



# Prevalence of and risk factors for vertebral fracture and low bone mineral density among Peruvian women aging with HIV

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## Abstract

**Summary** Osteoporosis and fracture risk among women with HIV in Latin America is understudied. In a sample of Peruvian women with and without HIV, women with HIV had lower femoral neck and total hip BMD and a higher proportion of vertebral fractures. Important treatment gaps were identified across both groups.

**Purpose** Studies have shown that patients with HIV are at increased risk for bone loss and fracture due to a combination of host, viral, and antiretroviral therapy (ART)-related factors. We aimed to explore the prevalence of vertebral fracture (VF) and low bone mineral density (BMD) among women aging with HIV in Peru and identify risk factors for osteoporosis and fracture in this population.

**Methods** We enrolled women living with and without HIV aged  $\geq 40$  years between 2019 and 2020. Participants completed a survey and obtained dual X-ray absorptiometry (DXA) test to assess BMD at the lumbar spine (LS), femoral neck (FN), and total hip (TH). A subset of patients also obtained lateral thoracolumbar X-rays. Presence of VF was determined using the Genant semiquantitative method. Regression analyses were used to model associations between key risk factors and BMD.

**Results** 104 women living with HIV and 212 women living without HIV were enrolled with a mean age of  $52.4 \pm 8.2$  and  $56.4 \pm 8.8$  years ( $p < 0.001$ ). Among postmenopausal women (257/316, 81.3%), 26.3% of women living with HIV and 25.9% of those without HIV had osteoporosis. Among the 88 women living with HIV and 178 women living without HIV who obtained thoracolumbar X-rays, 12.5% and 6.2%, respectively, had at least one VF. Based on DXA and the FRAX score, 22/104 women living with HIV met criteria for osteoporosis treatment according to national guidelines; however, none were on treatment. Propensity score matching revealed that women living with HIV had  $0.032 \text{ g/cm}^2$  lower FN BMD ( $p = 0.012$ ) and  $0.034 \text{ g/cm}^2$  lower TH BMD ( $p = 0.041$ ) compared to women without HIV.

**Conclusion** In this study, women living with HIV on long-standing ART had increased VF prevalence compared to the slightly older group of women without HIV. Age and BMI were independent predictors for BMD at the lumbar spine, hip, and femoral neck among women living with HIV, and there was a treatment gap among women who met criteria for osteoporosis treatment. Larger studies are needed in this region to identify individuals at risk for fracture and to inform prevention guidelines.

**Keywords** Osteoporosis · Fracture · HIV · Women · Aging · Peru

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## Background

Osteoporosis has been defined as a systemic skeletal disease that is characterized by low bone mass and micro-architectural deterioration of tissue, with a consequent increase in bone fragility and susceptibility to fracture [1]. This disease causes almost 9 million fractures worldwide each year, generating costs to healthcare systems and leading to significant morbidity and mortality, particularly among women [2]. Vertebral fractures (VF) are the hallmark of these osteoporotic fractures, where prevalent VF are shown to be an independent risk factor for future fragility fractures [3].

In many low and middle-income countries (LMICs), such as Peru, the epidemiology of osteoporosis remains poorly characterized, and patients may be at increased risk due to poor nutrition and demographic changes from industrialization, combined with limited resources for osteoporosis diagnosis and management. The Peruvian Social Health Insurance, based on national epidemiology reports, estimated that 12–16% of women older than 50 years will have a hip fracture annually, another common osteoporotic fracture location. Based on the average population of 2.7 million women aged 50 years and over, this would produce between 342,000 and 432,000 fractures in this population per year [4]. Nonetheless, few studies have evaluated fracture risk among vulnerable populations such as women with HIV.

In recent decades, with the introduction of antiretroviral therapy (ART), life expectancy for people living with HIV has dramatically increased. However, a number of aging-associated comorbidities, many of which are common in the general population, have been observed to develop prematurely in people living with HIV [5]. The skeleton is one of the many tissues affected by HIV and its treatment, and many studies have demonstrated that people living with HIV have lower bone mineral density (BMD) and increased VF risk compared to people without HIV [6–8]. Likewise, a meta-analysis including 85,411 people living with HIV across 26 studies concluded that people with HIV had higher risk of VF compared to subjects without HIV [9].

Research focused on the bone health of women with HIV has primarily been carried out in upper-income countries and to a lesser extent in Africa. In contrast, only one study has examined fracture rates among women with HIV in Latin America and the Caribbean (LAC) region [10]. The aim of the present study was to determine prevalence of VF and measure BMD in a cohort of women aging with and without HIV in Lima, Peru, in order to identify risk factors for osteoporosis and fracture in this population.

## Methods

### Study design and participants

A hospital-based cross-sectional study was conducted between October 2019 and March 2020 comparing prevalence of fracture and low BMD between a cohort of middle-aged and older women living with and without HIV in Lima, Peru. Study procedures included skeletal imaging and a self-administered questionnaire. Specifically, we enrolled women living with HIV aged  $\geq 40$  years at an outpatient HIV clinic from Hospital Nacional Arzobispo Loayza (HNAL), a large public tertiary care hospital in Lima. Two strategies were used in terms of recruiting the control group, including inviting community-dwelling women from close neighborhoods and advertising the study among hospital staff (nurses, office administrators). Exclusion criteria for both groups included pregnancy (determined by urine pregnancy test at recruitment), previous diagnosis of, or treatment for, osteoporosis, primary residence outside Lima, and insufficient literacy to complete the study questionnaire.

### Data collection and measures

Participants completed a questionnaire regarding sociodemographic characteristics (age, marital status, ethnicity, and education level), fracture-associated risk factors (smoking history, current alcohol use, parental or personal history of fracture, history of fall, and current use of corticoids, among others), and dietary calcium and vitamin D intake using the Six-Item Calcium Screening Tool, a brief screening tool for low calcium intake validated among individuals living with HIV in China [11]. Data regarding HIV-related factors (CD4+ T-cell count, viral load (with viral suppression defined as  $< 50$  copies/ml), and ART history) were obtained from clinical records. Anthropometric measures (body mass index) were obtained using the same standardized stadiometer for each patient.

### Bone mineral density and vertebral fracture evaluation

For each participant, areal BMD measured in  $\text{g}/\text{cm}^2$  was obtained using the same Hologic dual X-ray absorptiometry (DXA) Discovery WI 2009 series 84453 scanner (Hologic Inc., Waltham, MA, USA) at the following regions of interest: lumbar spine (LS), femoral neck (FN), and total hip (TH). The World Health Organization criteria for osteoporosis were used for classification purposes: a

T-score of  $\geq -1.0$  denoted normal bone mineral density; low bone density (or osteopenia) is defined as a T-score between  $-1.0$  and  $-2.5$ , and a T-score of  $\leq -2.5$  denotes osteoporosis for postmenopausal women and men aged 50 and older [12].

A subset of participants obtained lateral thoracic and lumbar X-rays at the HNAL Department of Radiology following a standardized protocol with the thoracic film centered at T7 and the lumbar film centered at L2. Presence and grade of vertebral fracture were ascertained by two independent and experienced musculoskeletal radiologists (W.Y. and W.G.) using the validated Genant semiquantitative classification for VF [3]. In this classification, vertebrae T4-L4 are graded on visual inspection and without direct measurement as normal (grade 0), mildly deformed (grade 1, approximately 20–25% reduction in anterior, middle, and/or posterior height and a reduction in area of 10–20%), moderately deformed (grade 2, approximately 25–40% reduction in any height and a reduction in area 20–40%), and severely deformed (grade 3, approximately 40% reduction in any height and area) [13].

### Fracture risk assessment (FRAX) and osteoporosis self-assessment tool (OST) scores

The FRAX, developed in 2008 at the University of Sheffield, is a web-based algorithm which helps providers identify patients who may be candidates for pharmacological therapy for osteoporosis. It calculates the 10-year probability of major osteoporotic fracture (clinical vertebral, hip, and forearm) and the 10-year probability of hip fracture in men and women 40–90 years of age based on 11 clinical risk factors and, when available, BMD of the FN [14]. In addition to the clinical risk factors, the geographic area is factored into the risk calculation. Currently, the FRAX score website [15] includes a wide range of countries from Latin America, including Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, and Venezuela. We calculated FRAX scores using the Colombian setting based on similar ethnic and socioeconomic characteristics between both countries, in which mestizo populations predominate [16]. “Yes” was selected for the secondary osteoporosis risk factor for all patients living with HIV, as studies have shown doing so more accurately predicts fracture risk in this population [17]. We further evaluated risk of osteoporosis using the OST [18], a simple, validated screening tool for risk of osteoporosis that has been used in other LMICs to identify individuals who should be referred for DXA [19, 20].

### Data analysis

Sample characteristics were described using standard frequencies, means, standard deviations, and proportions, as appropriate. Differences between women with and without

HIV were assessed using the t-test for independent means, chi-square and Fisher exact test, as appropriate. Associations between vertebral fracture outcome and risk factors were explored using unadjusted and adjusted logistic regression models. We first assessed for possible multicollinearity of the independent variables. Variables with a high correlation coefficient ( $r > 0.40$ ) were deemed collinear and excluded from the models. We fit the multivariate models using backward regression [21], starting with all the variables that showed a hypothesized relationship ( $p < 0.10$ ) in the bivariate model. We then removed non-significant ( $p > 0.05$ ) variables one at a time beginning with the least significant (largest  $p$  value), in order to achieve the most parsimonious model.

We used propensity score matching to reduce confounding and assess the potential effect of HIV infection among BMD outcomes including FN, TH, and LS, with the following covariates: age, BMI, educational level, and ethnicity. All statistical analyses were conducted using STATA 16.0 (StataCorp, College Station, Texas, US). A two-sided  $p < 0.05$  was considered statistically significant.

### Ethics

The study was reviewed and approved by the ethics committees from the Yale School of Medicine (Approval #CR00011720), Universidad Peruana Cayetano Heredia (Approval #104254), and HNAL (Approval #14503). Written informed consent was obtained from all patients prior to their enrollment in the study. All participants received DXA results and counseling regarding osteoporosis and fracture prevention.

## Results

### Sociodemographic and clinical characteristics

A total of 316 women were recruited, including 104 women living with HIV and 212 women living without HIV. Women living with HIV were slightly younger ( $52.4 \pm 8.2$  vs.  $56.4 \pm 8.8$   $p < 0.01$ ), had lower BMI ( $26.4 \pm 5.1$  vs.  $27.6 \pm 4.1$ ,  $p < 0.01$ ), and had lower education level (65.4% vs. 85.4%,  $p < 0.001$ ) than the control group. 12.5% and 2.9% of women living with HIV had a personal history of fracture and current use of corticosteroids, respectively, but with no significant differences compared with the group without HIV. Only 6.7% of women living with HIV had a prior bone density test, compared with 27.8% of women without HIV ( $p < 0.001$ ). In terms of dietary calcium intake, total mean intake score was lower for women living with HIV compared with women without HIV (30.8 vs. 32.54,  $p < 0.001$ ). Among women living with HIV, mean time since

diagnosis was  $11.8 \pm 6$  years, and all were on combination ART. Mean duration of treatment was  $9.9 \pm 5.3$  years with 99% of patients receiving a nucleoside/nucleotide reverse transcriptase inhibitor (including tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), abacavir (ABC), zidovudine (AZT), lamivudine (3TC)), 68.3% on a non-nucleoside reverse transcriptase inhibitor (efavirenz (EFV), nevirapine (NVP)), 30.8% on a protease inhibitor (lopinavir/ritonavir (LPV/r)), and 2.9% on an integrase inhibitor (dolutegravir (DTG)). Mean CD4+ T-cell count of  $593.2 \pm 297.5$  cells/mm<sup>3</sup> and 78.8% had an undetectable viral load (Table 1).

### Osteoporosis risk, bone mineral density, and osteoporosis

In terms of osteoporosis risk, the proportion of women with moderate to severe risk of osteoporosis based upon the OST was similar in both groups (37.5% vs. 38.2%) (Table 2). DXA results showed mean FN BMD ( $0.74$  vs.  $0.76$  g/cm<sup>2</sup>), TH BMD ( $0.92$  vs.  $0.98$  g/cm<sup>2</sup>), and LS BMD ( $0.90$  vs.  $0.86$  g/cm<sup>2</sup>) were similar across both groups. Prevalence of osteoporosis based upon WHO criteria was 26.3% and 25.9% among postmenopausal women living with and without HIV, respectively ( $p=0.97$ ).

Propensity score matching revealed that women living with HIV had  $0.032$  g/cm<sup>2</sup> lower FN BMD ([95% CI  $-0.06$ ,  $-0.01$ ],  $p=0.012$ ) and  $0.034$  g/cm<sup>2</sup> lower TH BMD ([95% CI  $-0.06$ ,  $-0.001$ ],  $p=0.041$ ) compared to women without HIV. Moreover, 23.1% (24/104) of women living with HIV and 24.1% (51/212) of women without HIV met criteria for treatment initiation according to the Osteoporosis Guidelines by the National Peruvian Social Insurance [22]; however, none were currently receiving treatment.

### FRAX score and vertebral fracture prevalence

The mean FRAX score for major osteoporotic fracture was 2.65% for women living with HIV and 2.6% for the women without HIV, and mean FRAX score for 10-year risk of hip fracture was 0.59% for women living with HIV and 0.55% for women without HIV (Table 2). No women in our study had FRAX scores for 10-year risk of major osteoporotic fracture above the U.S. National Osteoporosis Foundation (NOF) or the Peruvian national guidelines' recommended threshold to initiate treatment ( $\geq 20\%$ ), and only 10 women (5 women living with HIV and 5 women without HIV) had FRAX scores for 10-year risk of hip fracture above the NOF or the Peruvian national guidelines' threshold ( $\geq 3\%$ ).

Among the 88 women living with HIV and 178 women without HIV who obtained thoracolumbar X-rays, vertebral fracture prevalence was found to be 12.5% and 6.2%, respectively, which trended toward significance ( $p=0.078$ ). Among both groups, the majority had mild (10.2% vs.

5.1%, respectively), followed by moderate (3.4% vs. 0.6%,  $p=0.073$ ) fractures. The most common fracture level for women living with HIV was T7 (Fig. 1).

### Association between clinical risk factors and bone mineral density

Regarding BMD, univariate logistic regression analyses among women living with HIV for altered bone mineral density (including both osteopenia and osteoporosis) showed that older age ( $p=0.001$ ), postmenopausal status ( $p=0.003$ ), and increased years since ART initiation ( $p=0.05$ ) were independent predictors for increased odds of altered BMD. Moreover, a higher OST score was an independent predictor for decreased odds of altered BMD. Likewise, in the multivariable analyses, both increased age (OR 1.13, 95% CI 1.05–1.22,  $p=0.001$ ) and increased OST remained an independent predictor of altered BMD (OR 0.78, 95% CI 0.63–0.97,  $p=0.025$ ) (Table 3).

Among women without HIV, univariate analyses showed that increased odds of altered BMD was associated with older age ( $p < 0.001$ ), postmenopausal status ( $p < 0.001$ ), and history of prior bone density test ( $p=0.030$ ). A decreased odds for altered BMD was associated with higher BMI ( $p < 0.001$ ), education level higher than high school ( $p=0.033$ ), and a higher OST ( $p < 0.001$ ). In the multivariable logistic regression analysis, altered BMD was associated with increased age (OR 1.06, 95% CI 1.02–1.11,  $p=0.004$ ) and postmenopausal status (OR 2.74, 95% CI 1.24–6.08,  $p=0.013$ ) and inversely associated with higher BMI (OR 0.84, 95% CI 0.79–0.90,  $p < 0.001$ ) and higher education level (OR 0.47, 95% CI 0.23–0.99,  $p=0.046$ ).

### Association between clinical risk factors and vertebral fractures

In terms of VF diagnosis, univariate logistic regression analyses among women living with HIV showed that the presence of VF was independently associated with older age ( $p=0.006$ ) and mestizo ethnicity ( $p=0.041$ ). Moreover, increased current CD4+ T-cell count trended to significance as well ( $p=0.059$ ), but with an OR of 1.002 (95% CI 1–1.004). Furthermore, in the multivariable model, increased age (OR 1.14, 95% CI 1.04–1.25,  $p=0.008$ ) and mestizo ethnicity (OR 10.14, 95% CI 1.19–86.50,  $p=0.034$ ) remained independent predictors for VF, and current CD4+ T-cell count (OR 1, 95% CI 0.99–1.005,  $p=0.057$ ) trended to significance as well (Table 4).

Among women without HIV, univariate analyses showed that presence of VF was inversely associated with increased FN ( $p=0.011$ ), TH ( $p=0.019$ ), and LS ( $p=0.027$ ) BMD. However, only the association with total hip BMD trended to significance (OR 0.004, 95% CI 1.2E08–1.07,  $p=0.053$ ).

**Table 1** Sociodemographic and clinical characteristics by HIV status

	HIV-infected		Uninfected	
	(N = 104)		(N = 212)	
<b>Sociodemographic characteristics</b>				
Age, mean (SD)	<b>52.38</b>	<b>(8.2)</b>	<b>56.37</b>	<b>(8.8)<sup>Y</sup></b>
Marital status, n (%)				
Single/divorced/separated/widowed, n (%)	<b>74</b>	<b>(71.2)</b>	<b>95</b>	<b>(44.8)<sup>Y</sup></b>
Married/cohabitant, n (%)	30	(28.9)	117	(55.2)
Ethnicity				
Caucasian, n (%)	3	(2.9)	24	(11.3)
Mestizo, n (%)	<b>97</b>	<b>(93.3)</b>	<b>185</b>	<b>(87.3)*</b>
Black, n (%)	4	(3.9)	3	(1.4)
Education level				
High school education or above, n (%)	<b>68</b>	<b>(65.4)</b>	<b>181</b>	<b>(85.4)<sup>Y</sup></b>
<b>Clinical characteristics</b>				
Body mass index (kg/m <sup>2</sup> ), mean (SD)	<b>26.44</b>	<b>(5.1)</b>	<b>27.63</b>	<b>(4.1)*</b>
Smoking ever, n (%)	28	(26.9)	39	(18.4)
Current alcohol use, n (%)	25	(24.0)	60	(28.3)
Prior bone density test, n (%)	<b>7</b>	<b>(6.7)</b>	<b>59</b>	<b>(27.8)<sup>Y</sup></b>
Current use of bone nutritional supplements, n (%)	5	(4.8)	11	(5.2)
Parental history of hip fracture, n (%)	10	(9.6)	26	(12.3)
Personal history of fracture, n (%)	13	(12.5)	39	(18.4)
Current use of assistive walking device, n (%)	1	(0.9)	2	(0.9)
History of fall within last year, n (%)	45	(43.3)	94	(44.3)
Current use of corticoids, n (%)	3	(2.9)	9	(4.3)
Rheumatoid arthritis diagnosis, n (%)	–		6	(2.8)
<b>HIV-related clinical data</b>				
Years since HIV diagnosis mean (SD)	11.8	(6.2)	–	
Nadir CD4+ cell count mean (SD)	264.3	(174.3)	–	
Peak HIV viral load mean (SD)	128,200.2	(275,567.1)	–	
Current CD4+ cell count mean (SD)	593.2	(297.5)	–	
Current HIV viral load mean (SD)	30,887.2	(222,988.9)	–	
AIDS diagnosis, n (%)	8	(7.7)	–	
Years since ART initiation mean (SD)	9.86	(5.3)	–	
NRTI exposure, n (%)	103	(99.0)	–	
NNRTI exposure, n (%)	71	(68.3)	–	
PI exposure, n (%)	32	(30.8)	–	
INSTI exposure, n (%)	3	(2.9)	–	
Viral suppression, n (%)	82	(78.9)	–	
<b>Six-Item Calcium Screening Tool<sup>a</sup></b>				
Average dairy products, mean (SD)	<b>6.3</b>	<b>(2.0)</b>	<b>6.7</b>	<b>(1.9)*</b>
Average soy products, mean (SD)	2.4	(2.2)	2.6	(2.2)
Average vegetables, mean (SD)	7.2	(1.76)	7.4	(1.4)
Average nuts, mean (SD)	<b>3.7</b>	<b>(2.22)</b>	<b>4.8</b>	<b>(2.1)<sup>Y</sup></b>
Average seafood, mean (SD)	5.0	(1.61)	5.2	(1.3)
Average vitamin D-rich products, mean (SD)	5.8	(1.34)	5.9	(1.3)
Total score, mean (SD)	<b>30.4</b>	<b>(5.86)</b>	<b>32.5</b>	<b>(5.2)<sup>Y</sup></b>
<b>Reproductive health-related factors</b>				
Menarche, mean (SD)	13.2	(1.96)	13.2	(2.2)
Menstrual status				
Premenopausal, n (%)	24	(23.1)	35	(16.5)
Postmenopausal, n (%)	80	(76.9)	177	(83.5)



Table 1 (continued)

	HIV-infected		Uninfected	
	(N = 104)		(N = 212)	
Prior removal of one or both ovaries, n (%)	10	(9.6)	33	(15.6)
Use of hormone replacement therapy, ever, n (%)	2	(1.9)	10	(4.7)

SD standard deviation, ART antiretroviral treatment, AIDS acquired immune deficiency syndrome, PI protease inhibitors, NRTI nucleoside/nucleotide reverse transcriptase inhibitors, NNRTI non-nucleoside reverse transcriptase inhibitor, INSTI integrase inhibitors

\* $p \leq 0.05$

† $p \leq 0.01$

‡ $p \leq 0.001$

<sup>a</sup>Each food category was measured with a Likert-type scale for consumption frequency (1 = never in past year, 2 = once a year, 3 = several times a year, 4 = once a month, 5 = several times a month, 6 = once a week, 7 = several times a week, 8 = once a day, and 9 = several times a day). The total intake score for each participant was done by summing responses of all categories (range 6–54)

in the multivariable model. The major osteoporotic fracture component of the FRAX score was not associated with the presence of VF on women living with HIV (OR 0.9, 95% CI 0.70–1.01,  $p = 0.07$ ) nor women living without HIV (OR 1.0, 95% CI 0.88–1.19,  $p = 0.80$ ).

## Discussion

Increased survival among PWH is leading to an increase in aging-related comorbidities, among which bone disease is becoming an important comorbidity of interest, especially among women [23]. In Peru, the epidemiology of HIV has also shifted over the past decade, with increasing viral suppression rates from 36% (2014) to 65% (2018) as access to antiretroviral therapy has expanded [24, 25]. However, data examining this epidemiological transition of individuals aging with HIV in Peru or LAC is scarce [26, 27]. Our study is the first to explore osteoporosis and fracture outcomes among women living with HIV in Peru using gold standard tools to explore both BMD and vertebral fractures. Women aging with HIV, as showed by propensity score-matched data, had a lower FN and TH BMD compared to women without HIV.

Alterations in BMD, including osteopenia and osteoporosis, due to accelerated bone loss have been reported in the setting of both long-term HIV infection and ART [28, 29]. With a growing prevalence of HIV among middle-aged and older people, there is an important need to better understand the impact of HIV on the skeletal system [30], especially in women, who bear additional consequences of estrogen withdrawal after menopause. In our study, both osteopenia and osteoporosis prevalence was higher among postmenopausal women living with HIV, and premenopausal women living with HIV also had a higher prevalence of low BMD for age compared to the premenopausal group without HIV. These comparisons were not statistically significant; however,

after propensity score matching, a statistically significant deleterious effect of HIV infection on FN and TH BMD was observed. A systemic review of studies focused on postmenopausal women living with HIV aged 45–65 years on ART found that, of four studies comparing women living with and without HIV, three reported women living with HIV had more bone loss than women without HIV, whereas one found no difference [31]. Furthermore, another study among 103 premenopausal women living with HIV from India found a significantly lower BMD compared to controls, and women with low BMD had significantly longer duration of ART exposure [32]. Similar trends were observed in the one prior study from the LAC region, which compared 273 Brazilian women living with HIV and 264 Brazilian women without HIV and found a higher prevalence of low lumbar spine BMD among the group living with HIV compared to the control group (14.6% vs. 4.6%,  $p < 0.01$ ) [33].

Although years since ART initiation was a significant factor for decreased BMD for women living with HIV in the univariate regression for our study population, this factor was not significant in the multivariable analysis. It has been reported that ART initiation is associated with loss of BMD at both the spine and hip; however, the mechanisms underlying accelerated bone loss during the early stages of ART remain poorly understood but may be associated with increased cytokine activity in the setting of immune reconstitution [34, 35]. Furthermore, certain antiretrovirals such as TDF and LPV/r have been associated with decreases in bone mineral density and increased risk for fracture [36, 37], whereas other agents such as integrase inhibitors or tenofovir alafenamide are considered “bone-sparing” [38, 39]. It is important to note that, in our population of patients living with HIV, almost all patients were treated with one of the free combination ART regimens sponsored by the National HIV/STI and Hepatitis Program. The endorsed first-line regimen consists of TDF, 3TC or FTC, and EFV. Second-line regimens may be TDF-, ABC-, or AZT-based, with one

**Table 2** Bone-related markers by HIV status

	HIV-infected (N= 104)		Uninfected (N= 212)	
BMD categorical outcome <sup>a</sup>				
<i>Premenopausal women, n (%)</i>	24	(23.1)	35	(16.5)
Normal BMD for age, n (%)	13	(54.2)	23	(65.7)
Low BMD for age, n (%)	11	(45.8)	12	(34.3)
<i>Postmenopausal women, n (%)</i>	80	(76.9)	177	(83.5)
Osteopenia, n (%)	42	(52.5)	83	(46.9)
Osteoporosis, n (%)	21	(26.3)	46	(25.9)
Absolute BMD (g/cm <sup>2</sup> )				
Femoral neck	0.741	(0.12)	0.761	(0.10)
Total hip	0.918	(0.14)	0.944	(0.12)
Lumbar spine	0.904	(0.15)	0.885	(0.15)
FRAX score, mean (SD)				
Major osteoporotic fracture	2.65	(2.4)	2.96	(2.3)
Hip fracture	0.59	(1.1)	0.55	(0.99)
OST, n (%)				
Low risk of osteoporosis	65	(62.5)	131	(61.8)
Moderate-severe risk of osteoporosis	39	(37.5)	81	(38.2)
Met criteria for treatment initiation <sup>b</sup> , n (%)				
Vertebral fracture evaluation <sup>c</sup>	(N= 88)		(N= 178)	
Presence of vertebral fracture, n (%)	11	(12.5)	11	(6.2)
Severity				
Mild, n (%)	9	(10.2)	9	(5.1)
Moderate, n (%)	3	(3.4)	1	(0.6)
Severe, n (%)	–		1	(0.6)
Number of fractures				
1, n (%)	7	(7.9)	7	(3.9)
2, n (%)	4	(4.5)	2	(1.1)
3, n (%)	–		–	
4, n (%)	–		2	(1.1)

BMD bone mineral density, FRAX fracture risk assessment, OST osteoporosis self-assessment tool, SD standard deviation, BMD bone mineral density

\* $p \leq 0.05$

<sup>†</sup> $p \leq 0.01$

<sup>‡</sup> $p \leq 0.001$

<sup>a</sup>According to the WHO guidelines

<sup>b</sup>Criteria for treatment initiation according to Osteoporosis Guidelines by the National Peruvian Social Insurance: DXA-based measure of lumbar spine and/or total hip T-score  $\leq -2.5$ ; or lumbar spine and/or total hip T-score between  $-1$  and  $-2.5$  and FRAX 10-year risk scores of  $\geq 3\%$  for hip fracture or  $\geq 20\%$  for major osteoporotic fracture

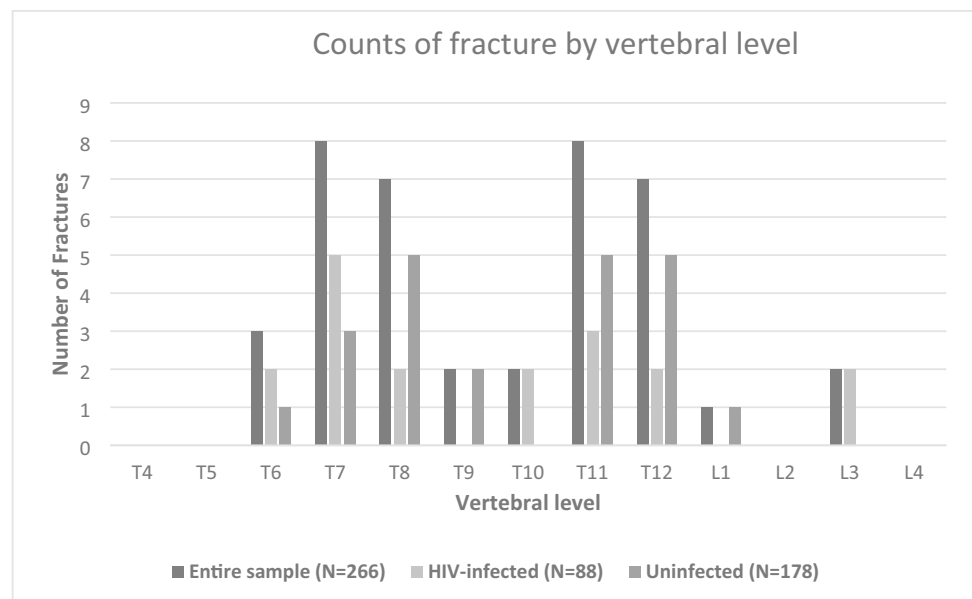
<sup>c</sup>According to the Genant method

NNRTI plus LPV/r or DTG or two NNRTIs. As a significant majority of patients living with HIV in our study were on a TDF-based regimen, we were not able to separately analyze the association between this agent and our outcomes of interest.

In a subgroup analysis of the START study [40], which followed a racially diverse group of 424 men and women, who were on average 32 years old, for approximately 4.5 years after initiation of ART, the authors concluded that significant reductions in TH and LS BMD plateau one year

out from ART initiation and subsequently become similar to BMD loss in groups without HIV. Furthermore, another study that looked at BMD among 457 Chinese PWH (mean age 36.1 years, 8.3% women) through 5 years after ART initiation found a stabilization of BMD after the first 3 years of treatment; then, FN and TH BMD remained low at 5 years relative to baseline and only LS BMD at 5 years was similar to baseline [41]. The multivariable analysis of our smaller dataset and comparison of the BMD between our two groups is consistent with the START study results,

**Fig. 1** Counts of fracture by vertebral level



but further investigation looking at a larger sample of older women on ART for over 4.5 years may be informative to understand the BMD trends and fracture risk over time for Latin American women on ART.

Furthermore, in our study, 23.1% (24/104) of women living with HIV and 24.1% (51/212) women without HIV met criteria for treatment initiation according to the Osteoporosis Guidelines by the National Peruvian Social Insurance [22], but none of them were officially diagnosed nor on treatment. Criteria for treatment initiation in Peru include history of a previous fragility fracture during adulthood, meeting criteria for osteoporosis based upon DXA-measured BMD at the LS, TH, or FN or based upon the FRAX algorithm. This highlights the fact that the public health burden of fractures will continue to increase unless the at-risk individuals are identified and subsequently treated, considering both pharmacologic and non-pharmacologic interventions. While international guidelines exist for screening or management of osteoporosis in PWH, to our knowledge, no current guidelines exist in Peru or other Latin American countries [42]. Nor are there any organized training programs for HIV providers related to this subject. Our findings suggest that screening with a simple tool such as the OST may be one valuable approach to identifying patients who may benefit from DXA screening or FRAX assessment, as not all HIV care settings may have direct access to DXA.

In this study, a larger percentage of women living with HIV had vertebral fractures (12.5% vs. 6.2%) despite having a younger average age than the women without HIV. There was also a larger percentage of women in the group living with HIV that had more than one fracture (4.5% vs. 2.2%). This trend is in keeping with the existing data from other regions comparing vertebral fracture risk among populations

living with and without HIV [9]. The higher burden of multiple fractures in the younger group living with HIV speaks to the need for targeted prevention and treatment strategies for this population.

The most significant risk factors for vertebral fracture among women living with HIV in this study were age and mestizo ethnicity, which were not statically significant factors in the group without HIV. This finding may have been due to population differences between the two groups given that the group living with HIV had a higher number of women identifying as mestizo ethnicity and on average were younger than their counterpart living without HIV. Although the literature suggests that race/ethnicity influences risk for fracture, for example, with studies showing higher rates of fractures among white women [43], in other studies, differences in ethnicity have not been shown to have a greater effect on fracture risk than other determinants such as age or BMI [44]. The effect of ethnicity on vertebral fractures and bone mineral density has not yet been explored in Peru. The cultural, socioeconomic, and dietary differences which may contribute to this finding should also be investigated further.

This study has some important limitations. First, as a single-center study, our results are not necessarily generalizable to all women with HIV in Peru or within LAC due to different environmental and cultural factors. However, as this study was based in one of the largest reference HIV clinics in the capital city of Peru, and more than 70% of Peruvian persons living with HIV are from Lima, we feel it provides important information. Second, due to the study's cross-sectional design, associations between BMD, vertebral fracture, and the sociodemographic and clinical factors cannot be inferred to suggest causality. Nonetheless, we aimed to perform an initial examination of this understudied



**Table 3** Unadjusted and adjusted logistic regression for altered bone mass density (osteopenia and osteoporosis) by HIV status ( $N=266$ )

Independent variables	Altered bone mineral density (osteopenia and osteoporosis)							
	HIV-infected women				Uninfected women			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age	<b>1.13</b>	<b>1.05 to 1.21<sup>¥</sup></b>	<b>1.13</b>	<b>1.05 to 1.22<sup>¥</sup></b>	<b>1.09</b>	<b>1.05 to 1.14<sup>¥</sup></b>	<b>1.06</b>	<b>1.02 to 1.11<sup>‡</sup></b>
BMI	0.94	0.86 to 1.102	–	–	<b>0.82</b>	<b>0.75 to 1.14<sup>¥</sup></b>	<b>0.84</b>	<b>0.79 to 0.90<sup>¥</sup></b>
Mestizo ethnicity	0.29	0.05 to 1.69	–	–	0.83	0.35 to 1.93	–	–
Married/cohabited marital status	1.48	0.56 to 3.94	–	–	0.93	0.53 to 1.66	–	–
Education level higher than high school	0.75	0.230 to 1.86	–	–	<b>0.34</b>	<b>0.13 to 0.91*</b>	<b>0.47</b>	<b>0.23 to 0.99*</b>
Smoke, ever	1.02	0.39 to 2.66	–	–	0.59	0.29 to 1.19	–	–
Current alcohol use	1.06	0.39 to 2.87	–	–	1.01	0.54 to 1.90	–	–
Parental history of hip fracture	0.57	0.15 to 2.19	–	–	0.94	0.40 to 2.24	–	–
Personal history of fracture	2.44	0.51 to 11.7	–	–	1.86	0.83 to 4.17	–	–
History of fall within the last year	1.21	0.51 to 2.86	–	–	0.81	0.46 to 1.43	–	–
Use of hormone replacement therapy, ever	0.40	0.02 to 6.57	–	–	0.74	0.20 to 2.73	–	–
Current use of corticosteroids	0.81	0.07 to 9.23	–	–	4.21	0.52 to 34.36	–	–
Postmenopausal status	<b>4.38</b>	<b>1.67 to 11.50*</b>	–	–	<b>5.15</b>	<b>2.38 to 11.15<sup>¥</sup></b>	<b>2.74</b>	<b>1.24 to 6.08*</b>
Prior removal of one or both ovaries	0.94	0.23 to 3.91	–	–	0.86	0.40 to 1.87.	–	–
Current use of bone nutritional supplements	1.66	0.18 to 15.47	–	–	0.87	0.25 to 3.09	–	–
Prior bone density test	0.51	0.11 to 2.45	–	–	<b>2.16</b>	<b>1.08 to 4.34*</b>	–	–
Total Six-Item Calcium Score	1.03	0.96 to 1.11	–	–	1.01	0.96 to 1.07	–	–
OST	<b>0.70</b>	<b>0.58 to 0.86<sup>‡</sup></b>	<b>0.78</b>	<b>0.63 to 0.97*</b>	<b>0.63</b>	<b>0.54 to 0.63<sup>¥</sup></b>	–	–
Years since HIV diagnosis	1.06	0.99 to 1.14	–	–	–	–	–	–
Years since ART initiation	<b>1.09</b>	<b>1.00 to 1.19*</b>	1.08	0.99 to 1.18	–	–	–	–
Nadir CD4+ count	1.00	0.99 to 1.004	–	–	–	–	–	–
Current CD4+ count	1.00	0.99 to 1.002	–	–	–	–	–	–
AIDS diagnosis	1.24	0.24 to 6.50	–	–	–	–	–	–
Viral suppression status	1.20	0.43 to 3.31	–	–	–	–	–	–

*BMI* body mass index, *AIDS* acquired immune deficiency syndrome, *ART* antiretroviral treatment, *OST* osteoporosis self-assessment tool for women

\* $p \leq 0.05$

<sup>‡</sup> $p \leq 0.01$

<sup>¥</sup> $p \leq 0.001$

population to promote future research on this topic among LAC regions. Third, while we excluded patients with a known history of osteoporosis or treatment for osteoporosis, we did not systematically collect data or exclude patients based upon other causes of secondary osteoporosis such as endocrinopathies, gastrointestinal disorders, or medications outside of glucocorticoids and ART. Finally, due to the COVID-19 pandemic and extended closures of outpatient clinics, we did not reach our original recruitment goals of 255 women living with HIV and 255 women without HIV. However, we were able to demonstrate decreased BMD in women living with HIV versus counterparts without HIV in a propensity score-matched model and a trend towards statistically significant differences in VF prevalence between women living with and without HIV. We therefore believe

that this study provides an important foundation for further research on bone health among women aging with HIV in Peru and LAC.

In summary, as access to ART has improved over time, the sources of morbidity and mortality among individuals living with HIV have gradually shifted away from AIDS defining illnesses toward aging-associated conditions such as bone disease and other non-communicable illnesses due to a combination of host, viral, and ART-related risk factors. In addition to providing new data regarding risk and prevalence of low BMD and vertebral fractures in this vulnerable population, our study highlights a critical treatment gap among women with osteoporosis, which needs to be addressed to avoid complications that carry a high burden and disability among women such as vertebral fractures.

**Table 4** Unadjusted and adjusted logistic regression for vertebral fracture diagnosis by HIV status ( $N=266$ )

Independent variables	Vertebral fracture diagnosis							
	HIV-infected women				Uninfected women			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Age	<b>1.13</b>	<b>1.04 to 1.23<sup>‡</sup></b>	<b>1.15</b>	<b>1.04 to 1.27<sup>‡</sup></b>	1.01	0.94 to 1.08	–	–
BMI	1.05	0.95 to 1.17	–	–	0.92	0.79 to 1.08	–	–
Mestizo ethnicity	<b>8.41</b>	<b>1.09 to 64.65*</b>	<b>10.14</b>	<b>1.19 to 86.50*</b>	3.59	0.36 to 36.33	–	–
Married/cohabited marital status	1.52	0.40 to 5.74	–	–	0.98	0.29 to 3.33	–	–
Education level higher than high school	0.51	0.14 to 1.84	–	–	0.38	0.09 to 1.56	–	–
Smoke, ever	2.02	0.53 to 7.71	–	–	0.50	0.06 to 4.04	–	–
Current alcohol use	1.23	0.30 to 5.13	–	–	0.62	0.13 to 2.99	–	–
Parental history of hip fracture	4.44	0.93 to 21.26	–	–	–	–	–	–
Personal history of fracture	1.33	0.25 to 7.01	–	–	1.06	0.22 to 5.15	–	–
Current use of assistive device	–	–	–	–	16.60	0.967 to 285.35	4.95	0.24 to 102.50
History of fall within last year	1.05	0.30 to 3.75	–	–	0.65	0.18 to 2.31	–	–
Postmenopausal status	–	–	–	–	0.91	0.19 to 4.42	–	–
Prior removal of one or both ovaries	1.00	0.11 to 9.00	–	–	–	–	–	–
Prior bone density test	1.18	0.13 to 10.87	–	–	0.64	0.13 to 3.08	–	–
Femoral neck BMD	0.20	0.6E–02 to 243	–	–	<b>0.001</b>	<b>4.6E–08 to 0.12*</b>	–	–
Total hip BMD	1.39	0.02 to 115.25	–	–	<b>0.001</b>	<b>6.1E–08 to 0.35*</b>	0.004	1.2E–08 to 1.07
Lumbar spine BMD	0.12	0.1E–02 to 12	–	–	<b>0.003</b>	<b>2.08E–08 to 0.52*</b>	–	–
Total Six-Item Calcium Score	–	–	–	–	0.99	0.88 to 1.11	–	–
FRAX score—major osteoporotic fracture	0.90	0.70–1.01	–	–	1.00	0.88–1.19	–	–
Years since HIV diagnosis	1.00	0.90 to 1.11	–	–	–	–	–	–
Years since ART initiation	1.04	0.91 to 1.18	–	–	–	–	–	–
Nadir CD4+ count	1.00	0.99 to 1.00	–	–	–	–	–	–
Current CD4+ count	1.00	1.00 to 1.004	1.00	0.99 to 1.005	–	–	–	–
Viral suppression status	3.51	0.42 to 29.17	–	–	–	–	–	–

*BMI* body mass index, *BMD* bone mineral density, *ART* antiretroviral treatment, *FRAX* fracture risk assessment tool

\* $p \leq 0.05$

<sup>‡</sup> $p \leq 0.01$

<sup>‡</sup> $p \leq 0.001$

Larger prospective studies are needed in this region to identify individuals at risk for fracture and to inform prevention guidelines in order to assure subsequent quality of life among women aging with HIV.

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## Declarations

**Ethical approval and consent to participate** All procedures performed were in accordance with the ethical standards of the institutional

research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

**Conflicts of interest** None.

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