fig. 1. Absolute changes in total weight, BMI, and lean body mass by treatment arms. Mean and 95% confidence intervals are represented by symbols and error bars; *P*-value from comparison between arms at 96 weeks; TDF/FTC, tenofovir-emtricitabine; ABC/3TC, abacavir-lamivudine; EFV, efavirenz; ATV/r, atazanavir-ritonavir. (a) Changes in total weight between the nucleoside reverse transcriptase inhibitor (NRTI) and nonnucleoside reverse transcriptase inhibitor/protease inhibitor (NNRTI/PI) components. (b) Changes in BMI between NRTI and NNRTI/PI components. (c) Changes in lean body mass between NRTI and NNRTI/PI components.

Table 2. Univariate and multivariable linear regression to assess the association between baseline factors and change in measures of body mass, adjusted for treatment arm.

		Univariate analyses		Multivariable analyses	
End point	Baseline covariate	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Change in body weight (kg)	Male	1.63 (−1.59, 4.85)	0.32		
	Age[a]	−0.09 (−0.21, 0.02)	0.12		
	Race/ethnicity (vs. white non-Hispanic)		0.83		
	Black non-Hispanic	0.92 (−1.71, 3.54)			
	Hispanic	1.19 (−2.21, 4.59)			
	Other	−0.78 (−7.22, 5.67)			
	Baseline HIV-1 RNA[b]	4.39 (2.75, 6.03)	<0.001	2.94 (1.19, 4.70)	0.001
	Baseline $CD4^+$ cell count[c]	−0.91 (−1.24, −0.58)	<0.001	−0.65 (−1.00, −0.29)	<0.001
	Baseline BMI[d]	−0.07 (−0.33, 0.18)	0.57		
Change in BMI (kg/m^2)	Male	0.32 (−0.74, 1.37)	0.55		
	Age[a]	−0.03 (−0.07, 0.01)	0.12		
	Race/ethnicity (vs. white non-Hispanic)		0.69		
	Black non-Hispanic	0.36 (−0.50, 1.21)			
	Hispanic	0.56 (−0.55, 1.67)			
	Other	−0.26 (−2.36, 1.85)			
	Baseline HIV-1 RNA[b]	1.44 (0.91, 1.98)	<0.001	0.97 (0.40, 1.54)	0.001
	Baseline $CD4^+$ cell count[c]	−0.30 (−0.41, −0.19)	<0.001	−0.21 (−0.33, −0.09)	<0.001
Change in lean body mass (kg)	Male	0.81 (−0.47, 2.08)	0.21		
	Age[a]	−0.03 (−0.08, 0.02)	0.20		
	Race/ethnicity (vs. white non-Hispanic)		0.15		
	Black non-Hispanic	0.58 (−0.47, 1.63)			
	Hispanic	1.47 (0.15, 2.80)			
	Other	1.22 (−1.75, 4.19)			
	Baseline HIV-1 RNA[b]	1.55 (0.87, 2.23)	<0.001	0.76 (0.05, 1.46)	0.035
	Baseline $CD4^+$ cell count[c]	−0.43 (−0.56, −0.31)	<0.001	−0.37 (−0.51, −0.23)	<0.001
	Baseline BMI[d]	−0.04 (−0.14, 0.06)	0.41		

CI, confidence interval.
[a]per 1 year older.
[b]per $\log_{10}$ copies/ml higher.
[c]per 50 cells/μl higher.
[d]per 1 kg/m^2 higher.

BMI across all treatment arms, consistent with prior studies [14–16,18]. A significantly greater gain in total body mass and BMI was observed in the ATV/r arm compared with the EFV arm. Lower baseline $CD4^+$ cell count and higher HIV-1 RNA had a strong association with a positive gain in total body mass, BMI and LBM. These findings likely reflect HIV disease severity and cachexia prior to ART initiation and the return to health phenomenon in patients with more advanced disease.

In the present study, we demonstrated an average increase in LBM among all participants by 96 weeks, with no significant difference between NRTIs but a trend towards greater gain in those assigned to ATV/r compared with EFV. Prior studies of ART initiation or change in ART found an increase in LBM when using older treatment regimens (primarily zidovudine or stavudine based) [14,16,27,28] despite the potential for the thymidine NRTIs to induce mitochondrial toxicity in the muscle tissue [29,30]. Our randomized study reports an increase in LBM for the first time with contemporary first-line ART regimens [31]. Observational cohorts including both ART-treated and ART-naive populations demonstrate stable [32] or increased LBM over time, particularly among those on ART [33–35]. However, these findings have not been consistent across observational cohorts as other studies have demonstrated a decrease in LBM [36,37].

Low BMD and its resultant bone fractures are more prevalent in HIV-infected participants on ART compared with HIV-uninfected populations [38]. The cause of low BMD is unclear but is likely multifactorial. In cross-sectional and longitudinal data of older, HIV-uninfected individuals (primarily women), greater LBM and fat mass are associated with greater BMD [1,6,39]. Furthermore, cross-sectional studies suggest that total body mass may be one of the most significant determinants of BMD of HIV-infected persons [9,10,13]. A cross-sectional study of 221 HIV-infected men (85% on ART) found that weight, LBM, total fat mass, and limb fat were significantly higher among men with normal BMD; older age, lower LBM, and greater stavudine exposure were independently associated with lower BMD in multivariate regression [40]. A recent publication from the Women's Interagency HIV Study cohort (83% on ART) measuring change in BMD over a 5-year period found that among both HIV-infected and uninfected women, higher LBM was associated with increased BMD at the lumbar spine, total hip, and femoral neck and that higher total body fat

Table 3. Linear regression identifying significant variables in BMD change with antiretroviral initiation, adjusted for treatment arm.

	Univariate analyses		Multivariable analyses	
Covariate	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
Hip BMD (% change week 0–96)				
Male	0.00 (−1.63, 1.63)	1.00		
Age[a]	−0.05 (−0.11, 0.02)	0.15		
Race/ethnicity (vs. white non-Hispanic)		0.75		
Black non-Hispanic	0.43 (−0.93, 1.80)			
Hispanic	0.90 (−0.90, 2.70)			
Other	−0.39 (−4.21, 3.44)			
Baseline HIV-1 RNA[b]	−0.53 (−1.44, 0.37)	0.24		
96 week HIV-1 RNA suppression[c]	−2.30 (−4.00, −0.60)	0.008		
Baseline $CD4^+$ count[d]	0.06 (−0.12, 0.25)	0.51		
96 week $CD4^+$ count change[d]	−0.20 (−0.37, −0.03)	0.020	−0.24 (−0.40, −0.08)	0.004
Hepatitis C antibody	−0.60 (−2.89, 1.70)	0.61		
History of fracture	−1.42 (−2.65, −0.19)	0.024	−1.60 (−2.78, −0.41)	0.008
Baseline weight[e]	0.05 (0.01, 0.10)	0.013	0.07 (0.03, 0.11)	0.001
96 week weight change[e]	0.08 (0.00, 0.15)	0.040		
Baseline BMI[f]	0.16 (0.02, 0.29)	0.021		
96 week BMI change[f]	0.24 (0.02, 0.46)	0.031		
Baseline lean body mass[e]	0.02 (−0.04, 0.09)	0.50		
96 week lean body mass change[e]	0.25 (0.08, 0.43)	0.005	0.28 (0.11, 0.45)	0.001
Baseline limb fat[e]	0.17 (0.04, 0.29)	0.008		
96 week limb fat change[e]	0.19 (−0.05, 0.42)	0.12		
Baseline visceral abdominal fat[g]	0.00 (−0.01, 0.01)	0.65		
96 week visceral abdominal fat change[g]	0.02 (0.00, 0.04)	0.044		
Lumbar spine BMD (% change week 0–96)				
Male	0.41 (−1.45, 2.27)	0.66		
Age[a]	−0.04 (−0.11, 0.03	0.25		
Race/ethnicity (vs. white non-hispanic)		0.73		
Black non-hispanic	0.23 (−1.35, 1.82)			
Hispanic	−0.78 (−2.78, 1.21)			
Other	−1.47 (−5.88, 2.94)			
Baseline HIV-1 RNA[b]	−2.00 (−3.00, −1.01)	<0.001	−1.22 (−2.25, −0.19)	0.021
96 week HIV-1 RNA suppression[c]	1.96 (−0.02, 3.93)	0.052	2.19 (0.38, 4.00)	0.018
Baseline $CD4^+$ count[d]	0.48 (0.28, 0.68)	<0.001	0.34 (0.13, 0.55)	0.002
96 week $CD4^+$ count change[d]	−0.16 (−0.35, 0.04)	0.11		
Hepatitis C antibody	0.44 (−2.21, 3.09)	0.74		
History of fracture	0.11 (−1.32, 1.55)	0.87		
Baseline weight[e]	0.02 (−0.03, 0.07)	0.45		
96 week weight change[e]	−0.14 (−0.23, −0.06)	0.001		
Baseline BMI[f]	0.01 (−0.14, 0.16)	0.90		
96 week BMI change[f]	−0.42 (−0.67, −0.17)	0.001		
Baseline lean body mass[e]	0.03 (−0.04, 0.11)	0.38		
96 week lean body mass change[e]	−0.39 (−0.59, −0.19)	<0.001		
Baseline limb fat[e]	0.00 (−0.14, 0.15)	0.97		
96 week limb fat change[e]	−0.27 (−0.54, −0.00)	0.048		
Baseline visceral abdominal fat[g]	0.00 (−0.01, 0.01)	0.97		
96 week visceral abdominal fat change[g]	−0.02 (−0.04, −0.00)	0.030		

For multivariate analyses, only those with $P < 0.05$ and antiretroviral therapy arm (regardless of *P*-value) are reported; ABC/3TC, abacavir-lamivudine; ATV/r, atazanavir-ritonavir; BMD, bone mineral density; CI, confidence interval; EFV, efavirenz; TDF/FTC, tenofovir-emtricitabine.
[a]per 1 year older.
[b]per $\log_{10}$ copies/ml higher.
[c]<50 copies/ml.
[d]per 50 cells/μl higher.
[e]per 1 kg higher.
[f]per 1 kg/m^2 higher.
[g]per 1 cm^2 higher.

was associated with increased BMD at the total hip and femoral neck [41].

Consistent with these studies, we demonstrate for the first time in a randomized ART-initiation study that the increase in LBM over 96 weeks was associated with an increase in hip BMD. Surprisingly, we found that increased LBM was associated with greater bone loss at the lumbar spine, although this association was not seen in the multivariable analyses. Furthermore, increased visceral fat over 96 weeks was associated with increased BMD at the hip but associated with decreased BMD at the lumbar spine. The association of visceral fat on hip BMD that we observed may be the result of the mechanical loading effect. Indeed, other studies have demonstrated an increased hip BMD among both men

and women with central obesity [42–44]. Similarly, these studies and others found no correlation or a negative correlation between direct or surrogate markers (waist circumference) of visceral adipose tissue and lumbar spine BMD [44–46]. The negative association of adipose tissue with lumbar spine BMD is hypothesized to be the result of pro-inflammatory cytokines [47].

As demonstrated in the Table 3 univariate analyses, week 96 changes in weight, BMI, and LBM were significantly associated with week 96 changes in both hip and lumbar spine BMD. Furthermore, randomization to TDF/FTC led to a greater percentage decrease in both hip and lumbar spine BMD at 96 weeks compared with ABC/3TC, and ATV/r led a greater percentage decrease in lumbar spine BMD change at 96 weeks compared with EFV (previously published [23]). Because of these findings and the significant difference between ATV/r and EFV on week 96 change in weight and BMI presented here, we feel that the effect of the NNRTI/PI component on lumbar spine BMD change may be mediated through changes in weight, BMI, LBM or another factor associated with both weight and BMD change. In addition to the body composition factors presented here, additional metabolic and HIV-related factors could be incorporated using structural equation models or causal mediation analysis to fully assess direct and indirect effects of regimen components.

The study has several limitations. First, the duration of follow-up for bone endpoints was relatively short and the impact of ART or body composition changes on BMD could take several years. Second, the study population was relatively young for bone measures and results may not be applicable to older HIV-infected populations. Third, assignment of ATV/r vs. EFV was not blinded and changes in the NRTI backbone occurred relatively frequently. However, the intent-to-treat results were consistent with the as-treated results, suggesting that changes in the backbone regimens do not explain our results. The A5224s study did not collect smoking, alcohol, menopause status, or physical activity data, which could affect body composition measures, but it is likely that these were evenly distributed at baseline between treatment arms given the randomized study design. Finally, a large number of analyses were performed without adjustment, increasing the probability of committing one or more type I errors, and therefore results should be interpreted with caution. However, this was an exploratory analysis and it will be important for our findings to be confirmed in other studies.

In summary, our study shows that assignment to ATV/r leads to greater gain in body weight and BMI than EFV. Although overall gain in LBM was observed, there were no significant differences in LBM gain between NRTI or NNRTI/PI components. Furthermore, we found both an independent effect of NRTIs and a positive association of increased LBM with change in hip BMD. These findings support the role of lifestyle interventions such as resistance exercise and nutrition to increase lean mass in order to potentially attenuate the initial decline in BMD observed with ART initiation. Prospective studies are needed to assess the role of such lifestyle interventions.

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Conflicts of interest

E.S.D. has received grant support from Abbott, Gilead, Merck, Pfizer and ViiV as well as been consultant/advisor for Bristol Myers Squibb, Gilead, Merck, ViiV and Janssen. G.A.McC. has served as a scientific advisor or speaker for Bristol Myers Squibb, GlaxoSmithKline, Janssen, Merck, and Gilead Sciences, has received research grants from Bristol Myers Squibb, GlaxoSmithKline, and Gilead Sciences, and is currently serving as the Data Safety and Monitoring Board Chair for a Pfizer-sponsored study. K.M. is an employee of Gilead Sciences. B.H. is an employee of ViiV Healthcare/GlaskoSmithKline. P.E.S. is a consultant for Abbott, Bristol- Myers Squibb, Gilead, GlaxoSmithKline, Merck, Janssen, and receives grant support from Bristol-Myers Squibb, Gilead, Merck, and GlaxoSmithKline. P.T. has served as a consultant for Merck, is currently serving on a Data Safety and Monitoring Board for Cytheris and on an adjudication committee for GlaxoSmithKline. C.T. is a member of a Data Safety and Monitoring Board for a Tibotec/Janssen hepatitis C drug.

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