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Original Article

Monitoring early developed low bone mineral density in HIV-infected patients by intact parathyroid hormone and circulating fibroblast growth factor 23

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Abstract *Background/purpose:* HIV-infected patients have a high prevalence of low bone mineral density (BMD), but BMD changes remain unclear. This cross-sectional retrospective observational study aimed to characterize the prevalence and associated factors of low BMD in HIV patients.

Methods: Between 1 January 2015 and 31 December 2016, all patients aged 20 years or greater who sought for HIV care were included. BMD was measured by dual-energy X-ray absorptiometry. Multivariable analyses of the association with HIV disease status, treatment and anthropometric parameters were performed. Circulating fibroblast growth factor 23 and intact parathyroid hormone were measured.

Results: A total of 137 patients was included; their median age was 39 years old; 97.8% were treated with combination antiretroviral therapy (cART); Body mass index (BMI) was 21.97 kg/m^2. Sixty-one patients (44.5%) showed low BMD (osteopenia and osteoporosis) based on the WHO criteria. The median BMD was −0.80 g/cm^2 (IQR, −1.5 to −0.2). The prevalence rate of low BMD was 37% in those who were aged 20–29 years, 45.2% in those who were aged 30–39 years, 45.2% in those who were aged 40–49 years, 45.8% in those who were aged 50–59 years, and 53.8% in those who were aged ≧60 years. More than half of patients (50.4%, 69/137) were younger than 40 years. Compared with normal BMD group, the low BMD group has a higher proportion of secondary hyperparathyroidism (18.0% vs 5.3%, p: 0.026) and a lower

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median C-terminal FGF23 level (48.92 vs 62.61 pg/ml, p: 0.008). Univariate and multivariate analyses of the factors associated with low BMD. We found that only serum intact-parathyroid hormone (iPTH) > 69 pg/ml (OR, 3.86; 95% CI, 1.14—13.09) was statistically significant associated with low BMD in multivariate analysis.

Conclusions: This cohort-based survey showed a high prevalence of low BMD among HIV-infected adults which included young-age patient in an university hospital. Secondary hyperparathyroidism was significantly associated with low BMD. There was no association between FGF23 and low BMD.

Introduction

Advances in combination antiretroviral therapy (cART) have led to an increased survival of human immunodeficiency virus (HIV) infected patients.[1,2] Prolonged life expectancy and cART exposure has been associated with potential comorbidities affecting the bone, liver, kidney, cardiovascular, and central nervous system.[3—5] Low bone mineral density (BMD) has been reported in many studies involving HIV-infected individuals,[6—8] and an increased susceptibility to fracture has been documented.[9]

A meta-analysis review HIV-infected patients had 3 times higher prevalence of osteoporosis.[10] Traditional risk factors of low BMD include low body mass index (BMI), age, menopause, vitamin D deficiency, tobacco, and alcohol use, and hormone effect.[11,12] The causes of low BMD among HIV-infected patients have not been fully established and appear to be multifactorial. It identify a complex pathogenetic interaction involving viral infection, common risk factors and cART.[13]

Fibroblast growth factor-23 (FGF23) is a 32-kDa bone-derived hormone that plays an important role in the regulation of phosphate by decreasing the reabsorption of phosphate in the kidney proximal tubule,[14] and in the control of vitamin D and parathyroid hormone (PTH) metabolism.[15] The FGF23 levels have also been associated, not only in chronic kidney disease (CKD) patients but also in HIV-infected patients with normal renal function, with metabolic disturbances, fat distribution, and risk of cardiovascular and kidney diseases.[16,17] Some observational studies that analyzed the correlations between FGF23 and BMD in the general population yielded conflicting results.[18—20] One study revealed higher FGF23 levels were associated with greater lumbar spine and total hip BMD.[18] Two studies showed no significant correlation between FGF23 and BMD after adjusting for confounding variables.[19,20] To the best of our knowledge, there are very few studies identify the correlation in HIV-infected patients.

Epidemiologic studies of low BMD among HIV-infected patients are still lacking among Asian populations. The aim of our study was to determine the prevalence of and associated factors with low BMD among HIV-infected patients from an university hospital in Taiwan.

Materials and methods

Study population and setting

HIV-infected patients ≥20 years old, who sought for HIV care were invited to participate in a cross-sectional survey of BMD between 1 January 2015 and 31 December 2016 at Tri-Service General Hospital. Exclusion criteria were pregnancy, previous bone abnormality or having other diseases that affect bone health, recent opportunistic infection, and current treatment with immunosuppressants, chemotherapy and hormonal agents including testosterone, megestrol, or thyroid replacement therapy. The study was approved by the Research Ethics Committee of the hospital and all participants signed written informed consent. (IRB: 2-103-05-135).

Laboratory investigations

A case record form was used to collect information on the demographic and clinical characteristics of the patients at diagnosis including age, gender, weight and height, and the history of HIV infection and cART were collected. These data included transmission route of HIV acquisition, time of HIV infection (from the first positive western blot test or polymerase chain reaction for HIV RNA), and the composition and duration of current cART. Blood samples were collected for the determination of HIV-related parameters (nadir CD4+, CD4+, CD8+ lymphocyte count and HIV RNA load). Glomerular filtration rate (GFR) was estimated by using the chronic kidney disease (CKD)-epidemiology collaboration equation. Also, patients were screened for hepatitis B and C virus coinfection, serum total calcium, magnesium, inorganic phosphorus, parathyroid function (serum intact-parathyroid hormone, iPTH).

The BMD of the lumbar spine and total hip were evaluated by dual energy X-ray absorptiometry (DEXA) technique. The BMD T scores comparing the absolute BMD results of participants to the young normal reference value.

Measurement of FGF23

Intact FGF23 is biologically active with direct effects on phosphate, vitamin D, and PTH metabolism.[15] It is secreted

and cleaved to inactive c-terminal fragments within osteocytes.[21] We measured serum intact and C-terminal FGF23 by using commercial enzyme-linked immunosorbent assays (Immutopics, San Clemente, CA, USA).

Definitions

BMI was calculated as weight in kilograms divided by height squared in meters. Base on the WHO standards for Asian populations, the cut-off value of underweight was <18.5 kg/m^2.[22] HBV infection was diagnosed in presence of hepatitis B surface antigen or HBV DNA test. HCV infection was diagnosed in presence of a positive serology against HCV. Secondary hyperparathyroidism was defined as an elevated serum iPTH above 69 pg/ml, and the possibility of primary hyperparathyroidism was excluded in presence of elevated serum calcium (>11 mg/dl). Length of time after HIV diagnosis was defined as the interval between the date of the first documented HIV-confirmed test result and the date of enrollment into this study. Combination ART was divided into 3 classes, including backbone nucleoside reverse transcriptase inhibitors (NRTI) plus non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), or integrase inhibitors (II). Use of tenofovir disoproxil fumarate (TDF) was defined as taking cART that contain TDF. Duration on cART was calculated by the number of months of cART used. Participants with a BMD T-score between -1 and -2.5 were categorized as having osteopenia, and participants with a BMD T-score less than or equal to -2.5 were categorized as having osteoporosis according to the World Health Organization (WHO) criteria.[23] The prevalence and associated factors of low BMD was determined based on the first DEXA scan available. For the purposes of our study, we divided the participants into 2 groups. Participants with osteopenia or osteoporosis were considered to have low BMD. Normal group was defined as with normal BMD values. This classification has been applied by other authors extensively.

Statistical analysis

Categorical variables were analyzed using X^2 tests and continuous variables were compared using the Student's *t* test. A *P*-value of <0.05 was considered statistically significant. Factors associated with low BMD were identified using the univariate logistic regression model. Candidate variables with a *P*-value <0.2 in univariate analyses and variables that were considered clinically relevant were selected for subsequent multivariable analyses. Ninety-five percent confidence intervals (CIs) of odds ratios (ORs) were computed to estimate the effects of each variable. All statistical analyses were performed with the SPSS software version (SPSS Inc., Chicago, IL, USA).

Results

The baseline demographics and clinical characteristics between patients with low and normal BMD are shown in Table 1. Overall, 137 patients were included in the analysis; 127

Table 1 Demographic and clinical characteristics of patients with HIV infection stratified by bone mineral density.

	All (n = 137)	Normal (n = 76)	Osteopenia + Osteoporosis (n = 61)	*p* value
n (% or interquartile range)				
Male	127 (92.7)	70 (92.1)	57 (93.4)	1.000
Age, years	39 (30–50)	38.5 (29.0–49.0)	41.0 (30.5–50.0)	0.328
>65 years	8 (5.8)	2 (2.6)	6 (9.8)	0.139
MSM	119 (86.9)	65 (85.5)	54 (88.5)	0.624
Length of time after HIV diagnosis, years	5.53 (2.46–10.49)	6.34 (2.28–11.68)	4.40 (2.77–9.92)	0.470
BMI, kg/m^2	21.97 (20.74–24.61)	22.00 (20.39–24.89)	21.97 (20.78–24.42)	0.697
BMI <18.5 kg/m^2	9 (6.6)	6 (7.9)	3 (4.9)	0.518
HBsAg positivity	17 (12.4)	7 (9.2)	10 (16.4)	0.297
Anti-HCV positivity	12 (8.8)	8 (10.5)	4 (6.6)	0.548
Nadir CD4+ count	212 (55–336)	219 (49–351)	209 (58–320)	0.823
Current CD4+ count	539 (387–700)	520 (420–652)	556 (373–732)	0.703
Current CD8+ count	795 (587–1036)	810 (598–1137)	775 (572–991)	0.176
CD4/CD8	0.68 (0.45–0.87)	0.68 (0.44–0.82)	0.74 (0.50–0.97)	0.144
Plasma HIV RNA load <400 copies/ml	126 (92)	69 (90.8)	57 (93.4)	0.754
Plasma HIV RNA load, log10 copies/ml	<1.30 (1.30–1.30)	<1.30 (1.30–1.30)	<1.30 (1.30–1.30)	0.569
On cART	134 (97.8)	75 (98.7)	59 (96.7)	0.585
Duration on cART, mo	45.50 (24.27–90.60)	46.82 (23.44–91.33)	44.20 (27.28–85.18)	0.891
Use of Tenofovir	42 (30.7)	21 (27.6)	21 (34.4)	0.457
NRTI + NNRTI	54 (39.4)	29 (38.2)	25 (41.0)	0.860
NRTI + PI	68 (49.6)	39 (51.3)	29 (47.5)	0.732
NRTI + II	12 (8.8)	7 (9.2)	5 (8.2)	1.000

Data are median value (interquartile range) for continuous variables and number of cases (%) for categorical variables.
BMI = body mass index; cART = combination antiretroviral therapy; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; II = integrase inhibitor; IQR = interquartile range; MSM = men who have sex with men; NRTI = nucleoside reverse transcriptase inhibitor; nNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

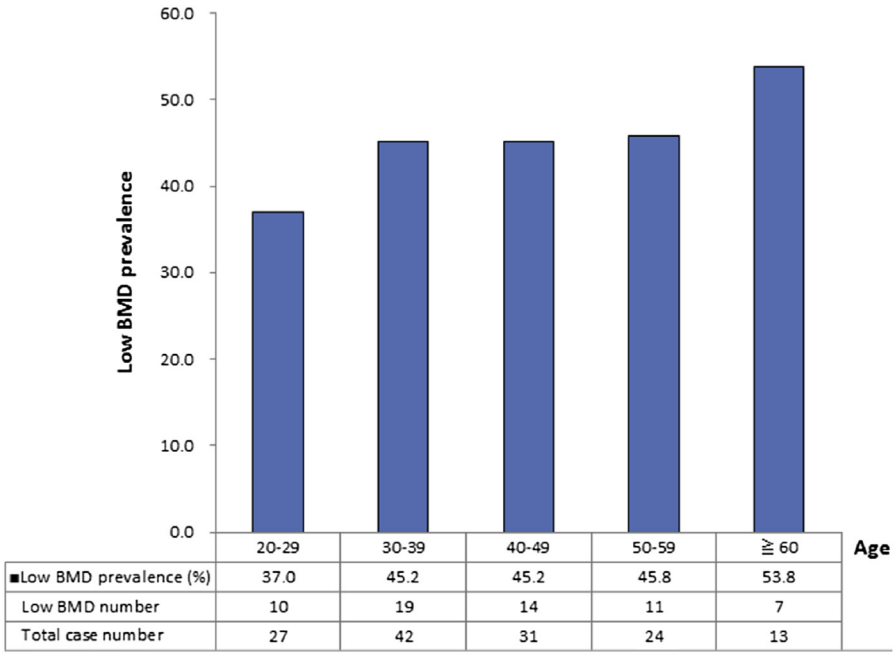

Figure 1. Prevalence of low bone mineral density in each age group.

(92.7%) were male. The median age was 39.0 years (IQR, 30.0—50.0), median time since HIV diagnosis was 6 years (IQR, 2.5—10.5), mode of HIV transmission was predominantly men who has sex with men (MSM) (86.9%). Most patients were on cART (97.8%), in 54 cases (39.4%) based in NRTI + NNRTI, 68 (49.6%) based in NRTI + PI, 12 (8.8%) based in NRTI + II, and 42 (30.7%) were receiving TDF in their antiretroviral regimens. The median cumulative duration on treatment was 44.3 months. The median BMI was 21.97 kg/m^2 (IQR, 20.74—24.61). BMI was <18.5 kg/m^2 in 9 of these patients (6.6%).

Risk factors and prevalence of low BMD

In this study, 61 patients (44.5%) showed low BMD (osteopenia and osteoporosis) based on the WHO criteria. The median BMD was −0.80 g/cm^2 (IQR, −1.5 to −0.2). The prevalence of low BMD in each age group is shown in Fig. 1: 37.0% in those who were aged 20—29 years, 45.2% in those who were aged 30—39 years, 45.2% in those who were aged 40—49 years, 45.8% in those who were aged 50—59 years, and 53.8% in those who were aged ≧60 years. More than half of patients (50.4%, 69/137) were younger than 40 years.

Laboratory values of low BMD patients are shown in Table 2. Compared with the normal BMD group, the low BMD group was more likely to have secondary hyperparathyroidism (18.0% vs 5.3%, p: 0.026) and a lower median FGF-23 level (48.92 vs 62.61 pg/mL, p = 0.008). Univariate and multivariate analyses of the factors associated with low BMD are shown in Table 3. We found that only iPTH>69 pg/ml (OR, 3.86; 95% CI, 1.14—13.09) was statistically significant associated with low BMD in multivariate analysis.

Discussion

In this cross-sectional study, we found that the overall prevalence of low BMD was 44.5% in our cohort. Patients

Table 2 Laboratory values of patients with HIV infection stratified by bone mineral density.

	All patients (n = 137)	Normal (n = 76)	Osteopenia + Osteoporosis (n = 61)	*p* value
n (% or interquartile range)				
eGFR (ml/min/1.73 m^2)	98.4 (85.90—111.60)	97.40 (87.13—111.48)	102.70 (83.45—112.75)	0.737
Total Ca (mg/dL)	9.50 (9.30—9.80)	9.50 (9.30—9.70)	9.50 (9.25—9.85)	0.835
Mg (mg/dL)	2.10 (2.00—2.20)	2.10 (2.00—2.20)	2.10 (2.00—2.20)	0.722
IP (mg/dL)	3.20 (3.00—3.65)	3.25 (2.90—3.60)	3.20 (3.00—3.75)	0.601
iPTH>69 pg/ml	15 (10.9)	4 (5.3)	11 (18.0)	0.026
Intact FGF23 (μmol/L)	43.6 (33.4—55.7)	40.4 (32.7—56.4)	43.6 (34.0—52.5)	0.842
C-terminal FGF23 (μmol/L)	54.6 (42.5—79.8)	62.6 (48.1—83.8)	48.9 (36.6—62.4)	0.008

Data are median value (interquartile range) for continuous variables and number of cases (%) for categorical variables.
Ca = calcium; eGFR = estimated glomerular filtration rate; FGF23 = fibroblast growth factor 23; IP = inorganic phosphorus; iPTH = intact parathyroid hormone; IQR = interquartile range.

Table 3 Logistic analysis to identify factors associated with low bone mineral density.

Variables	Univariate analysis		Multivariable analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Male	1.22 (0.33–4.54)	0.765		
>65 years	4.04 (0.79–20.77)	0.095	1.017 (0.99–1.05)	0.241
MSM	1.31 (0.47–3.60)	0.606		
Length of time after HIV diagnosis	0.96 (0.90–1.02)	0.155		
BMI <18.5 kg/m^2	0.60 (0.15–2.52)	0.488	0.69 (0.16–3.01)	0.619
HBsAg positivity	0.52 (0.18–1.45)	0.211		
Anti-HCV positivity	1.68 (0.48–5.86)	0.418		
Nadir CD4+ count	1.00 (1.00–1.00)	0.495		
Current CD4+ count	1.00 (1.00–1.00)	0.516		
Current CD8+ count	1.00 (1.00–1.00)	0.902		
CD4/CD8	2.39 (0.89–6.48)	0.085	2.80 (0.97–8.07)	0.056
Plasma HIV RNA load	0.93 (0.69–1.25)	0.632		
On cART	0.39 (0.04–4.44)	0.451		
Duration on cART	1.00 (0.99–1.01)	0.688		
Use of tenofovir	1.38 (0.66–2.85)	0.392	1.42 (0.66–3.06)	0.369
NRTI + NNRTI	1.13 (0.57–2.24)	0.737		
NRTI + PI	0.86 (0.44–1.69)	0.661		
NRTI + II	0.88 (0.27–2.92)	0.835		
eGFR	1.00 (0.99–1.02)	0.710		
Total Ca	0.97 (0.42–2.28)	0.950		
Mg	0.56 (0.07–4.76)	0.592		
IP	1.36 (0.79–2.34)	0.268		
iPTH>69 pg/ml	3.96 (1.19–13.15)	0.025	3.86 (1.14–13.09)	0.030
Intact FGF23	1.00 (0.98–1.02)	0.802		
C-terminal FGF23	0.99 (0.99–1.00)	0.541		

BMI = body mass index; Ca = calcium; cART = combination antiretroviral therapy; eGFR = estimated glomerular filtration rate; FGF23 = fibroblast growth factor 23; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; II = integrase inhibitor; IP = inorganic phosphorus; iPTH = intact parathyroid hormone; IQR = interquartile range; MSM = men who have sex with men; NRTI = nucleoside reverse transcriptase inhibitor; nNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

with secondary hyperparathyroidism were independently associated with low BMD.

The range of the prevalence rate of low BMD is wide among different populations.[6,10,24–29] This discrepancy could be related to different methodologies used in these studies, thus leading to these discordant results. There were limited studies stratified patients according to age. Casado et al. reported 44% HIV-infected patients had osteopenia and osteoporosis, and 22% patients were less than 40 years old in that cohort.[12] Our patients were relatively younger and were earlier to had low BMD (<40 years, 50.4%) in their life time. It may mask the effect of traditional risk factors: age on BMD and result in no association between them.

In a meta-analysis study by Bolland et al., short-term BMD loss of 2–4% over 1–2 years when cART was started, followed by longer periods of BMD increase or stability. It reported BMD loss were associated with TDF regimens.[30] A cross-sectional study revealed HIV-infected patients receiving cART that contained PIs had lower BMD than those not receiving PIs or uninfected controls.[6] In this study, use of cART that included TDF or PIs was not associated low BMD. Bolland et al. also found that HIV infection per se did not cause low BMD.[30] Similar to the meta-analysis study, we found that nadir CD4+ T lymphocyte, CD4+ T lymphocyte, CD8+ T lymphocyte, CD4+/CD8+ ratio and serum HIV RNA load were not associated with low BMD. Tsai et al. found that the prevalence of osteopenia and osteoporosis in Taiwan patients with HIV infection was 39.4%.[24] The patients didn't contact TDF in that cohort. In our study, we included patients with all available cART regimen in this cohort. It may result in the higher prevalence of low BMD.

In our cohort of HIV-infected patients with low BMD, 18.0% of patients demonstrated secondary hyperparathyroidism with normal renal function. The multivariate analysis show that secondary hyperparathyroidism was independently associated with low BMD. Higher PTH levels have been related with greater reductions in BMD in general population,[31] even in HIV-infected patients.[12,32] The particular risk factor of secondary hyperparathyroidism in these special population is the use of cART. TDF has been associated to high PTH levels and bone metabolism.[33–35] Use of PIs may decrease transformation of 1,25$(OH)_2$-vitamin D from 25(OH)-vitamin D, leading to hyperparathyroidism, and increase rates of low BMD.[36,37] Besides, use of efavirenz may increase metabolism of 1,25$(OH)_2$-vitamin D, that inhibit PTH secretion, to inactive metabolites and lead to hyperparathyroidism.[37,38]

Initial laboratory values of patients with low BMD revealed that C-terminal FGF-23 level was lower in patients with low BMD than in patients with normal BMD. Havens et al. found that FGF23 decreased with low BMD in the high

drug exposure group of patients underwent pre-exposure prophylaxis (PrEP).[39] FGF23 directly suppresses PTH production in an animal model.[40] The decrease of FGF23 may result in elevation of PTH level. We didn't see the similar pattern in intact FGF23, and the results didn't remain statistically significance after adjusted.

There are several limitations in our study. First, as cross-sectional studies evaluate exposure and disease status, this study design is limited in its ability to determine causality. Second, the sample size was relatively small and the results may not represent general HIV-infected patients in Taiwan. Third, we did not have complete data of bone turnover markers, e.g., serum vitamin D, daily calcium intake and calcium loss. Thus, we were unable to fully explore potential mechanisms of low BMD. Fourth, we only measured BMD once in each participant and lacked the actual duration of each ART, because regimens had been changed during the treatment in the past. It may mask the true effect of TDF and PIs on BMD.

In conclusion, our study showed that a high prevalence of osteopenia and osteoporosis in HIV-infected patients and it was associated with secondary hyperparathyroidism even in age less than 40 years old patients. More data on the significance of elevated PTH levels on the development of low BMD are needed. Potential of using PTH to identify patients at risk for bone related complications should be investigated in further studies.

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Conflicts of interest

None declared.

References

1. van Sighem AI, Gras LA, Reiss P, Brinkman K, de Wolf F. Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals. *AIDS* 2010;**24**:1527–35.
2. Lin TY, Yang CJ, Liu CE, Tang HJ, Chen TC, Chen GJ, et al. Clinical features of acute human immunodeficiency virus infection in Taiwan: a multicenter study. *J Microbiol Immunol Infect* 2019;**52**:700–9.
3. Mocroft A, Brettle R, Kirk O, Blaxhult A, Parkin JM, Antunes F, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. *AIDS* 2002;**16**:1663–71.
4. Lupia R, Wabuyia PB, Otiato P, Fang CT, Tsai FJ. Risk factors for Kaposi's sarcoma in human immunodeficiency virus patients after initiation of antiretroviral therapy: a nested case-control study in Kenya. *J Microbiol Immunol Infect* 2017;**50**:781–8.
5. Lee YC, Hung CC, Tsai MS, Zhang JY, Wu PY, Yang SP, et al. Incidence and risk factors of herpes zoster in human immunodeficiency virus-positive patients initiating combination antiretroviral therapy in Taiwan. *J Microbiol Immunol Infect* 2018;**51**:38–44.
6. Tebas P, Powderly WG, Claxton S, Marin D, Tantisiriwat W, Teitelbaum SL, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 2000;**14**:F63–7.
7. Arnsten JH, Freeman R, Howard AA, Floris-Moore M, Santoro N, Schoenbaum EE. HIV infection and bone mineral density in middle-aged women. *Clin Infect Dis* 2006;**42**:1014–20.
8. Jones S, Restrepo D, Kasowitz A, Korenstein D, Wallenstein S, Schneider A, et al. Risk factors for decreased bone density and effects of HIV on bone in the elderly. *Osteoporos Int* 2008;**19**:913–8.
9. Young B, Dao CN, Buchacz K, Baker R, Brooks JT. Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS) compared with the US general population, 2000–2006. *Clin Infect Dis* 2011;**52**:1061–8.
10. Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006;**20**:2165–74.
11. Triant VA, Brown TT, Lee H, Grinspoon SK. Fracture prevalence among human immunodeficiency virus (HIV)-infected versus non-HIV-infected patients in a large U.S. healthcare system. *J Clin Endocrinol Metab* 2008;**93**:3499–504.
12. Casado JL, Banon S, Andres R, Perez-Elias MJ, Moreno A, Moreno S. Prevalence of causes of secondary osteoporosis and contribution to lower bone mineral density in HIV-infected patients. *Osteoporos Int* 2014;**25**:1071–9.
13. Brown TT, McComsey GA, King MS, Qaqish RB, Bernstein BM, da Silva BA. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. *J Acquir Immune Defic Syndr* 2009;**51**:554–61.
14. Shimada T, Urakawa I, Yamazaki Y, Hasegawa H, Hino R, Yoneya T, et al. FGF-23 transgenic mice demonstrate hypophosphatemic rickets with reduced expression of sodium phosphate cotransporter type IIa. *Biochem Biophys Res Commun* 2004;**314**:409–14.
15. Bhattacharyya N, Chong WH, Gafni RI, Collins MT. Fibroblast growth factor 23: state of the field and future directions. *Trends Endocrinol Metab* 2012;**23**:610–8.
16. Domingo P, Lamarca MK, Gallego-Escuredo JM, Torres F, Domingo JC, Villarroya J, et al. Circulating fibroblast growth factor 23 (FGF23) levels are associated with metabolic disturbances and fat distribution but not cardiovascular risk in HIV-infected patients. *J Antimicrob Chemother* 2015;**70**:1825–32.
17. Atta MG, Estrella MM, Fine DM, Zook K, Monroy Trujillo JM, Stein JH, et al. Correlates and Longitudinal Renal and Cardiovascular Implications of FGF23 Levels in HIV-Positive Individuals. *PloS One* 2016;**11**, e0155312.
18. Jovanovich A, Buzkova P, Chonchol M, Robbins J, Fink HA, de Boer IH, et al. Fibroblast growth factor 23, bone mineral density, and risk of hip fracture among older adults: the cardiovascular health study. *J Clin Endocrinol Metab* 2013;**98**:3323–31.
19. Marsell R, Mirza MA, Mallmin H, Karlsson M, Mellstrom D, Orwoll E, et al. Relation between fibroblast growth factor-23, body weight and bone mineral density in elderly men. *Osteoporos Int* 2009;**20**:1167–73.
20. Isakova T, Cai X, Lee J, Katz R, Cauley JA, Fried LF, et al. Associations of FGF23 with change in bone mineral density and fracture risk in older individuals. *J Bone Miner Res* 2016;**31**:742–8.
21. Wolf M. Update on fibroblast growth factor 23 in chronic kidney disease. *Kidney Int* 2012;**82**:737–47.
22. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004;**363**:157–63.
23. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *Lancet* 2002;**359**:1929–36.

24. Tsai MS, Hung CC, Liu WC, Chen KL, Chen MY, Hsieh SM, et al. Reduced bone mineral density among HIV-infected patients in Taiwan: prevalence and associated factors. *J Microbiol Immunol Infect* 2014;**47**:109—15.
25. Bruera D, Luna N, David DO, Bergoglio LM, Zamudio J. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. *AIDS* 2003;**17**:1917—23.
26. Garcia Aparicio AM, Munoz Fernandez S, Gonzalez J, Arribas JR, Pena JM, Vazquez JJ, et al. Abnormalities in the bone mineral metabolism in HIV-infected patients. *Clin Rheumatol* 2006;**25**:537—9.
27. Cazanave C, Dupon M, Lavignolle-Aurillac V, Barthe N, Lawson-Ayayi S, Mehsen N, et al. Reduced bone mineral density in HIV-infected patients: prevalence and associated factors. *AIDS* 2008;**22**:395—402.
28. Bonjoch A, Figueras M, Estany C, Perez-Alvarez N, Rosales J, del Rio L, et al. High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study. *AIDS* 2010;**24**:2827—33.
29. Grijsen ML, Vrouenraets SM, Steingrover R, Lips P, Reiss P, Wit FW, et al. High prevalence of reduced bone mineral density in primary HIV-1-infected men. *AIDS* 2010;**24**:2233—8.
30. Bolland MJ, Grey A, Reid IR. Skeletal health in adults with HIV infection. *Lancet Diabetes Endocrinol* 2015;**3**:63—74.
31. Liu H, Paige NM, Goldzweig CL, Wong E, Zhou A, Suttorp MJ, et al. Screening for osteoporosis in men: a systematic review for an American College of Physicians guideline. *Ann Intern Med* 2008;**148**:685—701.
32. Jimenez B, Sainz T, Diaz L, Mellado MJ, Navarro ML, Rojo P, et al. Low bone mineral density in vertically HIV-infected children and adolescents: risk factors and the role of T-cell activation and senescence. *Pediatr Infect Dis J* 2017;**36**:578—83.
33. Noe S, Oldenbuettel C, Heldwein S, Wiese C, von Krosigk A, Pascucci R, et al. Secondary hyperparathyroidism in HIV-infected patients in central Europe. *Horm Metab Res* 2018;**50**:317—24.
34. Pocaterra D, Carenzi L, Ricci E, Minisci D, Schiavini M, Meraviglia P, et al. Secondary hyperparathyroidism in HIV patients: is there any responsibility of highly active antiretroviral therapy? *AIDS* 2011;**25**:1430—3.
35. Das S, Bopitya S, Taha H, David L. Relationship between vitamin D, parathyroid hormone, bone mineral density, fracture and antiretroviral therapy in HIV patients. *Recent Pat Antiinfect Drug Discov* 2014;**9**:6—13.
36. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;**357**:266—81.
37. Overton ET, Yin MT. The rapidly evolving Research on vitamin D among HIV-infected populations. *Curr Infect Dis Rep* 2011;**13**:83—93.
38. Herzmann C, Arasteh K. Efavirenz-induced osteomalacia. *AIDS* 2009;**23**:274—5.
39. Havens PL, Stephensen CB, Van Loan MD, Schuster GU, Woodhouse LR, Flynn PM, et al. Decline in bone mass with tenofovir disoproxil fumarate/emtricitabine is associated with hormonal changes in the absence of renal impairment when used by HIV-uninfected adolescent boys and young men for HIV preexposure prophylaxis. *Clin Infect Dis* 2017;**64**:317—25.
40. Rodriguez-Ortiz ME, Lopez I, Munoz-Castaneda JR, Martinez-Moreno JM, Ramirez AP, Pineda C, et al. Calcium deficiency reduces circulating levels of FGF23. *J Am Soc Nephrol* 2012;**23**:1190—7.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2018.08.017.