Continuous antiretroviral therapy decreases bone mineral density

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Objectives: To assess the effects of antiretroviral therapy (ART) on bone mineral density (BMD)

Design: Randomized comparison of continuous ART (viral suppression group; VS) with intermittent ART (drug conservation group; DC)

Setting: Outpatient clinics in the United States, Australia, and Spain.

Participants: Participants in the Strategies for Management of Antiretroviral Therapy (SMART) Body Composition substudy.

Main outcome measures: Annual hip and spine BMD by dual-energy radiographic absorptiometry (DXA) and spine BMD by quantitative computed tomography (qCT).

Methods: Comparisons were by intention-to-treat analysis, using longitudinal models for change in BMD. Risk factors for BMD loss were evaluated.

Results: The 214 participants (median 44 years, 19% female participants, 73% on ART; median *T*-scores −0.5 total hip, −0.7 spine DXA, −0.9 spine qCT; 98 randomized to VS and 116 to DC) were followed for a mean 2.4 years. With continuous ART, BMD declined per year by 0.8% (hip), 0.4% (spine DXA), and 2.4% (spine qCT). BMD declined significantly less with intermittent ART. Estimated DC minus VS group differences in mean BMD change through follow-up were 1.4% [hip; 95% confidence interval (CI) 0.6–2.3; $P = 0.002$], 1.3% (spine DXA; 95% CI 0.1–2.4, $P = 0.03$), and 3.0% (spine qCT; 95% CI 0.8–5.2, $P = 0.007$). No consistent drug-specific association with BMD decline was found. In the parent study, 10 of 2753 participants in the VS group and two of 2720 in the DC group reported serious fractures (hazard ratio 4.9; 95% CI 1.1–22.5; $P = 0.04$).

Conclusion: Continuous ART is associated with decline in BMD and possibly more fractures relative to intermittent, CD4 cell count-guided ART.

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Introduction

HIV-infected adults have a higher prevalence of low bone mineral density (BMD; 40–83%) than the general population [1–10] and perhaps a higher prevalence of fracture [11]. A systematic review of cross-sectional studies of adults with HIV infection found a 6.4-fold increased odds ratio of reduced BMD (*T*-score <-1.0) and a 3.7-fold increased odds ratio of osteoporosis (*T*-score <-2.5) [6]. Use of antiretroviral therapy (ART) was associated with low BMD in HIV-infected adults in several studies [any ART, thymidine analogue-nucleoside reverse transcriptase inhibitor (TA-NRTI) or protease inhibitor therapy], as were traditional risk factors (older age, female sex, menopause, corticosteroid therapy, low BMI, low serum testosterone level) and HIV-related factors (HIV duration, elevated plasma HIV viral load) [1–10,12–17]. Not all studies, however, evaluated all risk factors, and associations of individual ART drugs or drug classes with low BMD were not consistent.

Four prospective studies [18–21] have reported stable, decreasing, or increasing BMD with protease inhibitor therapy. In a randomized trial, BMD declined with both tenofovir and stavudine, but more with tenofovir [22].

No prospective, randomized trial has compared ART with no ART with respect to BMD. The INSIGHT Strategies for Management of Antiretroviral Therapy (SMART) study [23] was an international, randomized trial comparing intermittent, CD4 lymphocyte count-guided ART with continuous ART. We compared the randomized groups for BMD changes at the hip and spine in 214 participants in the SMART Body Composition substudy over a mean follow-up of 2.4 years. We hypothesized that BMD loss would be less with intermittent ART.

Methods

Participants

Eligibility criteria for participation in SMART were documented HIV-1 infection, age greater than 13 years, CD4 cell count above 350 cells/μl, and no pregnancy or breastfeeding.

SMART participants at 32 clinical sites in the United States, Australia, and Spain were offered coenrolment in the Body Composition substudy; persons for whom valid scan data could not be obtained (e.g., weight above 160 kg) were excluded. Sites were selected based on access to study-certified imaging equipment. The substudy was approved by the institutional review board at each site. Each participant gave written, informed consent.

Study design

Design and data collection of the SMART study have been published [23,24]. Participants were randomized to two groups: intermittent, CD4 cell count-guided ART [drug conservation (DC) group], in which ART was stopped or deferred at study entry, restarted when the CD4 cell count declined below 250 cells/μl, and stopped again at CD4 cell counts above 350 cells/μl; and continuous ART [viral suppression (VS) group]. ART drugs were not protocol-specified. The Body Composition substudy planned to enrol 300 participants and follow them for 5 years. The substudy was powered for adipose endpoints [25].

Enrolment into SMART was terminated early on 11 January 2006, and all participants were advised to receive continuous ART because of increased risks for death, opportunistic disease, and serious non-AIDS diseases in the DC group, identified at an interim review by the independent Data and Safety Monitoring Board [23]. The Body Composition substudy closed to follow-up on 30 June 2006.

Research questions and methodology

Research questions and methodology are as follows:

(1) Does ART contribute to BMD decline? We compared changes in BMD between the VS and DC groups from baseline through follow-up, and through the first year. The first-year comparison is closest to comparing continuous ART to no ART because, by study design, the between-group difference in ART use was greatest during the first year.
(2) What is the effect of specific drugs or drug classes on BMD? We performed two analyses: first, we evaluated associations of cumulative drug use with decline in BMD in the VS group. We restricted the analysis to the VS cohort because the duration of ART use in the DC group depended on factors that also may have influenced BMD; for example, participants who were healthier at study entry tended to use less ART during follow-up [26]. Second, among participants who were receiving ART at baseline, we compared the first-year DC–VS group difference between two subgroups: those participants whose baseline ART regimen did and did not include the target drugs. We hypothesized that stopping/continuing drugs associated with decline in BMD would result in larger DC–VS group differences than stopping/continuing other ART regimens.

The treatment group comparisons were prespecified in the protocol, but not the VS cohort analysis.

Bone mineral density outcome measures

For each participant, BMD was assessed at baseline and annually by dual-energy radiographic absorptiometry (DXA) of the total hip; DXA of the lumbar spine

(L1–L4); and quantitative computed tomography (qCT) of the spine (L2–L4). Spine qCT evaluated volumetric density of the trabecular bone. In contrast, DXA measures areal BMD and includes both cortical and trabecular bone.

For each scan, BMD, *T*-scores, and *Z*-scores were reported. *T*-scores compare the BMD to the mean of a healthy, young (20–30 years) reference population, matched by sex and race, and are expressed as number of standard deviations above or below the reference mean. For *Z*-scores, the reference population is also matched by age. *T*-scores and *Z*-scores were used as provided by the radiographic equipment manufacturer. BMD measurements were corrected by the central reading center for longitudinal and cross-sectional consistency based on scans of phantoms (see below).

We defined osteoporosis as the lower of the two DXA *T*-scores (spine and total hip) being less than −2.5, as recommended by the National Osteoporosis Foundation [27]. Low BMD (osteopenia or osteoporosis) was defined as at least one of the DXA *T*-scores being less than −1. WHO guidelines use similar *T*-scores, but concentrate on hip DXA [28–30].

Imaging procedures

The 10 radiographic imaging sites used standardized scanning protocols. Each patient had all scans performed by the same imaging site. Scans were centrally analyzed (Bio-Imaging Technologies, Inc., Newtown, Pennsylvania, USA) to ensure longitudinal consistency. Radiology equipment and personnel were certified by Bio-Imaging before protocol initiation. For women of childbearing potential, a negative serum or urine pregnancy test result was required within 14 days before each scan.

Dual-energy radiographic absorptiometry

DXA was performed according to the manufacturer's (GE Lunar or Hologic Inc., Bedford, Massachusetts, USA) specifications. Instruments were standardized and cross-calibrated using Bio-Imaging's Bona Fide Phantom; instrument quality control included regular scans of manufacturer-specified spine phantoms.

Quantitative computed tomography

For lumbar spine qCT, participants lay supine on a K2HPO4 CT calibration phantom; 40–45 slices were scanned, from the lower endplate of L1 to the upper endplate of L5. Instrument quality assurance included daily scans of a quality assurance phantom. Images were analyzed centrally using Mindways QCT PRO software (Mindways Software, Inc., Austin, Texas, USA).

Other data collection

In addition to the demographic, HIV, ART, and clinical data collected for all SMART participants [23], we recorded risk factors for low BMD (smoking status, history of alcohol abuse, but not menopausal status), body composition (clinician-assessed lipoatrophy or abnormal generalized fat accumulation), BMI, and drug treatment for osteoporosis.

Fractures were identified from grade 4 adverse event reports using the International Statistical Classification of Diseases and Related Health Problems-9 (ICD-9) codes, for all SMART participants through study completion in July 2007. Consequently, we identified only those fractures that met the definition of grade 4 events: potentially life-threatening, symptomatic events requiring medical intervention.

Statistical methods

All follow-up data were censored on the date of the participant's last BMD scan. Median time to first ART initiation in the DC arm was estimated from the Kaplan–Meier curve.

Randomized comparisons

Comparisons between the treatment groups were by intent-to-treat analysis. Changes in BMD were expressed as percentage of baseline BMD. The DC and VS groups were compared for changes in BMD from baseline through follow-up using longitudinal, mixed models, and for changes from baseline to a given visit using linear regression. Estimated DC−VS treatment differences with 95% confidence intervals (CIs) and *P* values for the differences were cited. As sensitivity analyses, treatment groups were also compared after adjusting for race, sex, and the race-by-sex interaction, because by chance more women were randomized to the VS group and the race distribution differed by sex; and after censoring follow-up at the start of osteoporosis treatment.

Treatment groups were compared for changes in BMD within predefined subgroups of participants by fitting separate models (longitudinal or regression) for each subgroup. Homogeneity across subgroups was assessed by testing for interaction between the subgroup factor and the treatment group indicator in a joint model.

Cox regression was used to compare treatment groups for incidence of osteoporosis in the substudy (through June 2006) and for incidence of fractures in the main SMART study (through July 2007).

Viral suppression cohort analyses

The rate of BMD decline in the VS group was estimated by the slope of the BMD change over time, using repeated measures models with zero intercept. Time-updated cumulative years of exposure to specific antiretroviral drugs were calculated from study entry to each annual scan date. The association of change in BMD with duration of ART since study entry was assessed by fitting two longitudinal mixed models. In the first model, time-updated covariates for cumulative use of TA-NRTIs, tenofovir, and protease inhibitors were included,

because these drugs were associated with loss of BMD in previous studies. The second model included cumulative use of specific drugs that were used by 10 or more participants (15 for NRTIs). Both models included follow-up time as covariate, along with race, sex, their interaction, age, smoking, BMI, history of alcohol abuse, and baseline BMD.

Analyses used SAS version 9.1 (SAS Institute, Cary, North Carolina, USA). All *P* values are two-sided.

Results

Baseline characteristics

From May 2002 to January 2006, the SMART Body Composition substudy coenrolled 275 patients at 32 sites in the United States, Australia, and Spain. The present analysis includes 214 participants (98 in the VS and 116 in the DC group) with at least one follow-up DXA or qCT; of 61 participants without follow-up scans, 57 (93%) had none because the study was terminated early (Fig. 1).

Baseline median age was 44 years, 19% were female participants, 28% were black, and 55% white (Table 1). The proportion of women was higher in the VS group. Among women, the proportion of blacks (66%) was higher than that among men (18%). More participants in the DC group had HIV-RNA of 400 copies/ml or less. Otherwise, treatment groups were well balanced, including for BMD. BMD measurements were slightly lower than in the general population of similar age, sex, and race, with median *Z*-scores of −0.2, −0.6, and −0.1 for the total hip DXA, spine DXA, and spine qCT BMD, respectively. Eight of 214 participants (4%) had osteoporosis. None was receiving osteoporosis therapy. Only 6% of participants were ART-naive and 27% were not receiving ART at baseline.

Compared with the parent SMART study, the proportion of women, of participants receiving ART at baseline, and of those with HIV-RNA of 400 copies/ml or less was lower in our cohort.

Treatment through follow-up

Participants were followed for a mean 2.4 years (range 0.9–4.1). Figure 2a shows the percentage of participants receiving ART by treatment group. VS group participants received ART for 93% of their follow-up time (2.3 of 2.5 years), compared with 41% (0.9 of 2.3 years) in the DC group. In the DC group, median time to first ART initiation after study entry was 1.2 years.

Four participants in the DC group and eight in the VS group started osteoporosis treatment.

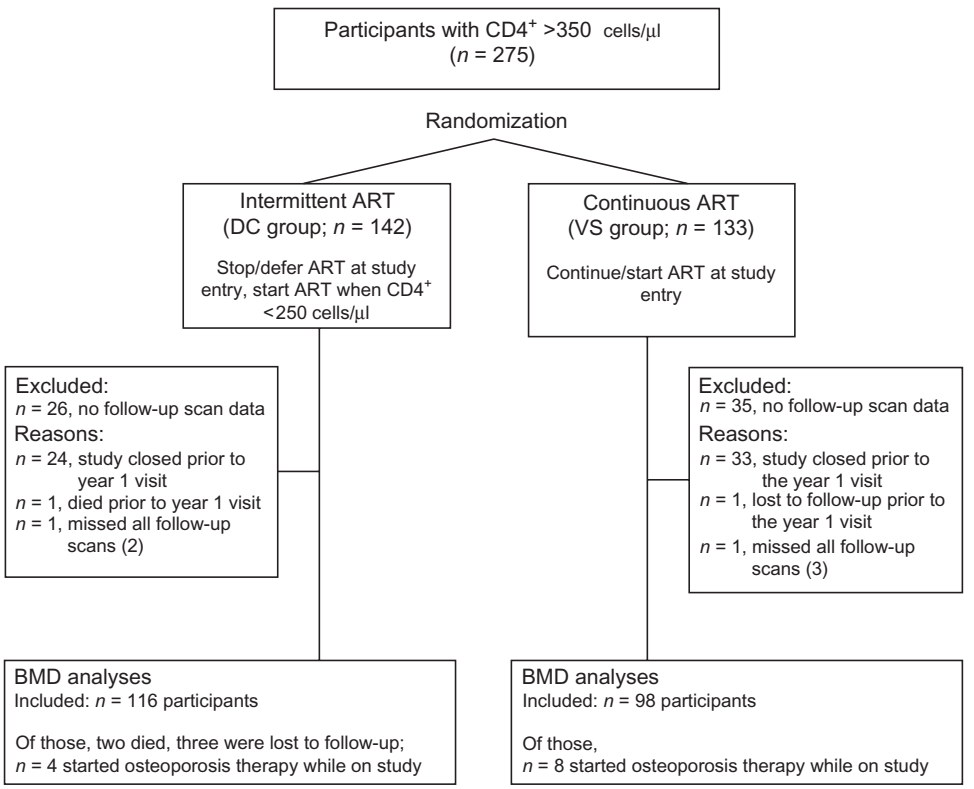

Fig. 1. Study design and patient disposition. BMD of the hip and spine by DXA and of the spine by qCT was obtained at baseline and annually; mean follow-up of 2.4 years. ART, antiretroviral therapy; BMD, bone mineral density; DC, drug conservation; VS, viral suppression.

Table 1. Baseline characteristics.

Characteristic	Participants with follow-up BMD data			SMART study
	DC group ($n=116$) % or median	VS group ($n=98$) % or median	Total ($n=214$) % or median (IQR)	Total ($n=5472$) % or median
Demographics				
Age (years)	45	43	44 (39–50)	43
Female participants (%)	14.7	24.5	19.2	27.2
Race/ethnicity (%)				
Black	25.9	29.6	27.6	29.1
Latino or Hispanic	17.2	14.3	15.9	21.1
White	55.2	55.1	55.1	43.6
Other or unknown	1.7	1.0	1.4	6.2
HIV transmission modes (%)				
Male–male sexual	69.8	57.1	64.0	49.9
Heterosexual	30.2	35.7	32.7	45.0
Intravenous drug use	14.7	14.3	14.5	9.7
Other or unknown	4.3	11.2	7.5	8.1
Clinical characteristics				
Duration of HIV infection (years)	8	9	9 (5–14)	8
Prior AIDS diagnosis (%)	24.1	22.4	23.4	23.9
Hepatitis B (%)	3.5	6.1	4.7	2.3
Hepatitis C (%)	16.4	17.3	16.8	14.8
Current smoker (%)	41.4	51.0	45.8	40.5
Steroid use (%)	2.6	5.1	3.7	2.0
CD4 cell count (cells/μl)	590	525	558 (439–758)	597
Nadir CD4 count (cells/μl)	235	268	253 (143–371)	250
HIV-RNA ≤400 copies/ml (%)	62.1	45.9	54.7	71.7
ART use at baseline				
ART-naive (%)	6.0	6.1	6.1	4.6
Duration of prior ART use (years)	6	6	6 (3–8)	6
Current ART use (%)	77.6	68.4	73.4	83.9
PI use (%)	42.2	29.6	36.4	45.2
Tenofovir use (%)	11.2	15.3	13.1	17.8
TA-NRTI use (%)	56.9	51.0	54.2	58.7
NRTIs other than tenofovir or TA-NRTIs (%)	12.9	9.2	11.2	10.9
NNRTI use (%)	34.5	34.7	34.6	49.0
Body composition				
BMI	26.2	26.1	26.2 (23.4–29.3)	25.9
Peripheral lipoatrophy[a] (%)	20.7	21.4	21.0	
Abnormal fat accumulation[a] (%)	21.6	21.4	21.5	
Bone mineral density				
Spine, qCT (mg/cm^3)	153	150	152 (128–173)	
Z-score	−0.1	−0.1	−0.1 (−0.9–0.6)	
T-score	−0.9	−0.9	−0.9 (−1.8–0.0)	
T-score <−2.5 (%)	7.8	12.2	9.8	
Spine, DXA AP (g/cm^2)	1.1	1.1	1.1 (1.0–1.2)	
Z-score	−0.4	−0.7	−0.6* (−1.3–0.3)	
T-score	−0.7	−0.7	−0.7 (−1.4–0.3)	
T-score <−2.5 (%)	4.4	3.1	3.8	
Total hip, DXA (g/cm^2)	1.0	1.0	1.0 (0.9–1.1)	
Z-score	−0.3	−0.1	−0.2** (−0.8–0.5)	
T-score	−0.5	−0.5	−0.5 (−1.0–0.3)	
T-score <−2.5 (%)	1.7	1.0	1.4	
Low BMD, by DXA *T*-scores[b] (%)	43.1	39.8	41.6	
Osteoporosis, by DXA *T*-scores[b] (%)	4.3	3.1	3.7	

AP, anterior–posterior; ART, antiretroviral therapy; BMD, bone mineral density; DC, drug conservation (intermittent ART); DXA, dual-energy radiographic absorptiometry; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; qCT, quantitative computed tomography; TA-NRTI, thymidine analogue-reverse transcriptase inhibitor; SMART, Strategies for Management of Antiretroviral Therapy; VS, viral suppression (continuous ART).

[a]Clinician-assessed, moderate or severe.

[b]Low BMD: at least one of the *T*-scores for DXA spine and hip was below −1; osteoporosis: at least one of the two DXA *T*-scores was below −2.5.

*Mean *Z*-score = −0.4 is significantly different from zero ($P=0.02$ for two-sided *t*-test).

**Mean *Z*-score = −0.1 is significantly different from zero ($P<0.001$ for two-sided *t*-test).

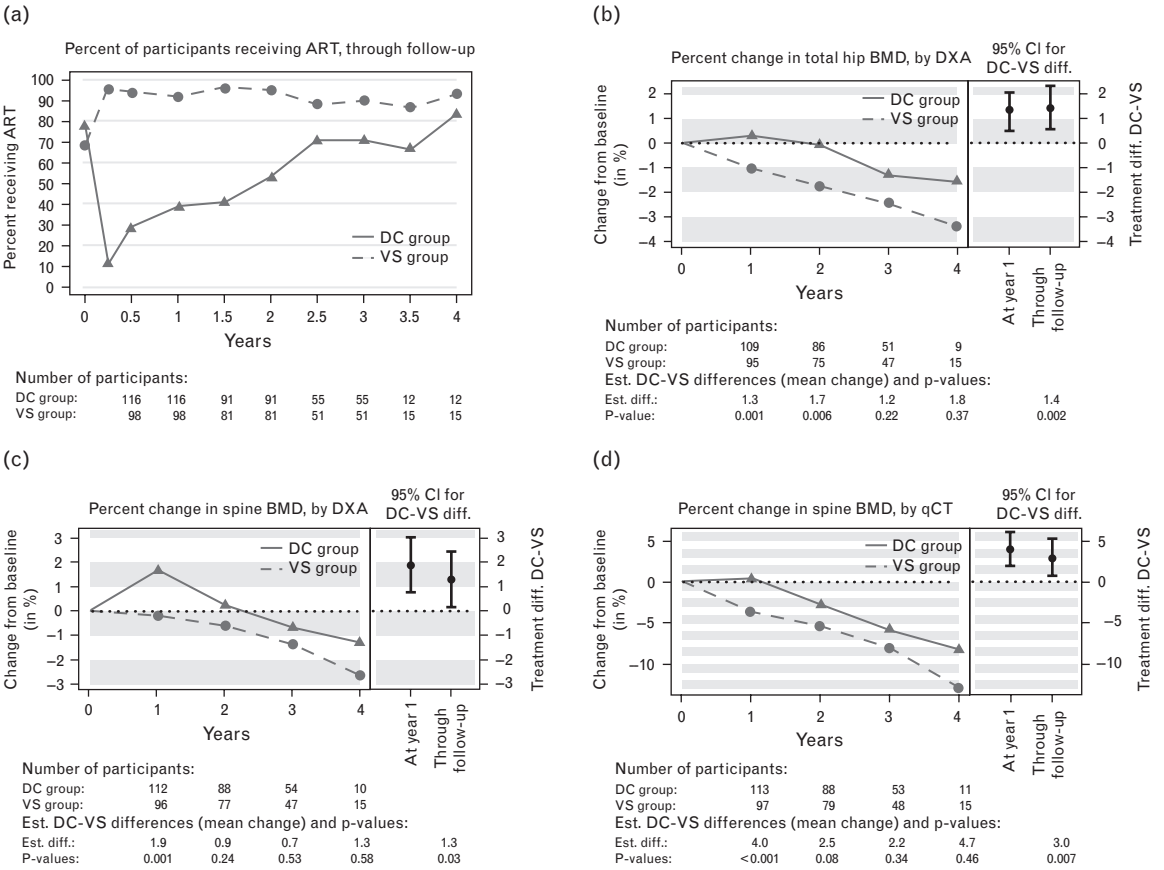

Fig. 2. Antiretroviral therapy use and mean change in bone mineral density by treatment group. (a) Percentage of participants receiving antiretroviral therapy (ART); (b) change in total hip bone mineral density (BMD) by dual-energy radiographic absorptiometry (DXA); (c) change in spine BMD by DXA; (d) change in spine BMD by quantitative computed tomography (qCT). Below panels b-d, estimates and *P* values for the DC−VS treatment differences are shown. The right-hand side of each panel shows treatment differences at year 1 and through follow-up with 95% confidence intervals (CIs). DC, drug conservation (intermittent ART group); VS, viral suppression (continuous ART group).

Changes in bone mineral density

By all three measures, changes in BMD favored the intermittent treatment arm (Fig. 2b–d). In the VS group, hip BMD declined on average by 0.8% per year ($P < 0.001$), spine DXA by 0.4% per year ($P = 0.04$), and spine qCT by 2.4% per year ($P < 0.001$). In the DC group, BMD remained stable or increased at year 1. After year 1, BMD appeared to decline at similar rates in both treatment groups. Estimated treatment differences (DC−VS) through follow-up were 1.4% for change in hip BMD (95% CI 0.6–2.3, $P = 0.002$), 1.3% for spine DXA (95% CI 0.1–2.4, $P = 0.03$), and 3.0% for change in trabecular BMD by spine qCT (95% CI 0.8–5.2, $P = 0.007$). Results were similar after adjustment for race, sex, and the race-by-sex interaction (data not shown). After censoring follow-up at the start of osteoporosis treatment, estimated treatment differences were 1.3% ($P = 0.004$), 1.0% ($P = 0.08$), and 2.8% ($P = 0.01$) for hip, spine DXA, and spine qCT BMD, respectively.

The DC−VS group difference in spine BMD through follow-up was larger among participants who were on ART at baseline (spine DXA: $P = 0.02$ for the interaction between ART status and treatment group; qCT: $P = 0.05$). Otherwise, the treatment effect did not vary by sex, race, age, or other baseline factors, including smoking, history of alcohol abuse, baseline and nadir CD4 lymphocyte counts, HIV-RNA of 400 copies/ml or less, prior AIDS, BMI, and baseline BMD ($P > 0.05$ for all interactions between factors and treatment groups; data not shown).

Risk factors associated with decline in bone mineral density in the viral suppression group

Associations between the cumulative use of specific ART drugs with change in BMD in the VS group are summarized in Table 2.

In the first model, TA-NRTIs, tenofovir, other NRTIs, protease inhibitors, and nonnucleoside reverse

Table 2. Association of cumulative use of antiretroviral therapy with loss of bone mineral density in viral suppression group (continuous antiretroviral therapy).

			Change in bone mineral density (% of baseline) per year of drug use								
	Participants with antiretroviral drug use since study entry (out of $n = 98$)		Spine, qCT			Spine, DXA			Hip, DXA		
Time-updated covariates	Number	Mean duration (years)	Coef.	SE	*P*	Coef.	SE	*P*	Coef.	SE	*P*
Model 1											
ART	98	2.3									
NRTIs	98	2.3									
TA-NRTIs	69	1.8	−2.3	1.0	0.02	−0.9	0.5	0.09	0.5	0.4	0.19
Tenofovir	56	1.8	−0.3	1.0	0.80	−0.6	0.6	0.28	−0.2	0.4	0.54
Other NRTIs[a]	23	1.3	−0.7	1.7	0.67	0.8	0.9	0.34	0.1	0.6	0.85
PIs	63	1.7	−1.8	1.0	0.08	0.2	0.5	0.77	−0.2	0.4	0.52
NNRTIs	53	2.0	−0.7	0.9	0.42	0.9	0.5	0.08	−0.1	0.3	0.78
Follow-up time (years)	98	2.5	0.7	1.1	0.49	−0.4	0.6	0.47	−0.8	0.4	0.04
Model 2											
ART											
NRTIs											
Abacavir	42	1.8	−1.8	0.8	0.03	−0.3	0.4	0.49	−0.0	0.3	0.91
Lamivudine	80	2.0	−0.1	0.9	0.91	0.1	0.5	0.80	0.1	0.3	0.73
Stavudine	30	1.6	−2.7	1.0	0.009	−1.4	0.5	0.01	0.6	0.4	0.13
Tenofovir	56	1.8	0.3	0.9	0.73	−0.7	0.5	0.14	−0.0	0.4	0.92
Zidovudine	46	1.7	−1.7	0.9	0.06	−1.1	0.5	0.02	0.3	0.3	0.35
PIs[b]											
Atazanavir	32	1.1	−0.5	1.2	0.69	0.2	0.7	0.71	−0.1	0.5	0.88
Lopinavir/r	23	1.4	−3.7	1.3	0.006	−0.5	0.7	0.51	−0.9	0.5	0.06
Nelfinavir	14	1.5	−1.9	1.4	0.20	0.3	0.8	0.72	−0.4	0.6	0.51
NNRTIs											
Efavirenz	34	1.8	−1.9	0.9	0.03	0.2	0.5	0.69	−0.4	0.3	0.31
Nevirapine	22	2.0	0.8	1.0	0.44	1.3	0.6	0.02	−0.0	0.4	0.92
Follow-up time (years)	98	2.5	0.9	1.1	0.43	0.1	0.6	0.88	−0.8	0.4	0.06

Coefficients estimate the change in BMD, as percentage of baseline BMD, per year of using the drug or class after study entry. Estimates and *P* values were obtained in longitudinal mixed models for change in BMD as percentage of baseline. Cumulative use of specific drugs and drug classes since study entry was included as time-updated covariates. Model 1 assesses the association of drug classes with change in BMD, whereas model 2 includes separate variables for the most frequently used PIs, NRTIs, and NNRTIs. All analyses were adjusted for race, sex, race-by-sex interaction, age, smoking (ever and at baseline), history of alcohol abuse, BMI (baseline and time-updated change), and baseline BMD. Among these traditional risk factors, only change in BMI was associated with change in femur BMD, coefficient 0.8 per unit BMI increase, $P < 0.001$. ART, antiretroviral therapy; BMD, bone mineral density; DXA, dual-energy radiographic absorptiometry; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; qCT, quantitative computed tomography; TA-NRTI, thymidine analogue-reverse transcriptase inhibitor.

[a]Use of NRTIs, but no concomitant use of TA-NRTIs or tenofovir.

[b]Lopinavir and most other PI use was boosted by ritonovir. To avoid confounding, ritonovir use was not included as separate covariate.

transcriptase inhibitors (NNRTIs) were assessed. Per year of use of a TA-NRTI after study entry, spine BMD by qCT declined by 2.3% ($P = 0.02$); TA-NRTI use was borderline associated with loss of spine BMD by DXA ($P = 0.09$), but not with change in hip BMD. The second model included those drugs used most often in each drug class. Among NRTIs, both stavudine and zidovudine were at least borderline associated with spine BMD loss. Among protease inhibitors, lopinavir/r was associated with decline in spine BMD by qCT ($P = 0.006$), but not DXA, and borderline with loss of hip BMD ($P = 0.06$). For all other drugs, trends for association with BMD change ($P \leq 0.10$) were present for at most one of the three BMD outcomes.

Models 1 and 2 also included additional covariates (see Table 2 footnote) that may be risk factors for low BMD; none of these covariates was associated with change in BMD in our analyses, except for a positive association of BMI change with hip BMD change. As sensitivity analysis, both models were also fitted without any of the additional covariates; results were similar (data not shown).

Subgroup analyses comparing stopping versus continuing antiretroviral regimens

Table 3 summarizes first-year DC minus VS treatment differences in BMD outcomes within subgroups defined by use of various ART regimens at study entry. In all subgroups, and for all three BMD outcomes, continuing ART led to less favorable changes than intermittent ART, and the treatment difference was statistically significant in most subgroups. However, when comparing the treatment effects across the subgroup pairs, there was no evidence that stopping regimens that included a TA-NRTI, tenofovir, a protease inhibitor, or lopinavir/r, respectively, was more favorable than stopping other ART

Table 3. Change in bone mineral density in the first year among those on antiretroviral therapy at study entry, within subgroups by type of antiretroviral therapy at baseline.

Bone site and technique/subgroup by ART at study entry	Number of participants in subgroup	Mean change (%) at 1 year		Difference DC−VS at 1 year			Interaction *P* value[a]
		DC	VS	Est. Diff.	95% CI	*P*	
Total hip, DXA							
On TA-NRTI	113	0.0	−0.7	0.7	−0.2–1.7	0.14	0.005
On ART, not on TA-NRTIs	37	1.8	−2.0	3.8	1.8–6.1	0.003	
On tenofovir	26	1.4	−1.9	3.1	−0.4–6.5	0.10	0.13
On ART, not on tenofovir[b]	124	0.3	−0.8	1.1	0.2–2.0	0.01	
On PI	74	0.4	−1.1	1.5	0.1–2.9	0.03	0.92
On ART, not on PIs	76	0.5	−1.0	1.4	0.1–2.7	0.04	
On lopinavir/r	24	0.3	0.1	0.2	−2.8–3.2	0.90	0.31
On ART, not on lopinavir/r	126	0.5	−1.2	1.6	0.7–2.6	0.001	
Spine, DXA							
On TA-NRTI	115	1.8	−1.1	2.9	1.6–4.2	<0.001	0.38
On ART, not on TA-NRTIs	38	2.9	1.2	1.6	−0.8–4.1	0.20	
On tenofovir	27	2.7	0.6	2.1	−0.9–5.0	0.19	0.64
On ART, not on tenofovir[b]	126	1.9	−0.9	2.8	1.5–4.1	<0.001	
On PI	76	2.4	−1.2	3.7	2.0–5.4	<0.001	0.07
On ART, not on PIs	77	1.5	0.0	1.5	−0.1–3.1	0.07	
On lopinavir/r	25	2.3	−1.0	3.3	−0.4–6.9	0.09	0.64
On ART, not on lopinavir/r	128	2.0	−0.5	2.4	1.2–3.7	<0.001	
Spine, qCT							
On TA-NRTI	116	0.1	−3.9	3.9	1.0–6.8	0.009	0.18
On ART, not on TA-NRTIs	40	4.8	−3.1	7.8	3.0–12.6	0.003	
On tenofovir	27	2.4	−4.7	7.2	−0.9–15.2	0.10	0.43
On ART, not on tenofovir[b]	129	1.1	−3.4	4.4	1.9–7.0	<0.001	
On PI	77	1.7	−4.0	5.7	1.6–9.9	0.008	0.52
On ART, not on PIs	79	0.7	−3.3	4.1	1.1–7.0	0.009	
On lopinavir/r	25	1.9	−7.2	9.1	−0.1–18.2	0.06	0.19
On ART, not on lopinavir/r	131	1.1	−3.2	4.3	1.8–6.7	0.001	

ART, antiretroviral therapy; CI, confidence interval; DC, drug conservation group (intermittent ART); NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitors; TA-NRTI, thymidine analogue-NRTI; VS, viral suppression group (continuous ART).

[a]Interaction between treatment group and subgroup, tests for homogeneity of the treatment effect across subgroups.

[b]In the VS group, 15 of 98 participants were taking tenofovir at baseline; 14 more started tenofovir immediately after study entry and are counted among those not on tenofovir at baseline.

regimens. Subgroup analyses that included the entire follow-up provided similar results (data not shown).

Osteoporosis and fractures

There was no difference between the DC and VS groups in incidence of osteoporosis ($P = 0.80$ by Cox regression). In years 1–3, 4.3, 4.2, and 5.0% of participants had a DXA hip or spine *T*-score below −2.5 (osteoporosis); of those, 25% were receiving osteoporosis therapy 1 year later.

In the main SMART study, fractures were reported as grade 4 adverse events for 10 of 2753 participants in the VS group and two of 2720 in the DC group, at a rate of 0.13 and 0.03 per 100 person-years of follow-up, respectively [hazard ratio (VS/DC) 4.9, 95% CI 1.1–22.5, $P = 0.04$; about 7500 person-years of follow-up per treatment group]. Most of these fractures were associated with some degree of trauma.

Discussion

In this SMART substudy of 214 participants with mean follow-up of 2.4 years, BMD steadily declined in the group receiving continuous ART, whereas BMD remained stable or increased in the first year of intermittent, CD4 cell count-guided ART. For all three BMD measures, the between-group differences were statistically significant at year 1 and persisted through follow-up. Continuous ART may also have been associated with higher risk of fracture than intermittent ART. The unfavorable effect of continuous ART on BMD is in contrast to clinical outcomes, including progression to AIDS, myocardial infarction, and end-stage liver or renal disease, all of which were more common with intermittent ART [23,24,31].

The randomized comparisons between the DC and VS groups provide evidence that ART causes BMD loss.

Moreover, the pattern of BMD change is consistent with the increasing percentage of DC participants receiving ART after the first year (Fig. 2a); BMD declined in both treatment groups during this period (Fig. 2b–d). We found no evidence that uncontrolled HIV replication reduced BMD, as was previously suggested [6,32,33]; on the contrary, BMD remained stable in the intermittent ART group during the first year, when most participants were not receiving ART.

The treatment difference and the rate of BMD decline appeared largest for spine qCT. This is consistent with studies in the general population, in which the age-related BMD decline varies by scan location and technique, and spine BMD measured by qCT declines faster than BMD by DXA of the spine or hip [34,35]. Trabecular bone turns over more rapidly and, therefore, tends to show greater effects of bone-active agents.

In the VS cohort, the annual BMD decline by DXA (total hip 0.8%, spine 0.4% per year) was steeper than in healthy white men from age 35 to 55 years (hip 0.2%, spine 0.2%); BMD loss at the hip was similar to that in postmenopausal white women from 55 to 75 years (hip 0.8%, spine 0.8%) [36,37]. Also, BMD declined throughout follow-up (Fig. 2b–c), whereas in a study comparing tenofovir with stavudine in 600 participants over 144 weeks, BMD stabilized after the first year. Their rate of BMD loss averaged through week 144 was similar to our study, however, at 1.0% per year at the hip and 0.6% spine [22].

We could not determine which antiretroviral drugs or drug classes were most responsible for the BMD declines we observed. In the analysis of the VS cohort, associations of cumulative use of specific drugs with BMD decline varied by bone site, and statistical evidence was weak. No association was confirmed in the randomized comparisons across subgroups by baseline ART regimen.

In the VS cohort, cumulative use of stavudine and zidovudine were each associated with loss in spine BMD, consistent with other studies [22,38,39]. Cumulative use of lopinavir/r was associated with BMD loss at the spine (by qCT) and total hip. Association of lopinavir/r with BMD loss has been reported previously [21,40]. Results of the cohort analysis are by design hypothesis-generating, not conclusive evidence.

The weak associations of specific drugs with BMD decline in the presence of a clear BMD difference between intermittent and continuous ART may be due to several factors. These factors include:

(1) Sample size and follow-up time were moderate.
(2) Several drugs may contribute to BMD decline, and the effects of individual drugs may have been too weak to be identified in the presence of other BMD-active ART.
(3) In the VS cohort, 93% of follow-up time was spent on ART and follow-up time was included as covariate in the regression. Therefore, *P* values for individual drugs assess only the added contribution beyond the average ART effect. Such analysis tends to give weaker statistical evidence for the effect of drugs that are taken by many participants.

Traditional risk factors for low BMD such as age, sex, race, smoking, or alcohol abuse at baseline were not associated with change in BMD. It is possible that the effect of these factors on BMD is evident only with longer follow-up.

The fracture data from the parent SMART trial suggest, but certainly do not prove, that continuous ART may increase the risk of fracture as compared with intermittent ART. Fracture events were not systematically collected, but identified from grade 4 adverse event reports.

The main strengths of our study are the randomized comparisons of intermittent versus continuous ART and the standardized assessment of BMD. The study has the following limitations:

(1) Mean follow-up was only 2.4 years and many participants had only 1 year of follow-up due to the early termination of the substudy. The subgroup analyses in particular were underpowered.
(2) Fractures were only passively collected.
(3) The study was conducted between 2002 and 2006; some antiretroviral drugs such as TA-NRTIs and first-generation protease inhibitors are less common today in industrialized countries.

Our study did not address management of low BMD in patients receiving continuous ART. Current US Department of Health and Human Services (DHHS) guidelines suggest to consider BMD assessments in adults receiving ART [41]. In clinical trials, the use of bone turnover markers in addition to BMD improved estimates of fracture risk in postmenopausal osteoporotic women; their diagnostic value in clinical practice is still unclear [42]. In small, randomized trials, bisphosphonates improved BMD in HIV-infected adults [43,44]; other potential agents such as parathyroid hormone have not been evaluated.

Given the current trend to initiate ART earlier in the course of HIV infection and the importance of maintaining continuous ART, our data suggest that low BMD may become more prevalent as more patients use ART for decades, possibly resulting in higher fracture rates. Studies are needed to better predict osteoporosis risk in HIV-infected persons in order to guide individualized recommendations for diagnosis and treatment of low BMD.

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