

Mexican patients with HIV have a high prevalence of vertebral fractures

José Antonio Mata-Marín,¹

Carla I. Arroyo-Anduiza,²

María de los Ángeles Berrospe-Silva,³

Alberto Chaparro-Sánchez,¹

Ana Gil-Avila,⁴ Jesús Gaytán-Martínez¹

¹Infectious Diseases Department, Hospital de Infectología, La Raza National Medical Center, Mexico City;

²Clinical Pathology Department, Central Blood Bank, La Raza National Medical Center, Mexico City; ³Infectious Diseases Department, Unidad de Infectología Juan I. Menchaca, Mexico City; ⁴Imagenology Department, Hospital de Infectología, La Raza National Medical Center, Mexico City, Mexico

Abstract

Low bone mineral density (BMD) and fragility fractures are common in individuals infected with HIV, who are undergoing antiretroviral therapy (ART). In high-income countries, dual energy X-ray absorptiometry is typically used to evaluate osteopenia or osteoporosis in HIV infected individuals. However, this technology is unavailable in low and middle income countries, so a different approach is needed. The aim of this study was to use X-ray scans of the spine to determine the prevalence of and associated risk factors for vertebral fractures in HIV-infected patients in a tertiary-care hospital in Mexico. We conducted a cross-sectional study of outpatients who were >40 years old and receiving ART at the Hospital de Infectología, La Raza National Medical Center in Mexico City, Mexico. We used semi-quantitative morphometric analysis of centrally digitized X-ray images to assess vertebral deformities in the spine. Anterior, middle and posterior vertebral heights were measured, and height ratios were calculated. For each vertebral body, fractures were graded on the basis of height ratio reductions, and a spine deformity index⁷ (SDI) value was calculated by summing the grades of the vertebral deformities: An SDI>1 was indicative of a vertebral fracture. We included 104 patients, 87% of whom were men. The median age was 49 years [interquartile range (IQR) 42-52]. The most common stage of HIV infection, as defined by the Centers for Disease Control,

was B2 in 40 (39%) of patients. Forty seven (45%) patients were on ART regimens that included protease inhibitors (PIs) and 100 (96%) being treated with tenofovir. The median time of ART was 6.5 years (IQR 1.6-9.0). Of the 104 patients in our study, 83 (80%) had undetectable viral load, as assessed by HIV-1 RNA levels, 32 (31%) showed evidence of a previous fracture, 4 (4%) were co-infected with hepatitis C virus, and 57 (55%) had a history of corticosteroid treatment. The prevalence of vertebral fractures was 25%, 95% confidence interval 17-34%. We assessed whether gender, HCV co-infection, previous corticosteroid use, AIDS, total HIV viral load, and current and previous use of PIs were associated with fractures in our study group, but we did not observe a significant association between any of these factors and vertebral fractures. The prevalence of vertebral fractures was high among HIV-infected patients. We propose that screening for bone disease should be performed in HIV individuals who are at risk of fragility fractures. Furthermore, we suggest that X-ray based assessment of the spine should be considered in patients who are at increased risk of fragility fractures, irrespective of BMD levels, particularly in elderly patients in low and middle income countries.

Introduction

Individuals with osteoporosis, a skeletal disorder characterized by compromised bone strength, have an increased risk of fracture.¹ Low bone mineral density (BMD), including that seen in individuals with premature osteopenia and osteoporosis, is more common in persons who are infected with human immunodeficiency virus (HIV)² than in uninfected persons, and there is evidence showing that antiretroviral therapy (ART) could increase bone loss. Low BMD is more prevalent in HIV infected subjects, and antiretroviral therapy (ART) can increase bone loss;³ this treatment is associated with a 2-6% decrease in BMD over the first 2 years, which is similar in magnitude to that observed during the first 2 years of menopause.⁴ Chronic hepatitis C co-infection are associated with higher incidences of fractures whereas older age, female gender, an acquired immune deficiency syndrome (AIDS) diagnosis, baseline plasma HIV RNA viral load, and low body mass index (BMI) are related with low BMD.⁵

A number of studies have described accelerated bone loss and increased rates of osteopenia and osteoporosis among HIV-

Correspondence: José Antonio Mata Marín, Instituto Mexicano del Seguro Social. Hospital de Infectología, "La Raza" National Medical Center, Seris y Jacarandas s/n, Colonia La Raza, Del Azcapotzalco, Mexico City, PO 02990, Mexico.

Tel.: +52.5530379053.

E-mail: jamatamarin@gmail.com

Key words: Mexican, HIV, prevalence, vertebral fractures.

Acknowledgements: the authors wish to thank all of the centers and investigators who participated in this study.

Contributions: JAMM conceptualized and designed the study, drafted the manuscript, and gave final approval of the version to be published. CIAA and ACS collected the data, wrote parts of the manuscript, reviewed the project, and gave final approval of the version to be published. MABS reviewed the project, drafted the manuscript and gave final approval of the version to be published. JGM gave final approval of the version to be published.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Received for publication: 29 September 2017.

Revision received: 26 January 2018.

Accepted for publication: 26 January 2018.

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0).

©Copyright J.A. Mata-Marín et al., 2018

Licensee PAGEPress, Italy

Infectious Disease Reports 2018; 10:7409

doi:10.4081/idr.2018.7409

infected individuals, as compared to those in a general population.⁶ Previous studies have suggested that antiretroviral drugs, which are commonly used to treat patients with HIV have a negative impact on bone health. Nucleoside reverse transcriptase inhibitors (NRTIs) as tenofovir (TDF) is associated with a greater decline in BMD as compared to that seen with abacavir (ABC).⁷ Exposure to protease inhibitors (PIs) decreases BMD, and it has recently been suggested that atazanavir is associated with an increased risk of osteoporosis, as compared to that with efavirenz.⁸ There are reports of bone disorders such as avascular necrosis of the hip and compression fracture of the lumbar spine in HIV-infected patients receiving PIs.⁹ Lower lumbar and thoracic spine BMD have been identified in up to 30% of HIV-infected individuals treated

with PIs.¹⁰ The prevalence of bone weakness (and/or fractures) in these patients needs regular screening. Dual energy X-ray absorptiometry (DEXA) is used to evaluate BMD in patients with HIV;¹¹ however, low and middle-income countries often do not have access to it. We hypothesized that a lateral spine X-ray could aid in the identification of a proportion of patients with vertebral fractures.

The aim of this study was to determine the prevalence of and factors associated with, vertebral fractures (since they are fragility fractures more easily measurable) in HIV infected patients in a tertiary level infectious disease care hospital in Mexico.

Materials and Methods

Design

We conducted a cross-sectional study from August 2015 to February 2016 at the Hospital de Infectología, La Raza National Medical Center, a tertiary-level hospital for infectious disease in Mexico City, Mexico.

Patients

Persons who came to the outpatient HIV clinic and were 40 years old, due to the fact that from that age the risk of fracture starts, and being treated with ART were invited to participate.

The study was approved by the Institutional Review Board number 3502 and protocol number is R-2016-3502-2. All participants provided written informed consent before completing a questionnaire that assessed the epidemiological, immunological, virological and clinical risk factors for osteoporosis. Except for the patients who had previously been prescribed steroids, we excluded any patients who were being treated with anti-osteoporotic drugs and/or with drugs that cause osteoporosis and fractures.

Questionnaire

Patients filled a questionnaire on personal characteristics (age, sex, and duration of HIV infection), body composition (height, weight and BMI), risk factors for low BMD (history of fractures, smoking status, corticosteroid use and alcohol consumption), hepatitis B and C coinfection, diabetes mellitus, chronic renal failure, CD4⁺ cell count, nadir of CD4⁺ cell counts, HIV-1 RNA viral load, AIDS diagnosis, and type and duration of ART.

Measurements

Each patient's spine was imaged by lateral spine X-ray. Vertebral deformities were identified using a semi-quantitative mor-

phometric analysis of centrally digitalized images. Anterior, middle and posterior vertebral heights were measured, and height ratios were calculated. For each vertebral body fractures were defined as mild, moderate and severe based on height ratio decreases of 20 -25% (grade 1), 26 -40% (grade 2) and >40% (grade 3), respectively;¹² the height relationships were calculated with a rule to evaluate the compression in millimeters. For each patient, the *spine deformity index* (SDI) was calculated by summing the grades of vertebral deformities according to the semiquantitative method described by Genant *et al.*¹² An SDI >1 was indicative of vertebral fracture according to its definition (reduction in vertebral height of 4 mm or 20-25%).

Statistical analysis

Analyses were performed using SPSS v.20 and EPIDAT v 3.8. The Kolmogorov-Smirnov test was used to determine the sampling distribution. Descriptive results were summarized using median and interquartile ranges (IQRs). The chi-squared test was used to compare categorical variables. Analyses of continuous variables were performed using the Mann Whitney test. $P < 0.05$ was considered to be statistically significant.

Results

A total of 104 patients were included in the study, 87% of whom were men. The median age was 49 years (IQR 42-52). Among the patients that were studied, the most common CDC stages were B2, a2, A1 and A3, accounting for 39%, 36%, 8% and 8%, respectively. Overall, 47 patients (45%) were being treated with PIs or had taken PIs in the past and 100 (96%) were taking TDF or had previously taken TDF. At the time of the study, 83 (80%) had an undetectable HIV-1 RNA viral load (HIV-1 RNA <20

copies/mL). Thirty-two (31%) patients had previously had a fracture, and 4 (4%) were co-infected with HCV. In addition, 57 (55%) patients had a history of corticosteroid treatment, with prednisone being the most prescribed corticosteroid in 47 (45% patients). Regarding family fractures, 19 (18%) patients were positive for this antecedent, and 7 (7%) used anticonvulsants in the past.

We found that 27 (25%, 95% CI 17-34%) patients in our study had vertebral fractures. Out of these patients, 17 (62%) had mild fractures, 8 (29%) had moderate fractures, and 2 (7%) had severe fractures. We assessed the following features for associations with an increased risk of fracture: female gender, HCV co-infection, and previous corticosteroid use showed a trend toward association with an increased risk of vertebral fracture, but this association was not statistically significant. In our cohort, none of the other factors assessed were significantly associated with spine fracture (Table 1).

Discussion and Conclusions

The combination of two factors (survival and prolonged exposure to ART) has led to the development of so-called non-AIDS events, which have gained significant relevance in the morbidity and mortality of the HIV-positive population.

The high prevalence of osteopenia and osteoporosis observed in the HIV-infected population and the increased risk of fragility fractures have prompted clinicians to establish screening programs aimed at identifying patients who are eligible for preventive therapy.

In our study, we found that the prevalence of vertebral fractures in patients who were >40 years old and infected with HIV was high; however, we were not able to identify risk factors associated with the

Table 1. Characteristics associated with an increased risk of fractures among patients in our study.

Characteristics	Odds ratio (95% CI)	P value
Female gender	0.50 (0.10-2.45)	0.39
HCV co-infection	3.1 (0.42-23.7)	0.23
Previous corticosteroids use	0.51 (0.20-1.25)	0.13
AIDS	0.53 (0.21-1.34)	0.18
HIV-1 RNA viral load >100,000 cop/mL	1.64 (0.29-9.12)	0.56
Current or previous PIs use	0.85 (0.34-2.09)	0.73
Current or previous TDF use	1.82 (0.54-3.2)	0.44

PIs, protease inhibitors; TDF, tenofovir.

incidence of fractures.

Many patients in our study were being treated with PIs at the time of the study or had previously been treated with PIs and were currently being treated with TDF. Several studies have suggested an association between BMD reduction and treatment with PIs or with TDF. Arnstern *et al.* reported that neither ART nor PI use is associated with decreased BMD.¹³ In contrast, in the TROOP study, switching from tenofovir to raltegravir in virologically suppressed, HIV-infected adults with low BMD who were stable on an PI-containing regimen resulted in statistically significant improvements in both hip and spine BMD at 48 weeks and significant reductions in plasma [BTMs (bone turnover markers)] by 24 weeks and a TDF switch to raltegravir yielded hip and spine BMD increases of 2.5 and 3.0%, respectively.¹⁴ In the ASSERT study, a greater BTM increase was found with TDF plus emtricitabine compared with ABC plus lamivudine.¹⁵ Bedimo *et al.* found that concomitant exposure to TDF and PIs was associated with an increased risk of osteoporotic fractures, as compared to patients exposed to TDF without PIs or to PIs without TDF and reported more minimal trauma fractures with TDF-based ART (relative risk 1.12 per year of TDF exposure).¹⁴⁻¹⁶

ART causes approximately 3-6% loss of BMD in the first year of ART, similar to the amount of BMD loss with menopause, this loss occurs on a background of lower BMD in the HIV-infected population, particularly with longer duration of HIV infection.¹⁴

Patient histories revealed that some of the subjects were co-infected with HCV and had a history of treatment with corticosteroids. Corticosteroids have well-established adverse effects on the bone with a clear relationship seen between corticosteroid use and fracture in the general population; in HIV-infected individuals, corticosteroid use also has been shown to be associated with fracture risk.¹⁶

The pathogenesis for an increased risk of osteoporosis associated with HIV is likely to be multifactorial and is not completely understood. Individuals who are infected with HIV have a high prevalence of traditional risk factors for osteoporosis including low BMD, poor nutrition, frequent use of glucocorticoids, smoking, vitamin D deficiency and co-infection with HCV.¹⁷

Studies comparing fragility fractures in HIV-infected and uninfected men have been inconclusive. Collin *et al.* reported that the incidence of the first fracture was 3.3/1000 patient-years (95% CI 2.0, 4.6).¹⁸ Arnstern

et al. explored associations of HIV infection with BMD and incident fractures in HIV-infected and at-risk men aged 49 years or older.¹¹ Triant *et al.* reported a higher prevalence of wrist, hip and vertebral fractures among HIV-infected men than among uninfected men (3.08/100 persons *versus* 1.83/100 persons; $P < 0.0001$).¹⁹ Borderi *et al.* performed lateral spine X-rays to assess the prevalence of subclinical vertebral fractures in 202 HIV-infected patients and reported a prevalence of 23.3% for vertebral fractures in these subjects,²⁰ which was similar to the findings of our study.

In a population-based nationwide cohort study using Danish registries, Hansen *et al.* reported that HIV-infected patients had a higher risk of fractures than compared with the population controls.²¹ Among HIV-infected patients, an increased risk was observed for a low-energy fracture but not for a high-energy fracture, and the increased risk of a low-energy fracture was only observed in ART-exposed patients.¹⁹ Fractures were reported in 15% of patients. However, that study focused on a young population. In our study, we only included vertebral fractures, that were low-energy fractures.

Risk of fragility fracture should be assessed primarily using the Fracture Risk Assessment Tool (FRAX), without dual-energy X-ray absorptiometry (DXA), in all HIV-infected men aged 40-49 years and HIV-infected premenopausal women aged ≥ 40 years.²²

Although there are numerous publications linking HIV infection to bone mineral decline, the World Health Organization (WHO), has not included HIV in the fracture elevation *score* (FRAX) to date.²²

Our study has some limitations, including the sample size and the absence of a control group; moreover there is heterogeneity of the population with regard to time, age, histories of the use of different antiretroviral and the variability of the treatment. In addition, we were not able to identify risk factors associated with vertebral fractures. We only considered vertebral fractures; although these fractures were once classified as fragility fractures, this classification was not mandated.

Finally, in some low and middle-income countries like Mexico that do not have access to a DEXA scan, the evaluation and treatment of bone disease is very difficult. In addition, this problem is complicated by reduced access to tests for bone markers. Thus, the radiological assessment of vertebral fractures could be an option for the evaluation of bone disease.

References

1. Yin MT, Brown TT. HIV and bone complications: understudied populations and new management strategies. *Curr HIV/AIDS Rep* 2016;13:349-582.
2. Cotter AG, Sabin CA, Simelane S, et al. Relative contribution of HIV infection, demographics and body mass index to bone mineral density. *AIDS* 2014;28:2051-60.
3. Borges AH, Hoy J, Florence E, et al. Antiretrovirals, fractures, and osteonecrosis in a large international HIV cohort. *Clin Infect Dis* 2017;64:1413-21.
4. Brown TT, McComsey GA, King MS, et al. Loss of bone mineral density after antiretroviral therapy initiation, independent of antiretroviral regimen. *J Acquir Immune Defic Syndr* 2009;51:554-61.
5. Womack JA, Goulet JL, Gibert C, et al. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. *PLoS One* 2011;6:e17217.
6. 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;51:937-46.
7. Haskelberg H, Hoy JF, Amin J, et al. Changes in bone turnover and bone loss in HIV-infected patients changing treatment to tenofovir-emtricitabine or abacavir-lamivudine. *PLoS One* 2012;7:e38377.
8. Womack JA, Goulet JL, Gibert C, et al. Increased risk of fragility fractures among HIV infected compared to uninfected male veterans. *PLoS One* 2011;6:e17217.
9. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 2000; 14: F63-7.
10. Focà E, Motta D, Borderi M, et al. Prospective evaluation of bone markers, parathormone and 1,25-(OH)₂ vitamin D in HIV-positive patients after the initiation of tenofovir/emtricitabine with atazanavir/ritonavir or efavirenz. *BMC Infect Dis* 2012; 12: 38.
11. Lorente Ramos RM, Azpeitia Armán J, Arévalo Galeano N, et al. Dual energy X-ray absorptiometry: fundamentals, methodology, and clinical applications. *Radiologia* 2012;54:410-23.
12. Genant HK, Fuerst T, Faulkner KG, Glüer CC. In evaluating bone density

- for osteoporosis, are any of the available methods clearly superior? *AJR AM J Roentgenol* 1996;167:1589-90.
13. Arnsten JH, Freeman R, Howard AA, et al. Decreased bone mineral density and increased fracture risk in aging men with or at risk for HIV infection. *AIDS* 2007;21:617-23.
 14. Bloch M, Tong WWY, Hoy W, et al. Switch from tenofovir to raltegravir increases low bone mineral density and decreases markers of bone turnover over 48. *HIV Med* 2014;15:373-80.
 15. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir/lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis* 2010;51:963-72.
 16. Grant P, Sheikh V, DerSimonian R, et al. Clinically indicated corticosteroids do not affect bone turnover during immune restoration of severely lymphopenic HIV-infected patients. *AIDS Res Hum Retroviruses* 2015;31:739-44.
 16. Bedimo R, Maalouf N, Zhang S, et al. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS* 2012;26:825-31.
 17. Collin F, Duval X, Le Moing V, Piroth L, et al. Ten-year incidence and risk factors of bone fractures in a cohort of treated HIV1-infected adults. *AIDS* 2009;23:1021-4.
 18. 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.
 19. Borderi M, Calza L, Colangeli V, et al. Prevalence of sub-clinical vertebral fractures in HIV-infected patients. *New Microbiol* 2014;37:25-32.
 20. Hansen ABE, Gerstoft J, Kronborg G, et al. Incidence of low and high-energy fractures in persons with and without HIV infection: a Danish population-based cohort study. *AIDS* 2012;26:285-93.
 21. Brown TT, J Hoy, M Borderi, et al. Recommendations for evaluation and management of bone disease in HIV. *Clin Infect Dis* 2015;60:1242-51.