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BRIEF REPORT

Long-term Bone Mineral Density Changes in Antiretroviral-Treated HIV-Infected Individuals

Philip M. Grant,[1] Douglas Kitch,[3] Grace A. McComsey,[5] Ann C. Collier,[7] Susan L. Koletar,[6] Kristine M. Erlandson,[8] Michael T. Yin,[9] Benedetta Bartali,[4] Belinda Ha,[10] Kathy Melbourne,[2] and Todd T. Brown[11]

[1]Division of Infectious Diseases, Department of Medicine, Stanford University, Palo Alto, and [2]Gilead Sciences, Foster City, California; [3]Center for Biostatistics in AIDS Research, Harvard T. H. Chan School of Public Health, Boston, and [4]New England Research Institute, Watertown, Massachusetts; [5]Division of Infectious Diseases, Departments of Pediatrics and Medicine, Case Western Reserve University, Cleveland, and [6]Division of Infectious Diseases, Department of Medicine, Ohio State University, Columbus; [7]Division of Infectious Diseases, Department of Medicine, University of Washington, Seattle; [8]Division of Infectious Diseases, Department of Medicine, University of Colorado, Aurora; [9]Division of Infectious Diseases, Department of Medicine, Columbia University, New York, New York; [10]Viiv Healthcare, Research Triangle, North Carolina; and [11]Division of Endocrinology, Diabetes, and Metabolism, Department of Medicine, Johns Hopkins University, Baltimore, Maryland

We compared adjusted bone mineral density (BMD) changes between human immunodeficiency virus (HIV)-infected individuals during the first approximately 7.5 years after antiretroviral therapy (ART) initiation and HIV-uninfected controls. HIV-infected individuals (n = 97) had significantly greater adjusted BMD decline than controls (n = 614) during the first 96 weeks of ART. Subsequently, the rate of BMD decline slowed in HIV-infected individuals but remained greater than the rate of decline in HIV-uninfected individuals at the lumbar spine but not at the hip. In HIV-infected individuals after 96 weeks, no HIV- or treatment-related characteristic was associated with BMD loss, but lower lean body mass was associated with greater BMD loss at both lumbar spine and hip.

Keywords. anti-HIV agents, administration and dosage, adverse effects; HIV infections, drug therapy/virology; bone density.

Low bone mineral density (BMD) occurs in 40%–90% of human immunodeficiency virus (HIV)-infected individuals [1]. The etiology of low BMD is multifactorial, with contributions from antiretroviral therapy (ART), HIV and its associated immune dysfunction, and traditional osteoporosis risk factors [2]. HIV-infected individuals have a 60% increased fracture risk as compared to uninfected individuals [3].

BMD loss is substantial during the first 2 years of ART, generally decreasing 2%–6% [4], although the loss may be less with some integrase inhibitor–containing regimens [5]. There are few studies on long-term BMD changes in ART-treated individuals. No study has compared long-term BMD changes in HIV-infected individuals initiating ART to changes in uninfected controls. This study's aim is to compare long-term BMD change after ART initiation in a well-characterized HIV-infected study population to that observed in HIV-uninfected individuals.

METHODS

Participants and Study Procedures

ART-naive HIV-infected individuals in AIDS Clinical Trials Group (ACTG) A5202 were randomly assigned to receive atazanavir/ritonavir (ATV/r) or efavirenz (EFV) combined with tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC) during 2005–2007 [6]. Participants in the metabolic substudy, ACTG A5224s, underwent baseline and follow-up whole-body and site-specific dual-energy x-ray absorptiometry (DXA), with primary end points reported at 96 weeks after ART initiation [3].

In 2013–2014, we attempted to contact participants previously enrolled in ACTG A5224s. Study exclusion criteria included previous receipt of osteoporosis medications, including bisphosphonates, teriparatide, denosumab, tamoxifen, or raloxifene. Participants had one follow-up whole-body and site-specific DXA of the lumbar spine and hip performed with a DXA machine from the same manufacturer (ie, Hologic or Lunar) that produced the initial DXA machines used in ACTG A5224s. DXA protocols were standardized at participating sites, and findings were compared to those from prior DXAs performed at a central location (Tufts University, Boston, Massachusetts). We obtained a medical/medication history and administered questionnaires to obtained data on substance use and physical activity. Each participant provided written informed consent. The study was approved by each site's institutional review board.

HIV-Uninfected Controls

For comparison to HIV-uninfected individuals, we gained access to participant-level data from 2 longitudinal studies, which performed DXA in young men and women. DXA data from baseline and year 7 of follow-up were obtained for 692 HIV-uninfected men enrolled in the Boston Area Community Health/Bone Survey [7]. In the metabolic substudy of the Women's Interagency HIV Study (WIHS), DXA was performed at baseline and year 5 of follow-up in 122 HIV-uninfected women [8]. We excluded data from participants in these studies who were outside the sex-specific age window of HIV-infected participants (the age of HIV-infected men and women at initial DXA was 20–64 years and 23–55 years, respectively) and assumed a linear rate of change in BMD among HIV-uninfected individuals.

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Correspondence: P. M. Grant, Division of Infectious Diseases and Geographic Medicine, Stanford University, 300 Pasteur Dr, Rm S-101, Stanford, CA 94305-5107 (pmgrant@stanford.edu).

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Statistical Analyses

We used repeated measures analyses with piecewise slopes to compare the rate of change, calculated as the percentage change in BMD per year, in lumbar spine and hip BMD between HIV-infected and uninfected individuals during the first 96 weeks of study (hereafter, the early period) and from 96 weeks to the end of study follow-up (hereafter, the late period), adjusting for age, sex, race, body mass index (BMI), self-reported physical activity level, cigarette and alcohol use, and receipt of relevant concomitant medications. We analyzed concomitant medications as 2 variables: medications that may increase BMD (ie, testosterone, calcium, vitamin D, hormone replacement, and parathyroid hormone) and those that may decrease BMD (ie, corticosteroids, hormonal contraceptives, anti–hepatitis C virus medications, anticonvulsants, selective serotonin uptake inhibitors, and proton pump inhibitors).

In HIV-infected individuals, we compared rate of change in BMD during the early period to that in the late period and performed multivariable analyses to examine associations during both the early and late periods between the rate of change in BMD and age, sex, race, baseline body mass index (BMI), randomized ART regimen, cumulative TDF and protease inhibitor (PI) exposure, and baseline and time-updated total lean body mass, receipt of relevant concomitant medications, $CD4^+$ T-cell count, and HIV RNA level.

Factors with univariate P values of <.20 were included in multivariable models, which used backward selection and retained factors with P values of <.05. Analysis was 2-sided with a type 1 error of 5%; thus, P values of <.05 were considered statistically significant without adjustment for multiple comparisons.

RESULTS

Patient Characteristics

Ninety-seven of 269 participants from ACTG A5224s enrolled in this study. Baseline characteristics between ACTG A5224s participants who were and those who were not enrolled in this study did not differ significantly. Briefly, among ACTG A5224s participants who were and those who were not enrolled, the median age at enrollment in ACTG A5224s was 40 years and 38 years, respectively; the proportion of males was 86% and 85%, respectively; and the median baseline $CD4^+$ T-cell count was 247 cells/μL and 229 cells/μL, respectively ($P > .05$ for all comparisons).

Characteristics of HIV-infected participants and HIV-uninfected controls differed; HIV-infected individuals were younger, had a lower BMI at both initial and final DXA, and had higher rates of never smokers and individuals reporting low-to-moderate alcohol consumption (Table 1). Median time between initial and final DXA in HIV-infected participants and controls was 7.6 years (interquartile range [IQR], 7.3–7.8 years) and 6.9 years (IQR, 6.5–7.3 years), respectively.

Table 1. Characteristics of Human Immunodeficiency Virus (HIV)–Infected Participants and Controls

Characteristic	HIV-Infected Participants (n = 97)	Controls (n = 614)	*P* Value
Age at initial DXA, y	40 (31–44)	46 (38–54)	<.001
Time between initial and final DXA, y	7.6 (7.3–7.8)	6.9 (6.5–7.3)	<.001
Male sex	86	87	.62
Race/ethnicity			<.001
White, non-Hispanic	47	35	
Black, non-Hispanic	34	33	
Hispanic (regardless of race)	14	31	
Other	5	1	
BMI[a]			
At initial DXA	24 (22–27)	28 (25–32)	<.001
At final DXA	27 (23–30)	29 (26–33)	<.001
Self-reported physical activity level[b]			.07
Low	32	25	
Moderate	25	53	
High	43	22	
Smoking[b]			<.001
Current	33	31	
Past	14	33	
Never	53	36	
Alcohol consumption[b]			.03
0 drinks/day	23	49	
<3 drinks/day	74	36	
≥3 drinks/day	3	14	
Concomitant medicine increasing BMD[c]			
At Initial DXA	7	9	.57
At Final DXA	18	22	.35
Concomitant medicine decreasing BMD[d]			
At initial DXA	14	13	.75
At final DXA	26	6	<.001
HCV antibody positive	6	ND[e]	NA
$CD4^+$ T-cell count, cells/μL			
At initial DXA	247 (130–333)	NA	NA
At final DXA	598 (408–707)		
HIV RNA level at initial DXA, $\log_{10}$ copies/mL	4.6 (4.2–4.8)	NA	NA
HIV RNA level <200 copies/mL at final DXA	86	NA	NA
Cumulative TDF exposure, y	5.8 (1.1–7.4)	NA	NA
Cumulative PI exposure, y	3.7 (0–6.9)	NA	NA

Data are median values (interquartile ranges) or percentage of participants.

Abbreviations: BMD, bone mineral density; DXA, dual-energy x-ray absorptiometry; HCV, hepatitis C virus; NA, not applicable; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

[a] Body mass index (BMI) is calculated as the weight in kilograms divided by the height in meters squared.

[b] At final DXA (not available at initial DXA for HIV-infected participants).

[c] Defined as receipt of testosterone, calcium, vitamin D, hormone replacement, or parathyroid hormone.

[d] Defined as receipt of corticosteroids, hormonal contraceptives, hepatitis C medications, anticonvulsants, selective serotonin uptake inhibitors, or proton pump inhibitors.

[e] No data (ND) were recorded for controls.

Among HIV-infected participants, median age at initial DXA was 40 years (vs 46 years among uninfected individuals; $P < .001$). Eighty-six percent of participants were male (vs 87% of uninfected

Table 2. Univariate and Multivariable Associations With Percentage Change in Lumbar Spine Percent Bone Mineral Density Among Human Immunodeficiency Virus (HIV)–Infected Participants

Interval, Covariate	Univariate Analysis		Multivariable Analysis	
	Percentage Change/Year (95% CI)	*P* Value	Percentage Change/Year (95% CI)	*P* Value
Initial to week 96				
Years from baseline to week 96	. . .		−0.91 (−1.29 to −.52)	<.001
Randomized to TDF/FTC vs ABC/3TC	−0.87 (−1.73 to −.02)	.045	−0.87 (−1.64 to −.10)	.028
Baseline $CD4^+$ T-cell count (per 50 cells/μL higher)	0.27 (.14–.41)	<.001	0.20 (.06–.34)	.005
Time-updated $CD4^+$ T-cell count (per 50 cells/μL higher)	0.07 (.02–.12)	.005	. . .	
Baseline HIV RNA load (per 1 $\log_{10}$ copy/mL higher)	−1.39 (−2.09 to −.69)	<.001	−0.79 (−1.50 to −.08)	.029
Week 96 to final				
Male vs female	0.75 (.18–1.32)	.011	. . .	
Baseline total lean body mass (per 1 kg higher)	0.04 (.01–.06)	.003	. . .	
Time-updated lean body mass (per 1 kg higher)	0.06 (.03–.08)	<.001	0.05 (.03–.08)	<.001

Only associations with a *P* value of <.05 are displayed. Data were evaluated for associations between bone mineral density change and age, sex, race, baseline body mass index, randomized antiretroviral therapy regimen, cumulative TDF and protease inhibitor exposure, and baseline and time-updated total lean body mass, receipt of relevant concomitant medications, $CD4^+$ T-cell count, and HIV RNA level.

Abbreviations: 3TC, lamivudine; ABC, abacavir; CI, confidence interval; FTC, emtricitabine; TDF, tenofovir disoproxil fumarate.

individuals; $P = .62$). Median $CD4^+$ T-cell count at initial and final DXA was 247 cells/μL and 598 cells/μL, respectively. Median HIV RNA level at initial DXA was 4.6 $\log_{10}$ copies/mL, and 86% of participants had an HIV RNA level of <200 copies/mL at final DXA. The median duration of TDF exposure during study follow-up was 5.8 years, and the median duration of PI exposure was 3.7 years. Seventy-one percent of HIV-infected participants were receiving TDF, and 45% were receiving a ritonavir-boosted PI at final DXA.

Rate of Change in BMD in HIV-Infected Individuals Versus That in Controls During the Early Period

Supplementary Figure 1*A* displays the unadjusted rate of change in BMD in HIV-infected and HIV-uninfected individuals at the lumbar spine over the study period. After adjustment, HIV-infected individuals had a greater rate of decline in lumbar spine BMD during the early period (ie, from initial DXA to 96 weeks), compared with HIV-uninfected individuals (−0.76%/year vs 0.09%/year; 95% confidence interval [CI] for the difference, −1.34%/year to −.37%/year; $P = .001$).

Supplementary Figure 1*B* shows the unadjusted rate of change in hip BMD, by serostatus. HIV-infected individuals had greater adjusted rate of decline in hip BMD during the early period, compared with HIV-uninfected individuals (−1.56%/year vs −0.31%/year; 95% CI for the difference, −1.71% to −.80%; $P < .001$).

Rate of Change in BMD in HIV-Infected Individuals Versus That in Controls During the Late Period

There was a trend toward a slowing rate of decline in lumbar spine BMD in HIV-infected individuals between the early and late periods (−0.76%/year vs −0.25%/year; 95% CI for the difference, −1.08% to .06%; $P = .08$). However, HIV-infected individuals continued to have a greater adjusted rate of decline in lumbar spine BMD during the late period, compared with uninfected individuals (−0.25%/year vs 0.09%/year; 95% CI for the difference, −.60%/year to −.09%/year; $P = .008$).

Between the early and late periods, the rate of decline in hip BMD in HIV-infected individuals slowed (−1.56%/year vs −0.31%/year; 95% CI for the difference, −1.80%/year to −.71%/year; $P < .001$). There was no difference in the rate of change in hip BMD between HIV-infected individuals and uninfected individuals during the late period (−0.31%/year vs −0.31%/year; 95% CI for the difference, −.23%/year to .23%/year; $P = .99$).

Factors Associated With Changes in BMD in HIV-Infected Individuals During the Early Period

During the early period, randomization to TDF/FTC arm, lower baseline and time-updated $CD4^+$ T-cell count, and higher baseline HIV RNA level were associated with greater BMD loss at the lumbar spine (Table 2; $P = .045$, $P < .001$, $P = .005$, and $P < .001$, respectively). In multivariable analysis, randomization to TDF/FTC arm, lower baseline $CD4^+$ T-cell count, and higher HIV RNA level remained associated with greater BMD loss at the lumbar spine ($P = .028$, $P = .005$, and $P = .029$, respectively).

Time-updated total lean body mass and time-updated receipt of concomitant medications that decrease BMD were associated with a change in BMD at the hip during the early period ($P = .001$ and $P = .03$, respectively; Table 3). Both factors remained statistically significant in multivariable analysis ($P = .001$ and $P = .03$, respectively).

Factors Associated With Changes in BMD in HIV-Infected Individuals During the Late Period

During the late period, in univariate analyses, female sex and lower baseline and time-updated total lean body mass were associated with greater decreases in lumbar spine BMD ($P = .011$, $P = .003$, and $P < .001$, respectively). In multivariable analysis,

Table 3. Univariate and Multivariable Associations With Percentage Change in Total Hip Bone Mineral Density Among Human Immunodeficiency Virus (HIV)–Infected Participants

Interval, Covariate	Univariate Analysis		Multivariable Analysis	
	Percentage Change/Year (95% CI)	*P* Value	Percentage Change/Year (95% CI)	*P* Value
Initial to week 96				
Years from baseline to week 96	. . .		−1.29 (−1.73 to −.86)	<.001
Time-updated lean body mass (per 1 kg higher)	0.08 (.03–.12)	.001	0.08 (.03–.12)	.001
Time-updated use of medications that lower BMD vs those that do not[a]	0.68 (.07–1.30)	.03	0.50 (.04–.97)	.03
Week 96 to final				
Years after week 96	. . .		−0.28 (−.45 to −.12)	.001
Time-updated lean body mass (per 1 kg higher)	0.06 (.03–.09)	<.001	0.06 (.03–.09)	<.001
Baseline use of medications that lower BMD vs those that do not[a]	0.72 (.29–1.14)	.001	0.78 (.38–1.18)	<.001
Baseline HIV RNA load (per 1 $\log_{10}$ copy/mL higher)	0.44 (.05–.84)	.027	. . .	

Only associations with a *P* value of <.05 are displayed. Data were evaluated for associations between bone mineral density change and age, sex, race, baseline body mass index, randomized antiretroviral regimen, cumulative tenofovir disoproxil fumarate and protease inhibitor exposure, and baseline and time-updated total lean body mass, receipt of relevant concomitant medications, $CD4^+$ T-cell count, and HIV RNA level.

Abbreviations: BMD, bone mineral density; CI, confidence interval.

[a] Defined as receipt of corticosteroids, hormonal contraceptives, hepatitis C medications, anticonvulsants, selective serotonin uptake inhibitors, or proton pump inhibitors.

only lower time-updated total lean body mass was significantly associated with greater BMD loss at the lumbar spine ($P < .001$).

In univariate analyses for changes in hip BMD during the late period, baseline receipt of concomitant medications that lower BMD, baseline HIV RNA level, and time-updated total lean body mass were associated with a change in hip BMD ($P = .001$, $P = .03$, and $P < .001$, respectively). In multivariable analysis, receipt of concomitant medications that lower BMD and time-updated total lean body mass remained associated with a change in hip BMD ($P < .001$ for both). There was no relationship between HIV-related or treatment-related factors and BMD loss at the lumbar spine or hip during the late period.

DISCUSSION

Few studies have evaluated long-term BMD changes in HIV-infected individuals after ART initiation. Most studies have been limited to 96 weeks [4, 5]. Longer-term BMD changes from Gilead 903 were reported, but the study lacked an HIV-uninfected control group [9]. Controlled studies include HIV-infected individuals already receiving ART at study initiation and generally have relatively short follow-up periods [10]. Here, we compared BMD changes 7.5 years after ART initiation in 97 HIV-infected individuals to changes in HIV-uninfected controls. We found that, during the first 96 weeks after ART initiation, HIV-infected individuals had a significantly greater adjusted rate of decline in BMD at both the lumbar spine and hip as compared to controls. The rate of decline in BMD after the first 96 weeks of ART slowed in HIV-infected individuals. However, the rate of decline in BMD was still faster at the lumber spine, although not at the hip, than that among HIV-uninfected controls.

Similar to other published work during the early ART period, BMD decline at the spine (but not at the hip) was associated with TDF use, lower $CD4^+$ T-cell count, and higher HIV RNA level [2, 4, 5, 11]. The relatively small sample size of HIV-infected individuals in the current study reduced our power to detect other potentially relevant associations.

During the period from 96 weeks after ART initiation to the final DXA, we found no relationship between HIV- or treatment-related factors and BMD change. Instead, we found a consistent relationship between greater total lean body mass and maintenance of BMD, a relationship also reported in uninfected individuals and in a study of HIV-infected individuals [8, 12]. We found no relationship between cumulative TDF or PI exposure and BMD decline during the late period. Several studies have shown that BMD increases after a switch from TDF to an alternative agent [13, 14]. However, our study suggests that, after the initial independent negative impact of TDF, there may not be continued BMD decrease attributable to TDF. Our data are reassuring in that even with Food and Drug Administration approval of tenofovir alafenamide, TDF likely will remain commonly used for HIV treatment in resource-limited settings (at least in the near future) and for preexposure prophylaxis globally.

There are several limitations to our study. Control populations were not specifically recruited for our study; unmeasured factors could account for differences in the rate of decline in BMD between the HIV-infected and control groups. Many ACTG A5224s participants were not enrolled in this study; however, similar baseline characteristics between those who were and those who were not enrolled provide reassurance that this is unlikely to be a major source of bias. We lacked complete data on covariates, such as hepatitis C virus infection, testosterone level, and vitamin D level, that could affect BMD. In the control population, spine BMD slightly increased, but this is consistent with what has been reported in other studies [15]. The difference in the rate of change in BMD between HIV-

infected individuals and uninfected individuals is relatively modest. However, the increased loss could be compounded in persons with preexisting low BMD or if the loss continues beyond the evaluated period. HIV-infected individuals reported high physical activity levels; BMD loss may be greater in sedentary individuals. ART has evolved since this study was completed. Whether our results would extend to individuals receiving newer antiretrovirals is unknown. We did not have complete data on ART interruptions, although there were high levels of adherence with ART at final DXA.

In conclusion, we found that HIV-infected individuals continue to lose BMD after the rapid decline during the first 2 years of ART, albeit at a slower rate. BMD loss in HIV-infected individuals remains greater than in uninfected controls at the lumbar spine but not at the hip through 7.5 years after ART initiation. Low lean body mass is a consistent predictor of BMD loss in long-term treated individuals. Fragility fractures may increase as HIV-infected individuals continue to receive ART for decades, and interventions to maintain or increase lean body mass may benefit long-term skeletal health.

Supplementary Data

Supplementary materials are available at http://jid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases (NIAID) or the National Institutes of Health (NIH).

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