The Brazilian Journal of
INFECTIOUS DISEASES

www.elsevier.com/locate/bjid

Original article

Osteopenia and osteoporosis among treatment-experienced people living with HIV

Bárbara Marques de Castro Lara[a], *Cristiane Menezes de Pádua*[b], *Cássia Cristina Pinto Mendicino*[b], *Gustavo Machado Rocha*[a,*]

[a] *Universidade Federal de São João del-Rei, Divinópolis, MG, Brazil*
[b] *Universidade Federal de Minas Gerais, Belo Horizonte, MG, Brazil*

ARTICLE INFO

Article history:
Received 28 January 2020
Accepted 28 May 2020
Available online 15 June 2020

Keywords:
Antiretroviral therapy
Osteoporosis
Osteopenia
Dual-Energy X-Ray absorptiometry screening

ABSTRACT

Introduction: Life expectancy of people living with human immunodeficiency (PLHIV) has increased mainly due to the accessibility and effectiveness of antiretroviral therapy (ART). However, adverse effects from long-term use of antiretrovirals, and the physiological changes associated with aging, may compromise the quality of life of PLHIV, in addition to causing new demands on the healthcare system.

Objectives: Estimate the frequency of osteoporosis and osteopenia in patients on prolonged ART and to verify their associated factors.

Methods: A cross-sectional study was conducted in Belo Horizonte, Minas Gerais, Brazil, from August 2017 to June 2018, in a sample of PLHIV (age ≥ 18 years) who started ART between 2001 and 2005. Data were collected through face-to-face interviews, physical evaluation, laboratory tests, and Dual-Energy X-Ray Absorptiometry Screening (DEXA). The outcome of interest was presence of bone alteration, defined as presence of osteopenia or osteoporosis in DEXA. The association between the explanatory variables and the event was assessed through odds ratio (OR) estimate, with 95% confidence interval (CI). Multiple logistic regression was performed to evaluate factors independently associated with bone alteration.

Results: Among 92 participants, 47.8% presented bone alteration (19.6% osteoporosis and 28.2% osteopenia). The variables that remained in the final logistic regression model were age ≥ 50 years (OR: 12.53; 95% CI: 4.37–35.90) and current alcohol use (OR: 2.63; 95% CI: 0.94–7.37).

Conclusions: This study showed a high frequency of bone changes, especially in PLHIV older than 50 years. This information is useful to stimulate the screening and timely intervention of this comorbidity of PLHIV on prolonged use of ART in order to prevent or minimize complications and new demands on the healthcare system.

* Corresponding author.
E-mail addresses: barbara_marquesdecastro@yahoo.com.br, barbara.fisio34@gmail.com (B.M. Lara), campadua@farmacia.ufmg.br (C.M. Pádua), cassiamendicino@gmail.com, cassiamendicino@ufmg.br (C.C. Mendicino), gusrocha@ufsj.edu.br (G.M. Rocha).
https://doi.org/10.1016/j.bjid.2020.05.008

Introduction

Antiretroviral therapy (ART) was introduced in the 1990s to control human immunodeficiency (HIV) replication in people living with HIV (PLHIV). As a result, an increase in expectancy and quality of life of PLHIV, and a significant decrease of HIV transmission in the general population were noticed. In addition, early initiation of ART contributes to immune recovery and prevents the occurrence of acquired immunodeficiency syndrome (AIDS) cases.[1] However, to achieve this therapeutic success, the individual must regularly take ART which is based on at least three distinct antiretroviral drugs. According to the Brazilian HIV guidelines, the first choice for treatment should include a combination of two nucleoside analog reverse transcriptase inhibitors (lamivudine and tenofovir) associated with a non-nucleoside reverse transcriptase inhibitor (efavirenz) or an integrase inhibitor (dolutegravir; incorporated from 2017, becoming preferred over efavirenz).[2]

Between 2005 and 2015, there was a 45% reduction in HIV/AIDS mortality worldwide, which reflected an increase in the number of PLHIV (from 28 million to 38.8 million). In Brazil, the number of PLHIV increased from 490,000 in 2005 to 860,000 in 2017. This drop in mortality rates was mainly due to a significant increase in the proportion of PLHIV on ART worldwide, from 4.8% in 2005 to 40.5% in 2015.[3,4] However, prolonged use of ART combined with the natural aging process may contribute to the occurrence of chronic diseases. Among the main comorbidities, metabolic alterations should be highlighted such as diabetes mellitus, dyslipidemia, liver disease, nephropathy, and bone changes including osteonecrosis of the femoral head, osteopenia, and osteoporosis.[5,6]

Osteopenia and osteoporosis are metabolic changes that lead to reduction of bone microarchitecture, bone fragility, and increased fracture risk.[7,8] PLHIV present higher fracture risk than the general population. In addition, PLHIV may present other risk factors associated with development of fractures in early ages, such as presence of multiple comorbidities, multiple drug use, peripheral neuropathy, and frailty.[9–11]

Despite the evidence that prolonged ART use leads to bone changes, this subject is poorly investigated in the Brazilian context. In an open cohort study with 108 PLHIV in Brazil, mean age 43 years and mean time on ART 5.2 years, the prevalence of low bone mineral density (BMD) was 23.2%.[12] When stratified by age, 54% of patients over 50 years old showed decreased BMD compared to only 15% in younger patients. In a cross-sectional study in 300 patients with similar mean age and time on ART, the general prevalence of decreased BMD was 54.7%, with higher prevalence among people aged 50 or over (73.7%).[13] Other studies in the US found high proportions of bone alteration in PLHIV, with a 2–6% decline in BMD during the first years of ART use, regardless of the antiretroviral regimen.[14–17] This significant bone loss resembles the population with chronic glucocorticoid use or the first year after menopause.[18,19]

Use of the antiretroviral tenofovir (TDF) has been more associated with increased bone loss when compared to other antiretroviral drugs.[20] Prolonged TDF exposure contributes to increased parathyroid hormone (PTH) activity, which decreases calcium concentration in bone tissue while increasing plasma concentration.[21] Actually, there is evidence that bone loss occurs with all ART regimens, possibly due to increased bone catabolism after viral suppression.[22–26]

Despite the knowledge about the risk of bone alteration, further contextualized studies are needed in the Brazilian HIV population, in order to investigate the impact on both quality of life and the healthcare system. In addition, guidelines are needed to address screening and preventive actions. The current knowledge is not satisfactorily applied in clinical practice, possibly due to lack of awareness and financial support in this issue. In this perspective, this study aimed to estimate the frequency of osteopenia and osteoporosis and their associated factors in a sample of PLHIV on prolonged ART use.

Methods

Study design and population

This was a cross-sectional study conducted in the city of Belo Horizonte, Minas Gerais state, Brazil, from August 2017 to June 2018. This study included patients from a historical cohort that aimed to evaluate adverse effects on prolonged ART use in PLHIV (≥ 18 years) who started ART between 2001 and 2005 and continued to receive regular care in a public referral center until 2017/2018.[27]

Outcome of interest and explanatory variables

The outcome of interest was presence of bone alteration (osteopenia or osteoporosis) diagnosed by the Dual-Energy X-Ray Absorptiometry (DEXA) method and classified according to BMD level. BMD classification was based on the World Health Organization (WHO) international standards. For individuals aged 50 years and over, the T score was: a) DEXA T score > −1 = absence of bone alteration; b) DEXA T score between −2.5 and −1.0 = osteopenia; and c) DEXA T score <−2.5 = osteoporosis. On the other hand, for individuals under 50 years of age, DEXA Z score < of −2.0 indicates bone change (without sub-classifications).[7,8,28]

Potentially explanatory variables were sociodemographic, clinical, lifestyle and dietary data, current use (yes or no) of alcohol, tobacco and illicit drugs, medication use, and healthcare system use. ART use was dichotomized by the median time of use. The level of physical activity was assessed by Baecke's questionnaire and categorized as insufficient (score < 8.0) or sufficient (score ≥ 8.0) levels.[29] This instrument evaluates habitual physical activity (at work, at leisure, or in locomotion activities) over the previous 12 months and had been validated in Brazil to the general and HIV population.[30] The reference values for biochemical exams were: a) calcium: 8.5–9.5 mg/dL; b) PTH: 15–68.3 pg/mL; c) vitamin D: > 30 ng/mL; d) phosphorus: 2.5–4.5 mg/dL; and e) creatinine: 0.7–1.0 mg/dL. HIV viral load (VL) was classified as detectable or undetectable (< 40 copies/mL), and TCD4+ lymphocyte count was categorized using 500 cells/mm^3 as the cut-off value. Body mass index (BMI) was calculated by anthropometric data registered during the interviews and classified according to WHO recommendations as normal (18.5–24.9 kg/m^2), underweight (< 18.4 kg/m^2) or overweight (≥ 25.0 kg/m^2).[31]

Recruitment and data collection

The recruitment of eligible patients was performed in-person at the public referral center, during medical appointments or ART dispensation. Patients were invited to participate in the study and, in case of agreement, to sign the Informed Consent Form. Face-to-face interviews were conducted using a semi-structured questionnaire. After the interview, weight and height were measured using a properly calibrated anthropometric scale. Biochemical examinations were performed in the clinical pathology laboratory of the Federal University of Minas Gerais (UFMG) and bone densitometry (DEXA) was assessed in a private laboratory (GE HealthCare - Lunar Prodigy Advance - PA + 130,267). The test results were attached to the participants' medical records and a copy delivered to them at the time of ART dispensation. The data were collected through Questionnaire Development System software, version 2.6.1.1.

Statistical analysis

Descriptive analyses were performed to characterize the study population. The difference between the proportions of the explanatory variables and outcome was assessed by Pearson's chi-square test in which variables presenting p-value <0.25 were included in the initial multivariate model. Variables presenting p-value <0.05 and those with epidemiological relevance were considered for the final logistic regression model. The magnitude of associations was estimated using odds ratio (OR), with 95% confidence interval (CI). Statistical analysis was performed using EpiInfo® version 7.2.2.6 and SAS® software version 9.2.

Ethical considerations

This study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (CAAE Number: 62710316.8.0000.5149) and by the Municipal Health Secretariat of the city of Belo Horizonte. All participants signed the Informed Consent Form prior to beginning data collection.

Results

Out of the 204 individuals included in the cohort study,[27] 45 (22.0%) did not participate in the current study due to death, treatment abandonment, or transfer to other healthcare services, and 48 (23.5%) could not be located. Among the 111 invited patients, 17 (15.3%) declined the invitation and 2 (1.8%) have turned in the DEXA exam. Thus, 92 participants were left for this analysis.

Mean age was 52 years (56.5% > 50 years old), and most participants were male (56.5%), single, divorced or widowed (59.8%), non-white (78.3%), had more than eight years of education (51.1%) and had an income less than or equal to R$ 2,000.00 (two thousand reais) (75.8%). The majority reported consuming milk (77.2%) or dairy products (79.1%) and three or more cups of coffee daily (43.5%). Regarding drug use, 40.2% consumed alcohol, 22.8% tobacco and 4.4% illicit drugs (Table 1).

Table 1 – Sociodemographic, clinical and laboratory profile of treatment-experienced PLHIV (N = 92).

Characteristics	N	%
Sex		
Male	52	56.5
Female	40	43.5
Age		
< 50 years old	40	43.5
50+ years old	52	56.5
Marital Status		
Single / divorced / widowed	55	59.8
Married / stable union	37	40.2
Skin color		
White	20	21.7
Non-white	72	78.3
Schooling		
8+ years	47	51.1
≤ 8 years	45	48.9
Monthly income[a]		
> R$ 2,000.00	22	24.2
≤ R$ 2,000.00	69	75.8
Milk consumption		
Yes	71	77.2
No	21	22.8
Dairy consumption[a]		
Yes	72	79.1
No	19	20.9
Daily coffee consumption		
≤ 3 cups	52	56.5
> 3 cups	40	43.5
Current alcohol use		
No	55	59.8
Yes	37	40.2
Current tobacco use		
No	71	77.2
Yes	21	21.8
Current illicit drug use		
No	88	95.7
Yes	4	4.3
Physical activity level		
Sufficient	35	38.0
Insufficient	57	62.0
Body mass index		
High (overweight)	43	46.7
Normal	45	48.9
Low (underweight)	4	4.4
Previous bone fracture		
No	56	60.9
Yes	36	39.1
Previous osteoporosis diagnosis		
No	91	98.9
Yes	1	1.1
Bone densitometry		
Normal	48	52.2
Altered	44	47.8
Osteopenia	26	28.2
Osteoporosis	18	19.6
ART time[a]		
≤ 15 years	37	43.0
> 15 years	49	57.0
Viral load[a]		
Undetectable	72	80.0
Detectable	18	20.0
TCD4+ lymphocyte count[a]		
Normal	68	77.3
Low	20	22.7

– Table 1 (*Continued*)

Characteristics	N	%
Creatinine[a]		
Normal	70	77.8
High	20	22.2
Calcemia[a]		
Normal	51	57.3
High	38	42.7
Phosphorus[a]		
Normal	82	93.2
High	6	6.8
Vitamin D[a]		
Normal	22	47.8
Insufficient	24	52.2
Parathyroid hormone[a]		
Normal	34	55.7
High	27	44.3
History of kidney disease		
No	88	95.7
Yes	4	4.3
History of liver disease		
No	90	97.8
Yes	2	2.2
History of lipoatrophy		
No	62	67.4
Yes	30	32.6
Vitamin D replacement		
No	90	97.8
Yes	2	2.2
Current use of tenofovir		
No	30	32.6
Yes	62	67.4
Current use of efavirenz		
No	55	59.8
Yes	37	40.2
Current use of protease inhibitor		
No	52	56.5
Yes	40	43.5
Current use of thiazide diuretics		
No	81	88.0
Yes	11	12.0
Current use of glucocorticoids		
No	89	96.7
Yes	3	3.3

[a] Excluded missing data.

Almost half of the participants were overweight, 4.4% underweight, and 62.0% had insufficient physical activity. The minimum time of ART use was 12 years, the maximum 17 years and the average time was 15 years (57.0% of participants had been on ART > 15 years). At the time of the interview, 67.4% had been taking TDF, 40.2% efavirenz and 43.5% protease inhibitor drugs. In addition, 12% had been taking thiazide diuretics, 3.3% glucocorticoids, and 2.2% vitamin D drug replacement (Table 1).

Out of the participants with available tests, 44.3% presented high PTH plasma levels, 52.2% insufficient vitamin D, 42.7% high calcium level, 22.2% high creatinine, and 6.8% high phosphorus levels. Most participants had undetectable VL (80.0%) and a TCD4+ lymphocyte count greater than 500 cells/mm^3 (77.3%). Concerning clinical diagnoses, 4.3% reported kidney and 2.1% liver diseases; and in 32.6% of the patients, lipoatrophy was diagnosed or noticed by the patient in some part of the body (Table 1).

Forty-four (47.8%) participants presented the outcome (28.2% osteopenia and 19.6% osteoporosis in DEXA), 36 (39.1%) reported a previous history of fracture. Only one participant had been diagnosed with osteoporosis (Table 1). Mean BMD of the femoral neck was 0.9363 g/cm^2 (standard deviation [SD]: 0.1659), and 1.1345 g/cm^2 (SD: 0.1838) in the lumbar spine (L1-L4). The median T score and Z scores were -1.2 (SD: 1.22) and -0.3 (SD: 1.12) for the femur, and -0.7 (SD: 1, 49) and -0.3 (SD: 1.43) for the lumbar spine, respectively (Table 2).

Univariate analysis showed that 71.2% of those older than 50 years presented bone alteration, compared to 17.5% of younger individuals (OR: 11.63; 95% CI: 4.22–32.0; p-value <0.001). A total of 57.1% of participants with normal or underweight BMI (OR: 2.25; 95% CI: 0.97–5.20; p = 0.056) and 75.0% of those with altered vitamin D levels (OR: 5.25; 95% CI: 1.48–18.66; p = 0.008) had bone alteration (Table 3). The variables age ≥ 50 years (OR: 12.53; 95% CI: 4.37–35.90) and current alcohol use (OR: 2.63; 95% CI: 0.94–7.37) remained in the final multivariate model (Table 4).

Discussion

In this study, the frequency of osteopenia and osteoporosis was considerably higher than in the general Brazilian population (ranging from 4.4%–27.4%).[32,33] However, these rates may be comparable to those of the elderly population (over 65 years old) in Brazil, which ranges from 33.3–57.4%.[34] Considering other studies in the HIV population, these results are similar to that found by Pinto Neto et al., in which 54.8% had bone alteration, and by Escota et al., who reported 61% alteration in a population on ART use for at least four years.[13,14] Although for some authors the prevalence and factors associated with osteoporosis in the Brazilian population are unclear, results of this study show that bone abnormalities are manifested earlier and more frequently in PLHIV on ART use compared to the general population. These findings underscore the importance of a specific approach to these changes aiming at reducing fragility fractures, complications, and generating new demands for the healthcare system.[35]

The frequency of osteoporosis found in the present study (19.6%), with a mean age of 52 years, was higher than the frequency found by Mary-Krause et al. (14.6%), with a mean age of 46 years.[20] In addition, the mean lumbar spine and femoral neck BMD found in the present study are close to the results found in a Brazilian study with a sample of older people.[36] This evidence corroborates the hypothesis that there is an earlier incidence and higher prevalence of bone disease among PLHIV.

As shown, a positive and significant association was observed between older age and bone alteration. Age is a major risk factor for declining BMD in both PLHIV and the general population. However, it is observed that this decline affects PLHIV on ART earlier than the general population. Kanis et al. reported that the prevalence of osteoporosis in PLHIV under 50 years old corresponds to the prevalence in European men over 75 years.[37] The European Clinical AIDS Society recommends screening for bone alteration by DEXA in PLHIV over 50 years in men, postmenopausal women, and adults with risk factors

Table 2 – Evaluation of DEXA quantitative variables in treatment-experienced PLHIV (N = 92).

Bone segment	Mean (SD) density (g/cm^2)	Median (SD) T score	Median (SD) Z score
Femoral neck	0.9363 (SD: 0.1659)	−1.2 (SD:1.2173)	−0.3 (SD: 1.1192)
Lumbar spine (L1-L4)	1.1345 (SD: 0.1838)	−0.7 (SD: 1.4879)	−0.3 (SD: 1.4268)

SD: Standard Deviation; g: grams; cm: centimeters.
Interpretation.
50+ years old.
T score ≥ -1.0: no significant bone alteration.
T score between −1.0 and −2.5: osteopenia.
T score ≤ −2.5: osteoporosis.
< 50 years old.
Z score ≤ −2.0: altered (without sub classifications).

such as history of fragility fracture, glucocorticoid treatment for more than three months, or high risk of falls.[38,39] Given these results, tracking bone alteration following these recommendations seems to be the best way to avoid fractures and other complications.

In univariate analysis, low vitamin D levels were associated with bone alteration, despite the large number of individuals with missing vitamin D results. Adequate absorption of calcium, an important element in bone remineralization, requires enough levels of vitamin D to stimulate its absorption from the intestine. Other effects of vitamin D action include regulation of bone reabsorption, enhancing calcium reabsorption in the distal renal tubules, and repression of PTH transcription and secretion.[40,41] As a result, the bone health guidelines for PLHIV advise considering intervention with bisphosphonate drugs, in addition to calcium and vitamin D replacement in cases of prior fracture or DEXA showing T score below −2.5 in any segment.[39] In a 48-week randomized clinical trial with 165 adults on ART, it was observed that calcium and vitamin D supplementation could attenuate bone decline.[42] However, further studies are needed to evaluate the preventive effect of calcium and vitamin D supplementation among PLHIV on ART in Brazil. Thus, according to the DEXA results shown in this study, 22 (25%) participants would have an effective indication for treatment.

The association between bone alteration and normal or low BMI found in this study seems to corroborate the results of other studies. Pinto Neto et al. found a similar association, although with greater magnitude (OR: 5.7 and 12.0, for normal and low BMI, respectively).[13] Mary-Krause et al. complement this association by recommending screening for men under 60 years of age and BMI < 20 kg/m^2.[20] A meta-analysis with 10 studies totaling 1371 HIV positive and 1644 negative adults (age and sex adjusted) observed that PLHIV presented a mean weight of 5.1 kg lower than HIV negative controls ($p < 0.001$).[43] Unadjusted analyses found significant lower BMD in all bone segments in PLHIV ($p < 0.01$). After adjustment for body weight, the association remained significant for total hip and femoral neck. Multifactorial determinants may cause bone decline in PLHIV, some of which are reversible. However, aging affects directly the bone changes and also muscle tissue, causing sarcopenia, which will directly influence bone tissue maintenance. Recommendations for lifestyle changes such as weight-bearing muscle strengthening and nutritional monitoring should be accessible to this population.

The multivariate analysis identified a positive independent association between current alcohol consumption and bone alterations. These results were corroborated by other studies. Tian et al. reported almost two-fold greater chance of bone alteration in postmenopausal women and elderly men with alcohol habits.[44] In addition, results from a meta-analysis also identified alcohol consumption as risk factor for bone mineral decline.[45] A population-based study conducted in Norway found higher risk of hip fracture in individuals with insufficient physical activity, history of smoking, and excessive alcohol consumption.[46] Thus, greater attention, guidance and screening should be offered especially to PLHIV on ART presenting other risk factors such as alcohol use.

PLHIV mortality rates decreased substantially after the introduction of highly effective combined ART, resulting in aging of this population, which is increasingly affected by age-related non-communicable conditions.[47] Several studies indicate a higher prevalence and earlier incidence of chronic diseases in PLHIV, compared to age-matched seronegative individuals, regardless of sex.[48,49] In this study, as already mentioned, despite the high frequency of bone alteration, only one participant reported previous osteoporosis diagnosis. This result is worrisome, showing lack of tracking and awareness concerning the problem, which can be preventable through lifestyle changes.

In this study no association was found between use of TDF and efavirenz with the presence of bone changes, probably due to the sample size and design limitations, which have neither allowed the estimation of time on drug exposure nor to establish a logical temporal exposure. However, the literature shows a positive association. A published meta-analysis found that although the proportion of individuals treated with protease inhibitors or TDF with osteopenia or osteoporosis was higher when compared to their respective controls, although these results did not reach statistical significance.[45] Thus, it is still unclear how and which drugs are truly associated with declining BMD, requiring more specific, longer, and more robust additional studies to conclude and refine future screening and management approaches and recommendations.

This study had some limitations, especially related to the sample size and the lack of complete information regarding laboratory results, reducing the study power. For this reason, some variables were analyzed in a dichotomous way and it

Table 3 – Factors associated with bone alteration in treatment-experienced PLHIV, Univariate Analysis (N = 92).

Variables	Total N	Bone Alteration (%)	OR (95% CI)	p-Value
Sex				
Male	52	55.7	1	
Female	40	37.5	0.48 (0.20–1.10)	0.082
Age				
< 50 years old	40	17.5	1	
50+ years old	52	71.2	11.63 (4.22–32.0)	<0.001
Marital Status				
Single / divorced / widowed	55	49.1	1	
Married / stable union	37	46.0	0.88 (0.38–2.03)	0.767
Skin color				
White	20	35.0	1	
Non-white	72	51.4	1.96 (0.70–5.49)	0.194
Schooling				
8+ years	47	44.7	1	
≤ 8 years	45	51.1	1.29 (0.57–2.94)	0.537
Monthly income[a]				
> R$ 2,000.00	22	31.8	1	
≤ R$ 2,000.00	69	53.6	2.48 (0.90–6.83)	0.074
Milk consumption				
Yes	71	45.1	1	
No	21	57.1	1.63 (0.61–4.34)	0.331
Dairy consumption[a]				
Yes	72	47.2	1	
No	19	47.4	1.01 (0.37–2.77)	0.991
Daily coffee consumption				
≤ 3 cups	52	53.9	1	
> 3 cups	40	40.0	0.57 (0.25–1.32)	0.188
Current alcohol use				
No	55	40.0	1	
Yes	37	59.5	2.20 (0.94–5.15)	0.067
Current tobacco use				
No	71	43.7	1	
Yes	21	61.9	2.10 (0.77–5.69)	0.142
Physical activity level				
Sufficient	35	42.9	1	
Insufficient	57	50.9	1.38 (0.69–3.95)	0.454
Body mass index				
High (overweight)	43	37.2	1	
Normal / Low	49	57.1	2.25 (0.97–5.20)	0.056
ART time[a]				
≤ 15 years	37	46.0	1	
> 15 years	49	51.0	1.23 (0.52–2.88)	0.641
Viral load[a]				
Undetectable	72	47.2	1	
Detectable	18	50.0	1.12 (0.40–3.14)	0.832
TCD4+ Lymphocyte count[a]				
Normal	68	47.1	1	
Low	20	55.0	1.38(0.51–3.74)	0.532
Creatinine[a]				
Normal	70	41.4	1	
High	20	65.0	2.63(0.93–7.39)	0.062
Calcemia[a]				
Normal	51	43.1	1	
High	38	52.6	1.46 (0.63–3.41)	0.374
Phosphorus[a]				
Normal	82	43.9	1	
High	6	66.7	2.56 (0.44–14.74)	0.279
Vitamin D[a]				
Normal	22	36.4	1	
Insufficient	24	75.0	5.25(1.48–18.66)	0.008
Parathyroid hormone[a]				
Normal	34	58.8	1	
High	27	40.7	0.48 (0.17–1.34)	0.160

– Table 3 (*Continued*)

Variables	Total N	Bone Alteration (%)	OR (95% CI)	p-Value
History of lipoatrophy				
No	62	46.8	1	
Yes	30	50.0	1.14(0.47–2.72)	0.771
Current use of tenofovir				
No	30	60.0	1	
Yes	62	41.9	0.48 (0.20–1.17)	0.104
Current use of efavirenz				
No	55	45.5	1	
Yes	37	51.4	1.27 (0.55–2.92)	0.578
Current use of protease inhibitor				
No	52	46.2	1	
Yes	40	50.0	1.17 (0.51–2.66)	0.714
Current use of thiazide diuretics				
No	81	46.9	1	
Yes	11	54.6	1.36 (0.38–4.81)	0.634

[a] Excluded missing data.

Table 4 – Final logistic regression model of factors associated with bone alteration among treatment-experienced PLHIV (N = 92).

Variables	Adjusted OR (95% CI)	p-Value
Age (50+ years old)	12.53 (4.37–35.90)	<0.001
Current alcohol use (yes)	2.63 (0.94–7.37)	0.066

was not possible to make stratified analysis by sex or age. The information was obtained from a sample of 92 patients followed-up in a single referral service, which might not represent the population of PLHIV on long-term ART use in the municipality. Thus, further studies with a larger sample and different conditions are needed to better evaluate the magnitude and factors associated with bone alteration in this population. However, despite these limitations, it was possible to notice a high frequency of bone alteration – osteoporosis and osteopenia – in this sample of PLHIV long time exposed to antiretroviral drugs, which reinforces the recommendation for routine bone alteration screening by densitometry in the SUS, as well as preventive measures, and when necessary, pharmacological treatment, in order to prevent or minimize complications and new demands for healthcare services.

Financing source

This work received financial support from the Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq (Process No. 474547-2013-2), from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES (postgraduate scholarship), and from the Fundação de Amparo à Pesquisa do Estado de Minas Gerais – FAPEMIG (postgraduate scholarship).

Declarations of interest

The authors declare no conflicts of interest.

REFERENCES

1. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA. 2012;308:387–402.
2. Brasil, Secretaria de Vigilância em Saúde. Protocolo Clínico e Diretrizes Terapêuticas para Manejo da Infecção pelo HIV em adultos. Brasília: Departamento de Vigilância, Prevenção e Controle das Infecções Sexualmente Transmissíveis, do HIV/Aids e das Hepatites Virais; 2018.
3. UNAIDS. Data 2018 UNAIDS. Geneva; 2018. Available from: http://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf. [Access 22 April 2018].
4. G.H. Collaborators. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980-2015: the Global Burden of Disease Study 2015. Lancet HIV. 2016;3:e361–87.
5. Grant PM, Cotter AG. Tenofovir and bone health. Curr Opin HIV AIDS. 2016;11:326–32.
6. Who Study Group. The Use of antiretroviral drugs for treating and preventing HIV infection. Switzerland; 2013. p. 272. Available from: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf. [Access 21 March 2017].
7. J.A., Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. Osteoporos Int. 1994;6:368–81.
8. Czerwiński E, Badurski JE, Marcinowska-Suchowierska E, Osieleniec J. Current understanding of osteoporosis according to the position of the World Health Organization (WHO) and International Osteoporosis Foundation. Ortop Traumatol Rehabil. 2007;4:337–56.
9. Önen NF, Patel P, Baker J, Conley L, et al. Frailty and pre-frailty in a contemporary cohort of HIV-Infected Adults. J Frailty Aging. 2014;3:158–65.
10. Womack JA, Goulet JL, Gibert C, et al. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. PLoS One. 2011;2:e17217.
11. Young B, Dao CN, Buchacz K, Baker R, Brooks JT, Investigators HOSH. 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;8:1061–8.

12. Chaba DCD, Soares LR, Pereira RMR, et al. Low bone mineral density among HIV-infected patients in Brazil. Rev Inst Med Trop Sao Paulo. 2017;59:e89.
13. Pinto Neto LF, Ragi-Eis S, Vieira NF, et al. Low bone mass prevalence, therapy type, and clinical risk factors in an HIV-infected Brazilian population. J Clin Densitom. 2011;4:434–9.
14. Escota GV, Mondy K, Bush T, et al. High prevalence of low bone mineral density and substantial bone loss over 4 years among HIV-infected persons in the era of modern antiretroviral therapy. AIDS Res Hum Retroviruses. 2016;1:59–67.
15. Moran CA, Weitzmann MN, Ofotokun I. The protease inhibitors and HIV-associated bone loss. Curr Opin HIV AIDS. 2016;3:333–42.
16. Duvivier C, Kolta S, Assoumou L, et al. Greater decrease in bone mineral density with protease inhibitor regimens compared with nonnucleoside reverse transcriptase inhibitor regimens in HIV-1 infected naive patients. AIDS. 2009;7:817–24.
17. McComsey GA, Tebas P, Shane E, et al. Bone disease in HIV infection: a practical review and recommendations for HIV care providers. Clin Infect Dis. 2010;8:937–46.
18. Recker R, Lappe J, Davies K, Heaney R. Characterization of perimenopausal bone loss: a prospective study. J Bone Miner Res. 2000;10:1965–73.
19. Aloia JF, Dhaliwal R, Shieh A, Mikhail M, Islam S, Yeh JK. Calcium and vitamin D supplementation in postmenopausal women. J Clin Endocrinol Metab. 2013;11:E1702–9.
20. Mary-Krause M, Viard JP, Ename-Mkoumazok B, et al. Prevalence of low bone mineral density in men and women infected with human immunodeficiency virus 1 and a proposal for screening strategy. J Clin Densitom. 2012;4:422–33.
21. Havens PL, Stephensen CB, Hazra R, et al. Vitamin D3 decreases parathyroid hormone in HIV-infected youth being treated with tenofovir: a randomized, placebo-controlled trial. Clin Infect Dis. 2012;7:1013–25.
22. Hoy J. Bone, fracture and frailty. Curr Opin HIV AIDS. 2011;4:309–14.
23. Grant PM, Kitch D, McComsey GA, et al. Low baseline CD4+ count is associated with greater bone mineral density loss after antiretroviral therapy initiation. Clin Infect Dis. 2013;10:1483–8.
24. Brown TT, McComsey GA. Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. Antivir Ther. 2010;3:425–9.
25. Mallon PW. HIV and bone mineral density. Curr Opin Infect Dis. 2010;1:1–8.
26. Ofotokun I, Titanji K, Vikulina T, et al. Role of T-cell reconstitution in HIV-1 antiretroviral therapy-induced bone loss. Nat Commun. 2015;6, http://dx.doi.org/10.1038/ncomms9282, 8282.
27. Pádua CAM, Moura CS. Availability of data on adverse reactions to antiretroviral drugs in medical charts according to the Naranjo algorithm: an example of a Brazilian historical cohort. Clin Drug Investig. 2014;34:395–402. Available from: https://www.ncbi.nlm.nih.gov/pubmed/24710738.
28. Genant HK, Cooper C, Poor G, et al. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. Osteoporos Int. 1999;4:259–64.
29. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr. 1982;5:936–42.
30. Florindo AA, Latorre Mdo R, Santos EC, Negrão CE, Azevedo LF, Segurado AA. Validity and reliability of the Baecke questionnaire for the evaluation of habitual physical activity among people living with HIV/AIDS. Cad Saude Publica. 2006;22:535–41.
31. Organização Mundial de Saúde. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. Geneva, Switzerland: Programme of Nutrition, Family and Reproductive Health; 1998. p. 276.
32. Baccaro LF, Machado VSS, Costa-Paiva L, Sousa MH, Osis MJ, Pinto-Neto AM. Factors associated with osteoporosis in Brazilian women: a population-based household survey. Arch Osteoporos. 2013:138.
33. Pinheiro MM, Ciconelli RM, Martini LA, Ferraz MB. Risk factors for recurrent falls among Brazilian women and men: the Brazilian Osteoporosis Study (BRAZOS). Cad Saude Publica. 2010;1:89–96.
34. Camargo MB, Cendoroglo MS, Ramos LR, et al. Bone mineral density and osteoporosis among a predominantly Caucasian elderly population in the city of São Paulo. Brazil. Osteoporos Int. 2005;11:1451–60.
35. Martini LA, Moura EC, Santos LC, Malta DC, Pinheiro MM. Prevalence of self-reported diagnosis of osteoporosis in Brazil, 2006. Rev Saude Publica. 2009:107–16.
36. Zerbini CA, Latorre MR, Jaime PC, Tanaka T, Pippa MG. Bone mineral density in Brazilian men 50 years and older. Braz J Med Biol Res. 2000;12:1429–35.
37. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. Osteoporos Int. 2005;6:581–9.
38. EACS. European AIDS Clinical Society Guideline; 2016. Available from: http://www.eacsociety.org/files/guidelines_8.1-english.pdf. [Access 20 March 2017].
39. Brown TT, Hoy J, Borderi M, et al. Recommendations for evaluation and management of bone disease in HIV. Clin Infect Dis. 2015;8:1242–51.
40. Ikeda K, Ogata E. Modulation of bone remodeling by active vitamin D: its role in the treatment of osteoporosis. Mech Ageing Dev. 2000;2–3:103–11.
41. Fishbein L. Multiple sources of dietary calcium-some aspects of its essentiality. Regul Toxicol Pharmacol. 2004;2:67–80.
42. Overton ET, Chan ES, Brown TT, et al. Vitamin D and calcium attenuate bone loss with antiretroviral therapy initiation: a randomized trial. Ann Intern Med. 2015;12:815–24.
43. Bolland MJ, Grey AB, Gamble GD, Reid IR. CLINICAL Review #: low body weight mediates the relationship between HIV infection and low bone mineral density: a meta-analysis. J Clin Endocrinol Metab. 2007;12:4522–8.
44. Tian L, Yang R, Wei L, et al. Prevalence of osteoporosis and related lifestyle and metabolic factors of postmenopausal women and elderly men: across-sectional study in Gansu province, Northwestern of China. Medicine (Baltimore). 2017;43.
45. Goh SSL, Lai PSM, Tan ATB, Ponnampalavanar S. Reduced bone mineral density in human immunodeficiency virus-infected individuals: a meta-analysis of its prevalence and risk factors. Osteoporos Int. 2018;3:595–613.
46. Pripp AH, Dahl OE. The population attributable risk of nutrition and lifestyle on hip fractures. Hip Int. 2015;3:277–81.
47. Gebo KA. Epidemiology of HIV and response to antiretroviral therapy in the middle aged and elderly. Aging Health. 2008;6:615–27.
48. Althoff KN, McGinnis KA, Wyatt CM, et al. Comparison of risk and age at diagnosis of myocardial infarction, end-stage renal disease, and non-AIDS-defining cancer in HIV-infected versus uninfected adults. Clin Infect Dis. 2015;4:627–38.
49. Schouten J, Wit FW, Stolte IG, et al. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGEhIV cohort study. Clin Infect Dis. 2014;12:1787–97.