



ORIGINAL ARTICLE

Reduced bone mineral density among HIV-infected patients in Taiwan: Prevalence and associated factors



Mao-Song Tsai^a, Chien-Ching Hung^a, Wen-Chun Liu^a,
Kuan-Lin Chen^b, Mao-Yuan Chen^a, Szu-Min Hsieh^a,
Wang-Huei Sheng^a, Hsin-Yun Sun^a, Tiffany T.F. Shih^{b,*}

^a Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University, College of Medicine, Taipei, Taiwan

^b Department of Medical Imaging and Radiology, National Taiwan University Hospital and National Taiwan University, College of Medicine, Taipei, Taiwan

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KEYWORDS

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Prevalence

Background: Reduced bone mineral density (BMD) is an emerging threat to the successful long-term management of human immunodeficiency virus (HIV) infection among patients with access to combination antiretroviral therapy (cART). Data on the prevalence and associated factors of reduced BMD in Asian populations remain scarce.

Methods: From March 2002 to April 2006, a cross-sectional survey was conducted among HIV-infected patients aged ≥ 20 years at the National Taiwan University Hospital. BMD of the lumbar spine was measured with the use of dual-energy X-ray absorptiometry. Osteopenia was defined as a BMD T-score between -1.0 and -2.5 , and osteoporosis was defined as a BMD T-score ≤ -2.5 . Linear and ordinal logistic regression analyses were performed.

Results: Among 320 patients with a median age of 37.3 years, body mass index (BMI) of 21.4 kg/m^2 and 94.4% on cART, osteopenia and osteoporosis were diagnosed in 35.6% and 3.8%, respectively. On multivariate linear analysis, factors associated with reduced BMD were increasing age ($p = 0.006$), longer duration on antiretroviral therapy ($p = 0.007$), and a decreasing BMI ($p = 0.002$). Using ordinal logistic regression, being underweight with a body mass index (BMI) $< 18.5 \text{ kg/m}^2$ was independently associated with reduced BMD (proportional odds ratio, 4.12; 95% confidence interval, 1.93–8.82).

* Corresponding author. Department of Medical Imaging and Radiology, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan.

E-mail address: ttfshih@ntu.edu.tw (T.T.F. Shih).

Conclusion: Reduced BMD was prevalent among HIV-infected Taiwanese adults on cART. Increased age, lower BMI, and exposure to antiretroviral therapy were significantly associated with decrease of BMD.

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Introduction

Widespread use of combination antiretroviral therapy (cART) has led to dramatic decline in human immunodeficiency virus (HIV)-related morbidity and mortality.¹ Prolonged antiretroviral therapy exposure has been associated with comorbidities including metabolic syndrome, cardiovascular disease, and osteoporosis.^{2,3} A meta-analytical review revealed 67% of HIV-infected patients had reduced bone mineral density (BMD).⁴ Compared with HIV-uninfected controls, HIV-infected patients had a 6.4-fold increased odds of reduced BMD and a 3.7-fold increased odds of osteoporosis.⁴ A large cohort study revealed that among 671 HIV-infected patients with a median follow-up of 2.5 years, 12.5% progressed to osteopenia and 15.6% to osteoporosis.⁵

For an individual, osteopenia carries a 2-fold increase in risk for fracture compared with normal BMD, and a history of osteoporosis without fracture carries a 4- to 5-fold; individuals with osteoporosis with a history of fracture increases the risk for recurrent fractures by 20-fold.^{6,7} In a population-based U.S. study, HIV-infected individuals had a higher fracture rate than non-HIV-infected patients (2.87 vs. 1.77 fractures per 100 persons).⁸

The mechanisms underlying changes in bone metabolism among HIV-infected patients are unclear but likely multifactorial. Traditional risk factors includes female sex, low body mass index (BMI), physical inactivity, steroid use, advanced age, decreased intake of calcium and vitamin D, duration of menopause, smoking, and low testosterone levels.^{9–12} Although racial differences in BMD have been reported,¹³ epidemiologic studies of BMD among HIV-infected patients are rarely conducted among Asian populations.¹⁴ Tenofovir, a nucleotide analog HIV reverse transcriptase inhibitor, was approved by the U.S. Food and Drug Administration on October 26, 2001. Metabolic bone abnormalities have been seen in young animals given high-dose tenofovir and HIV-infected adults treated with tenofovir.^{15,16} In Taiwan, tenofovir was approved for use in adults with HIV infection after August 2007. The objectives of this study were to determine the prevalence of and associated factors with reduced BMD in a cohort of HIV-infected adult patients before introduction of tenofovir in Taiwan.

Methods

The study was approved by the Research Ethics Committee of the hospital and all participants gave written informed consent.

Study setting and population

From March 2002 to April 2006, HIV-infected patients aged \geq 20 years who sought HIV care were invited to participate in

a cross-sectional survey of BMD at the National Taiwan University Hospital. Patients were excluded if they had received growth hormone, testosterone, bisphosphonates, immunosuppressants, chemotherapy, or steroids; were pregnant; or had a history of hospitalization or immobilization within the previous three months.

Epidemiologic investigation

After enrolment, a standardized case report form was used to collect information on demographics (age and sex), menopause, smoking habit, BMI, comorbid conditions (including kidney disease or chronic viral hepatitis), current and previous antiretroviral regimens, and cumulative duration of antiretroviral therapy from medical record review.

Laboratory and radiographic investigations

Routine laboratory testing (including hematologic, biochemical, immunologic, and virologic investigations) were performed every 3–6 months following the national guidelines for treatment and management of HIV-infected adults in Taiwan.¹⁷ The laboratory results were entered into a large computer database. Plasma HIV RNA load was quantified using the CobasAmplicor HIV-1 Monitor test (CobasAmplicor version 1.5, Roche Diagnostics Corporation, IN, USA) with a lower detection limit of 50 copies/mL (1.7 log₁₀ copies/mL), and CD4 lymphocyte count was determined using FACFlow (BD FACS Calibur, Becton Dickinson, CA, USA). The CD4 count and plasma HIV RNA load were monitored 1 month after initiation of cART in antiretroviral-naïve patients, or change of regimens in the face of virological failure; and every 3–6 months thereafter according to the national HIV treatment guidelines.

BMD was measured with the use of dual-energy X-ray absorptiometry (DXA) scan. The BMD and T score (expressed as standard deviation units in comparison with young normal reference value) of the lumbar spine were measured using the same DXA device (Lunar Prodigy; GE Healthcare, Diegem, Belgium).

Definitions

CART was defined as a combination of at least 3 antiretroviral agents that contained 2 nucleoside reverse-transcriptase inhibitors (NRTIs) plus 1 or 2 protease inhibitors or 1 non-nucleoside reverse-transcriptase inhibitor (NNRTI) or triple NRTIs.

Based on the World Health Organization (WHO) criteria,¹⁸ osteopenia was defined as a BMD T-score between -1.0 and -2.5 , and osteoporosis was defined as a BMD T-score less than or equal to -2.5 .

Being underweight was defined as having a BMI < 18.5 kg/m² based on the WHO standards for Asian populations.¹⁹

Duration on antiretroviral therapy was calculated by the number of days or weeks of an antiretroviral agent used. Length of time after HIV diagnosis was defined as the interval between the date of the first documented HIV-positive test result and the date of enrollment into this study.

The prevalence and associated factors of reduced BMD was determined based on the first DXA scan available. Variables from the DXA scan were treated as ordinal (normal values, osteopenia, or osteoporosis).

Statistical analyses

Parametric data were contrasted using an analysis of variance (ANOVA). Nonparametric data, expressed as median and interquartile range (IQR), were compared using the Kruskal-Wallis test. Categorical variables were compared using the chi-square test or the Fisher exact test. Multivariate linear regression and ordinal logistic regression models were applied to correlate the effect of the independent variables (clinical and demographic characteristics) with the results of DXA scan. The regression models were built using a stepwise procedure. The *p* value for inclusion of a covariate in the model was set at 0.15, and the *p* value for removal of the covariate was set at 0.20. The confidence interval (CI) was set at 95%. All statistical

tests were two-tailed, and *p* values < 0.05 were considered to be statistically significant. The analysis was conducted using the statistical package SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics

During the 4-year study period, 320 patients participated in the survey. The characteristics of the patients are shown in Table 1. There were 290 males (90.6%) and 30 females (9.4%). The median age was 36.5 years (IQR, 30.6–41.6) for males and 47.0 years (IQR, 35.6–53.7) for females (*p* < 0.01). The mode of HIV transmission among males was predominantly homosexual contact (69.3%), followed by heterosexual contact (30.3%), whereas all of the females acquired HIV through heterosexual contact.

At the time of the survey, 302 (94.4%) of the patients were receiving cART. The median cumulative duration on treatment was 14.3 months (IQR, 2.9–39.2) for NRTIs, 6.2 months (IQR, 0.0–18.6) for NNRTIs and 0.8 months (IQR, 0.0–21.4) for protease inhibitors.

Data on BMI were available for 317 patients (287 males and 30 females). The median BMI was 21.4 kg/m² (IQR, 19.8–23.0). BMI was < 18.5 kg/m² in 31 of these patients (9.7%). There was no statistically significant difference

Table 1 Baseline characteristics of the HIV-infected patients with normal bone mineral density, osteopenia, and osteoporosis

	All (<i>n</i> = 320)	Normal (<i>n</i> = 194)	Osteopenia ^a (<i>n</i> = 114)	Osteoporosis ^a (<i>n</i> = 12)	<i>p</i> value ^b
Male, <i>n</i> (%)	290 (90.6)	173 (89.1)	108 (94.7)	9 (75.0)	<0.01
Menopause, <i>n</i> (%)	14 (4.6)	7 (3.3)	5 (8.3)	2 (66.7)	0.07
Median age, (IQR), y	37.3 (31.4–44.5)	37.1 (31.3–43.4)	37.0 (30.5–44.5)	49.0 (40.2–56.1)	0.15
>65 y, <i>n</i> (%)	6 (1.9)	4 (2.1)	1 (0.9)	1 (8.3)	0.19
MSM, <i>n</i> (%)	201 (62.8)	127 (65.4)	70 (61.4)	4 (33.3)	0.08
Median length of time after HIV diagnosis (IQR), y	1.3 (0.4–3.3)	1.1 (0.3–3.2)	1.6 (0.6–3.4)	1.9 (0.5–3.6)	0.46
Median BMI (IQR), kg/m ²	21.4 (19.8–23.0)	21.8 (20.3–23.5)	21.0 (19.6–22.6)	19.2 (17.9–21.9)	<0.01
BMI < 18.5 kg/m ² , <i>n</i> (%)	31 (9.7)	11 (5.7)	15 (13.1)	5 (41.7)	<0.01
BMI, 18.5 to 23 kg/m ² , <i>n</i> (%)	203 (63.4)	121 (62.3)	76 (66.7)	6 (50.0)	0.45
Smoking, <i>n</i> (%)	133 (41.5)	83 (42.8)	47 (41.2)	3 (25.0)	0.48
Hepatitis B or C co-infection, <i>n</i> (%)	80 (25.0)	50 (25.7)	25 (21.9)	5 (41.7)	0.30
Median CD4+ count (IQR) (cells)	286 (169–455)	302 (168–478)	277 (174–425)	187 (111–364)	0.10
Plasma HIV RNA load < 400 copies/ml, <i>n</i> (%)	229 (72)	140 (72.1)	81 (71.1)	8 (66.7)	0.76
On cART, <i>n</i> (%)	302 (94.4)	179 (92.2)	111 (97.3)	12 (100)	0.12
Median duration on cART (IQR), mo	15.6 (3.6–42.1)	13.2 (2.4–41.9)	18.0 (6.1–40.8)	27.6 (13.2–44.4)	0.35
Cumulative antiretroviral exposure (IQR), mo					
NRTI	14.3 (2.9–39.2)	11.2 (2.0–40.6)	14.8 (5.6–39.1)	27.2 (13.5–44.2)	0.37
NNRTI	6.2 (0–18.6)	5.7 (0–17.0)	6.5 (0.2–19.1)	14.0 (0.8–20.9)	0.21
PI	0.8 (0–21.4)	0.3 (0–20.9)	2.2 (0–22.5)	7.2 (0.01–34.8)	0.71

^a See definitions in Methods section.

^b Comparison of the three groups.

BMI = body mass index; cART = combination antiretroviral therapy; HIV = human immunodeficiency virus; IQR = interquartile range; MSM = men who have sex with men; NNRTI = non-nucleoside reverse-transcriptase inhibitor; NRTI = nucleoside/nucleotide reverse-transcriptase inhibitor; PI = protease inhibitor.

between males and females in terms of BMI (21.9 vs. 20.8; $p = 0.12$).

Prevalence of low BMD and associated factors

Based on the WHO criteria, osteopenia was diagnosed in 114 patients (35.6%) and osteoporosis in 12 patients (3.8%). The median BMD was 0.94 g/cm^2 (IQR, $0.87\text{--}1.04$). There were statistically significant sex differences in the distribution of patients' diagnostic category ($p = 0.003$). Osteopenia was diagnosed in 37.2% and 20.0% of males and females, respectively. Osteoporosis was diagnosed in 3.1% and 10.0% of males and females, respectively. The median BMD was similar in both groups (0.94 vs. 0.96 g/cm^2 ; $p = 0.58$).

In univariate analysis, there was a statistically significant association between reduced BMD (osteopenia and osteoporosis) and being underweight ($p < 0.01$). No association was found between reduced BMD and a specific class of antiretroviral agents.

Taking the DXA value as a numeric variable, the correlations for age, cART duration, BMI, and BMD were shown in Fig. 1 with Pearson correlation coefficients -0.156 , -0.136 , and 0.197 , respectively. The following factors were significantly associated with reduced BMD in multivariate linear regression: lower BMI, increased age, and longer duration of antiretroviral therapy (Table 2).

When we analyzed DXA values as an ordinal variable by classifying the results as normal, osteopenia, or osteoporosis, the only significant factor related to reduced BMD was being underweight (BMI $< 18.5 \text{ kg/m}^2$; proportional odds ratio, 4.12; 95% CI, 1.93–8.82; $p = 0.0003$; Table 2), which was consistent with the result of dichotomous analysis (normal vs. low BMD, odds ratio, 3.28; 95% CI, 1.48–7.28; $p = 0.0003$).

Discussion

In this cross-sectional survey, we found that reduced BMD was common among HIV-infected adults in Taiwan. More than one third of the patients had osteopenia and 3.8% had osteoporosis. Compared with a nationwide representative sample of 1121 adult participants in Taiwan, the prevalence of osteopenia and osteoporosis at lumbar spine in our study (35.6% and 3.8%) was similar to older population aged 60–69 years (32.1% and 4.8%), respectively.²⁰

The prevalence of reduced BMD ranges from 23% to 89% in various HIV studies.^{21–26} Although the prevalence of our study falls within the range of those of other studies, the difference of prevalence of reduced BMD among the studies may be explained by the populations studied and the method of BMD measurement also contributes to difference in reported prevalence. Knobel et al²⁷ reported the highest prevalence (89%) in older participants that included more female patients (27%). The T-score at the femoral neck quantitatively evaluates the cortical bone tissue, whereas the T-score at the lumbar spine quantitatively evaluates the trabecular bone tissue. In our study, we only measured BMD of the lumbar spine by DXA, which precluded us from estimating the cortical bone demineralization. The prevalence of reduced bone mineral density was diverse at

different sites, and the prevalence ratio of femoral neck to lumbar spine among different age groups in previous study was around 1.6–3.6.²⁰ Additionally, we excluded patients who had received drugs potentially lowering bone mass or

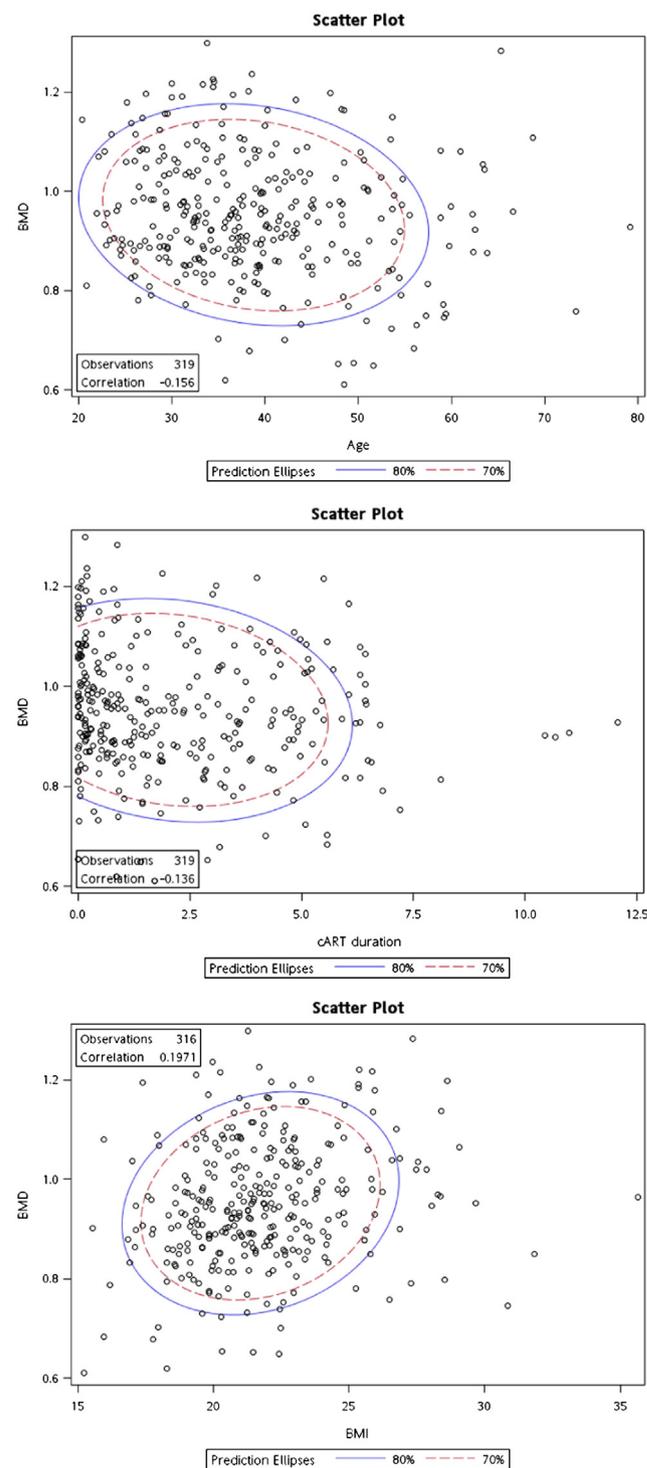


Figure 1. Correlations for age, cART duration, BMI, and BMD. Scatter plot with 70% and 80% prediction ellipses. Pearson correlation coefficient of BMD with age, cART duration, and BMI were -0.156 , -0.136 , and 0.197 respectively. BMD = bone mineral density; BMI = body mass index; cART = combination antiretroviral therapy.

Table 2 Regression models

Multivariate linear regression: factors associated with BMD

$$\text{BMD} = 0.846 \times 0.019 \times \text{Age} \times 0.016 \times (\text{duration of cART}) + 0.009 \times \text{BMI}$$

$$R^2 = 0.21, p < 0.001$$

Variable	Coefficient	95% CI		p value
Constant	0.846	0.717	0.975	0.001
Age (y)	-0.0019	-0.033	-0.005	0.006
Duration of antiretroviral therapy (mo)	-0.016	-0.025	-0.009	0.007
BMI (kg/m ²)	0.009	0.005	0.015	0.002

Variable	OR (95% CI)	p value, univariate	Adjusted OR (95% CI)	p value, multivariate
BMI < 18.5 kg/m ²	3.80 (1.81–8.01)	0.004	4.12 ^a (1.93–8.82)	0.0003

^a Adjusted for age and sex.

BMI = body mass index; BMD = bone mineral density; CI = confidence interval; OR = odds ratio.

had a history of immobilization/hospitalization within the previous 3 months. It was reasonable to infer that the prevalence of reduced BMD was underestimated.

In our study, two traditional factors (older age and lower BMI) were associated with reduced BMD. In a meta-analysis of 10 published studies, unadjusted BMD was lower by 4.4–7.0% in the HIV-infected groups than the healthy controls ($p < 0.01$), and after adjustment for body weight, residual between-groups differences in BMD were reduced 47–50%.²⁸ Lower BMI has been singled out as the most important factor associated with reduced BMD in HIV-infected patients.

Chronic inflammation caused by HIV infection has been associated with increased bone resorption in chronically infected patients with high plasma HIV RNA load.²⁹ A direct effect of HIV upon osteogenic cells, the persistent activation of proinflammatory cytokines, and alterations in the metabolism of vitamin D are observed in HIV-infected patients not receiving cART.^{30,31} In our participants, the median length of time after HIV diagnosis was 1.3 years, which was shorter compared with the median duration of cART for the participants in a meta-analytic review (4.1–10 years),⁴ and more than 70% of our patients had achieved virologic suppression, which may facilitate restoration of the bone-remodeling process.²⁹

In this cross-sectional study, we also identified the association between reduced BMD and time on cART. In a number of randomized controlled trials, accelerated bone loss has been demonstrated in the initial 6–12 months after initiation of cART followed by stabilization of BMD thereafter.^{32,33} Longitudinal follow-up studies are warranted to assess the long-term effect of cART and ageing on the evolution of BMD among HIV-infected patients.

Because cART comprises of a combination of 2 or more antiretroviral agents of the three classes of antiretroviral therapy, attribution of reduced BMD to a specific class of antiretroviral agent is not possible. Previous studies have associated protease inhibitors with loss of BMD,^{21,34} although the effect varies with the protease inhibitor analyzed.^{33,35} In addition, efavirenz has recently been associated with a significant decrease in vitamin D levels that could lead to accelerated bone loss.³⁶ Although other NRTIs such as stavudine and zidovudine have been demonstrated to be more likely than tenofovir to cause

mitochondrial toxicity,³⁷ tenofovir is the most widely cited antiretroviral agent that is involved in bone demineralization.^{16,33,38} Our study was conducted before introduction of tenofovir into Taiwan, and therefore we were not able to evaluate the association between specific class of antiretroviral agent and reduced BMD. However, with increasing use of tenofovir in Taiwan, long-term effects of tenofovir on BMD in Taiwanese population requires monitoring and further studies.

There are several limitations to our study. Being a cross-sectional study precluded us from establishing causal relationships between factors identified and reduced BMD. Second, the sample size was relatively small, and the majority of our patients were middle-aged males. The results may not be generalizable to all HIV-infected patients in Taiwan. Third, we did not have any information on bone remodeling biochemical markers and gonadal status of our patients; indeed, hypogonadism may complicate HIV infection and it is the main cause of male osteoporosis. Lastly, like the majority of HIV-infected persons who receive long-term antiretroviral therapy, many patients in our study switched antiretroviral regimens (67.2% had switched cART, and 40.4% had switched cART more than once (data, not shown)) during the follow-up because of virologic failure and/or intolerable side effects. The evaluation of the impact of specific classes of antiretroviral medications on reduced BMD was disallowed.

In conclusion, the prevalence of reduced BMD is high in HIV-infected patients in Taiwan, and is associated with increased age and time on antiretroviral treatment and being underweight. We suggest that HIV infection should be considered as a risk factor for bone disease. HIV-infected post-menopausal women and HIV-infected men ≥ 50 years should receive BMD screening especially those with additional risk factors for bone loss such as low BMI and exposure to cART. Smoking cessation, limitation of alcohol intake, adequate nutrition, particularly calcium (1000–1500 mg daily), and vitamin D intake (800–1000 IU of vitamin D daily) were recommended.³⁹

Conflicts of interest

All authors have no conflicts of interest to declare.

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