Bone Involvement in Antiretroviral-Therapy–Naïve HIV-Infected Young Men

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Abstract

Background: Low bone mineral density has been described as a non–AIDS (Acquired Immune Deficiency Syndrome)-related event in HIV (human immunodeficiency virus)-patients but it is poorly studied in young HIV-infected men who have received no previous antiretroviral therapy.

Methods: A cross-sectional study of 245 naïve-HIV-infected men over 21 and under 50 years old was carried out between January 2014 and September 2017.

Results: The mean age was 36.4 years, been 68% Caucasian and 29.3% Latin American. At the time of diagnosis, 91% of patients had stage-A (median CD4+ T-cell 481cells/ μ L, IQR, 320–659). 10% had a count below 200 CD4 cells/ μ L, and 40% had a CD4/CD8 cell-count-ratio below 0.4. Regarding lifestyle and risk factors, 14.1% presented underweight, 36.1% engaged in no regular exercise, 51.9% had previous exposure to tobacco and 35.3% reported drug use. Low levels of vitamin D were seen in 87.6% of the men studied. Low BMD (Z-score<2.0) was found in 22,8% of the patients.

Conclusions: We find prevalence of bone involvement among naïve HIV-infected men under 50 years old. Further studies are necessary to evaluate if BMD assessment should be recommended in young HIV-infected patients.

Background

With the development of antiretroviral therapy (ART), people living with HIV (PLWH) have considerably improved life expectancy.(1) In recent years, however, there has been a steady rise in so-called non–AIDS (Acquired Immune Deficiency Syndrome)-related events, such as cardiovascular events, non–AIDS-defining tumors, as well as bone involvement and abnormally low bone mineral density (BMD).(2)

Bone involvement, defined as the presence of osteopenia or osteoporosis on a dual energy x-ray absorptiometry (DXA) scan,(3,4) has been the subject of numerous studies, and have focused on bone toxicity associated with ART. A number of clinical trials have described reduced BMD during the first or second year of ART, independently of the type of therapy,(5,6) in particular, tenofovir disoproxil fumarate (TDF) and protease inhibitors (PIs) have been associated with higher rates of medium- and long-term bone toxicity.(7) As a result, the primary international practice guidelines recommend performing a DXA scan in HIV-infected individuals over the age of 50 years.(1,7)

The factors that contribute to bone involvement are widely known and include age, vitamin D deficiency, tobacco and alcohol consumption, a sedentary lifestyle, among others.(8,9) In addition to these factors, PLWH exhibit a marked proinflammatory state even after ART start.(10) Little is known, but it is expected, therefore that young HIV-infected individuals will have lower bone mass than similar uninfected population, even prior to initiation of ART. (11,12)

The aim of this study is to assess bone involvement and risk factors that may contribute to the onset of low BMD among young HIV-infected men (under 50 years of age), who are naïve to ART.

Methods

A cross-sectional study of HIV-infected men over 21 and under the age of 50 years who were naïve to ART in a tertiary teaching hospital in central Madrid, Spain.

Subjects and study design; Inclusion criteria and ethical concerns

245 adult men (over 21 and under the age of 50 years) who came to the Infectious Disease Division appointment in Hospital Fundación Jiménez Díaz in Madrid, from January 1st, 2014 to September 30th, 2017, with a recent diagnosis of HIV infection, without previous HIV treatment. All subjects underwent a baseline DXA scan (HOLOGIC QDR 4500C, Marlborough, MA, USA) performed prior to start ART. Further, all patients who started treatment between May 1st and September 30th, 2017 were invited to participate in a substudy on bone mineral metabolism. The protocol for this study was approved by the clinical research ethics committee of the Hospital Fundación Jiménez Díaz (approval code: PIC, 155-2016, approved on 20 December 2016) and is in adherence with the tenets of the Declaration of Helsinki. All patients provided signed informed consent before being included in the study.

Exclusion criteria were as follow: patients over 50 years old, previous HIV or bone-targeting treatment (denosumab, vitamin D), treatment with systemic corticosteroids, diagnosed of diabetes, rheumatologic and renal diseases, *thyrotoxicosis*, *advanced liver disease*, *malabsorption syndrome*, *neoplasms* or previous fragility fractures.

Measurements and reference values

We gathered such epidemiologic data as age, race, and country of birth. Lifestyle-related aspects used as study variables included alcohol, tobacco, and drug consumption, physical activity, and approximate calcium intake. Additionally, anthropometric data were collected for all patients. Blood test was done fasting, measured by Advia 2400 system (Siemens , Munich, Germany) for values related to calcium, phosphorus and vitamin D. Immunological and virologic parameters (i.e., CD4+, CD8+, and HIV-1 viral load) were measured by PCR (Roche, Basel, Switzerland).

Underweight was defined as a body mass index (BMI) of $<20 \text{ kg/m}^2$. The values related to bone and mineral metabolism used were the following: 25OH Vitamin D (30-50 ng/ml), and parathormone (PTH) (10–70 pg/ml). Patients considered smokers if they were current or past tobacco users; consumers of alcohol if their total intake was over 30 g/day; and drug users (cocaine, mephedrone, amphetamines, ketamine, GHB) if any of these drugs were taken at least once weekly. For the purposes of this study, sufficient physical exercise was a minimum of 120 minutes per week. Three servings of calcium-rich foods (e.g., milk, cheese, other dairy products) daily was considered an appropriate intake.

DXA scan was performed before the start of ART. BMD was determined by bone densitometry in lumbar spine (LS), and femoral neck (FN). Being our sample subjects under 50 year and according to the World Health Organization (WHO) guidelines, the subjects were classified with Z-score, considering Low BDM values under -2.(4)

Statistical Analysis

Qualitative variables were expressed in terms of frequency and percentages. Based on the results of the Kolmogorov-Smirnov test for normality, quantitative variables were measured as either mean and standard deviation or median and interquartile range (IQR). Qualitative variables were analyzed using the Chi-squared test or Fisher's exact test. Quantitative variables were compared using Student's t test. For all determinations, we used R software version 3.6.0 (R Core team (2020); R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $p < 0.05$.

Results

Epidemiology and lifestyle

A total of 245 patients were included, all of whom were men. The main patient characteristics appear in Table 1. The median age of the patients was 36.4 years, 68% of whom were Caucasian (87.7% Spanish), and 29.3% Latin American. All patients had been infected with the HIV virus through sexual intercourse (MSM). At the time of diagnosis, 91% of patients had stage-A disease according to the classic CDC (Center for Disease Control) classification system, and the median CD4+ T-cell count was 481 cells/ μ L (IQR, 320–659). Ten percent of these stage-A patients had a count below 200 CD4 cells/ μ L, and 41% had a CD4/CD8 cell-count ratio below 0.4. (Table 1). Among evaluated patients, 32,62% had high viral load (>100000 copies/ml) (Table 1).

Regarding lifestyle patterns and risk factors associated with lower BMD (Fig 1), 14.1% presented underweight with low BMI 36.1% engaged in no regular exercise, 51.9% had previous exposure to tobacco, 35.3% reported drug use, and 9.3% drank alcohol habitually. Abnormally low levels of vitamin D were seen in 87.6% of the men studied (Figure 1).

Bone alterations in naïve patients.

Basal DXA was performed previous ART initiation. The median time elapsed between diagnosis and DXA scan was 3.3 month (Table 1). As all the patients were under 50 years old Z-score was calculated, we found that 22,8% of the patients had a Z-score below -2 (Table 1). No significant differences were observed for the other risk factors studied.

In order to understand if any of the studied parameters affect Z-score at any location (LS or FN), a linear regression study was performed (Tables 2 and 3): We only observed a significant association of Z-Score in LS with CD8 and the CD4/CD8 ratio (Table 2) and also with alcohol for FN measurement (Table 3). Likewise, when doing a logistic regression study of Z-score, assuming in this case normal and non-normal values, versus the same parameters under study; only the CD4/CD8 ratio appears to be associated in this case (Table 4). Therefore, this data leads us to think about the possible relationship between viral load and infection itself with the progressive bone deterioration of the HIV patient.

Discussion

How it can be extracted from the data obtained in our work, the results reveal a significant prevalence of bone involvement among newly diagnosed HIV-infected men before initiation of ART without any known secondary causes of osteoporosis, with 22.8% of the patients with a BMD lower than that expected for their age (Z-score <-2). Additionally, a high percentage of these patients have low levels of vitamin D (87.6%).

Our data are similar to what has been previously described in other studies with patients of similar age groups. In this sense, Paccou J et al. (12) involving 49 naïve men, mean age was 31.6 (± 7.7) years demonstrated that the prevalence of low BMD was 24.5% [95% CI, 13.3-38.9], similar to our findings. In another study by Ceballos et al. (11) involving 70 naïve men, mean age 31 years (19-50), Low BMD (Z-score <-2.0) was found in 13% of the patients.

It is highly likely that the lifestyle of the study population, is an important factor behind such high rates of bone involvement. In our findings we observed tobacco use (51.9%), no regular exercise (36.1%) and intermittent drug abuse (35.3%) as the most prevalent risk factors in our cohort. Previous studies have described that these factors may contribute to a decrease in BMD and an increased risk of fracture among patients infected with HIV. Nearly all these conditions have been found to be more prevalent among subjects with chronic HIV infection and ART experienced.(13–16)

Special attention should be given to vitamin D status and its impact on bone metabolism in these patients. In our cohort, 87.6% of the patients had low levels of vitamin D. In recent years, a number of studies have suggested that patients living with HIV infection have a high prevalence of vitamin D deficit independently of their geographic origin.(17–19) In addition to its deleterious impact on patients with HIV infection, vitamin D deficiency is a well-established risk factor for bone disease within the general population.(20) Indeed, recent publications suggest that the functions of vitamin D go beyond the skeleton, and that vitamin D may play a role in regulating cardiovascular and immunologic parameters.(21–23) Though some studies have described a protective role played by vitamin D in which this vitamin prevents loss of bone mass,(24) much remains unknown as to the degree to which vitamin D deficiency contributes to this loss and to an increase in risk of fracture among HIV-infected patients, so vitamin D should be included in the screening of bone fragility in this population (25)

Currently, the primary guidelines and international consensus statements recommend that patients who are infected with the HIV virus undergo bone testing if they are over the age of 50 years(7,26,27) or with a history of pathologic fractures. These publications further advise clinicians to avoid ART regimens that pose a risk of bone toxicity, such as tenofovir disoproxil fumarate (TDF) and protease inhibitors, if the patient has existing bone involvement or fragility fracture.(1,7,16,28) Our findings suggest that this recommendation may be revised, as over 22% of our study population, which consisted of MSM under age 50, had low BMD levels for their age. As there is still no curative treatment for HIV infection, it is foreseeable that these patients will continue requiring ART for years to come, thus putting them at an increased risk of loss of bone mass.

Among the limitations of the study, it should be noted that this is a single-center study may have influenced the interpretation of some of our results, as a similar study performed in another geographic location may find an increase or a decrease in the same parameters observed, mostly due differences in demographic, social and lifestyle. A substudy by Carr, (29) with a total of 424 ART-naïve participants in six continents, with a mean age of 34 (10.1) years, showed that 1.9% of patients had osteoporosis and 35.1% had low BMD;. A second limitation concerns the lack of a study group consisting of individuals not infected with the HIV virus; nonetheless, our results can be contrasted with well-established findings from studies conducted in the general population. Though our cohort consists of individuals who have lived with HIV infection for a short time, certain bias may have been introduced in this regard, as some of the patients studied had no previous tests with a negative result, thus making exact data on cumulative time of infection unavailable. However, the fact that over 90% of patients had stage-A disease indicates an appropriate degree of homogeneity. The most significant limitation of our research stems from the lack of a validated means of screening for bone involvement in patients with HIV infection. Indeed, neither the Fracture Risk Assessment Tool (FRAX) nor densitometric methods have been validated in young people or in the population of individuals living with HIV infection.(1,26,30,31). Despite the limitations discussed above, we believe that the large number of patients included in this study lends validity to its findings and makes the case for baseline examinations of bone density to improve the clinical management of young men living with HIV infection.

In short, the inclusion of DXA densitometry measurements and bone marker analysis as part of baseline evaluation of HIV-infected patients, although alone they would not be used to diagnose the disease in particular, but would provide clinical data to the physician to improve the health of the patient's bone mass, improve lifestyle habits that promote this bone comorbidity and avoid prescribing antiretroviral therapy that leads to bone loss. Similarly, a diagnosis of low BMD at an early age would affect the follow-up approach given to certain patients who by age do not undergo or consider densitometric parameters in the same way. As noted above, an increased risk of bone fracture has been found among patients with HIV infection compared to HIV-negative people; however, these studies have not found a correlation between abnormal DXA measurements and subsequent fracture. (31) As a result, we

argue that the most appropriate strategy in treating young patients with bone involvement evidenced in DXA scanning should be in accordance with the general recommendations of scientific societies and should seek to control the risk factors associated with both antiretroviral and therapeutic treatment for bone comorbidity from the outset of follow-up.

Conclusions

We find a significative prevalence of bone involvement among naïve HIV-infected men under 50 years old. Further studies are necessary to evaluate if BMD assessment should be recommended in HIV-infected patients under 50 years of age.

List Of Abbreviations

AIDS: Acquired Immune Deficiency Syndrome

ART: antiretroviral therapy

BMD: bone mineral density

BMI: body mass index

CDC: Center for Disease Control

DXA: dual energy x-ray absorptiometry

FN: femoral neck

FRAX: Fracture Risk Assessment Tool

GHB: gamma hydroxybutyrate

HIV: human immunodeficiency virus

IQR: interquartile range

LS: lumbar spine

MSM: men who have sex with men

PCR: Polymerase Chain Reaction

PIs: protease inhibitors

PLWH: people living with HIV

PTH: parathormone

TDF: tenofovir disoproxil fumarate

WHO: World Health Organization

Declarations

Ethics approval and consent to participate

The protocol for this study was approved by the clinical research ethics committee of the Hospital Fundación Jiménez Díaz (approval code: PIC, 155-2016, approved on 20 December 2016) and is in adherence with the tenets of the Declaration of Helsinki. All patients provided signed informed consent before being included in the study.

Consent for publication

“Not applicable”. Our manuscript does not contain data from any individual person.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

All data generated or analysed during this study are included in this published article.

Competing interests

AC has received honoraria and speakers’ fees from Gilead Sciences, MSD and ViiV. MG has received speakers’ fees from ViiV. AM has filed a patent on use of adenosine A2AR agonists to prevent prosthesis loosening (pending) and a separate patent on use of A2AR agonists and agents that increase adenosine levels to promote bone formation/regeneration. AM was supported by grants from “Instituto de Salud Carlos III” through the “Miguel Servet” Program (CP15/00053), co-funded by “Fondo Europeo de Desarrollo Regional (FEDER)”. All authors have declared that no competing interests exist.

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Authors’ Contributions

PA, AC, AM and MG conceived the study, participated in its design, data analysis and drafted the manuscript. PA, AC, FMCB and RPT have participated in data collection, design and drafted the manuscript. LPP, BA, IC, RAP, MDC, FMCB, GHB and AM have participated in its design and drafted the manuscript. All the authors contributed to the final version of the manuscript.

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References

1. Negredo E, Domingo P, Gutiérrez F, Galindo MJ, Knobel H, Lozano F, et al. Executive summary of the consensus document on osteoporosis in HIV-infected individuals. *Enferm Infecc Microbiol Clin* [Internet]. 2018 May;36(5):312–4. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0213005X17301301>
2. Althoff KN, McGinnis KA, Wyatt CM, Freiberg MS, Gilbert C, Oursler KK, 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* [Internet]. 2015 Feb 15;60(4):627–38. Available from: <https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciu869>
3. Kanis JA, Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report. *Osteoporos Int* [Internet]. 1994 Nov [cited 2019 Nov 27];4(6):368–81. Available from: <http://link.springer.com/10.1007/BF01622200>
4. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO. Technical report series. Ginebra. Suiza 1994. In 1994.
5. Tinago W, Cotter AG, Sabin CA, Macken A, Kavanagh E, Brady JJ, et al. Predictors of longitudinal change in bone mineral density in a cohort of HIV-positive and negative patients. *AIDS* [Internet]. 2017 Mar;31(5):643–52. Available from: <http://journals.lww.com/00002030-201703130-00005>
6. Moran CA, Weitzmann M, Ofotokun I, Neale Weitzmann M, Ofotokun I. Bone Loss in HIV Infection. *Curr Treat Options Infect Dis* [Internet]. 2017 Mar [cited 2020 Aug 1];9(1):52–67. Available from: <https://pubmed.ncbi.nlm.nih.gov/28413362/>
7. European AIDS Clinical Society. EACS Guidelines. Version 71 [Internet]. 2014;44(November):1–87. Available from: http://www.eacsociety.org/files/guidelines_english_71_141204.pdf%5Cnpapers3://publication/uuid/42AB14E0-1B59-4F6B-BC57-2F49E5F4D986
8. Compston J. Osteoporosis and Fracture Risk Associated with HIV Infection and Treatment. *Endocrinol Metab Clin North Am* [Internet]. 2014 Sep;43(3):769–80. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0889852914000395>
9. Dong H V., Cortés YI, Shiao S, Yin MT. Osteoporosis and fractures in HIV/hepatitis C virus coinfection. *AIDS* [Internet]. 2014 Sep;28(14):2119–31. Available from: <http://journals.lww.com/00002030-201409100-00013>
10. Haskelberg H, Carr A, Emery S. Bone turnover markers in HIV disease. *AIDS Rev*. 2011;13(4):240–50.
11. Ceballos ME, Carvajal C, Jaramillo J, Dominguez A, González G. Vitamin D and Bone Mineral Density in HIV Newly Diagnosed Therapy-Naive Patients Without Any Secondary Causes of Osteoporosis. *Calcif Tissue Int* [Internet]. 2019 Jan 12 [cited 2019 Nov 20];104(1):42–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/30209528>
12. Paccou J, Viget N, Drumez E, Cortet B, Robineau O. Prevalence and risk factors for low bone mineral density in antiretroviral therapy-naive HIV-infected young men. *Médecine Mal Infect* [Internet]. 2018 Oct 1 [cited 2019 Nov 12];48(7):442–8. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0399077X17307035>
13. Battalora L, Buchacz K, Armon C, Overton ET, Hammer J, Patel P, et al. Low bone mineral density and risk of incident fracture in HIV-infected adults. *Antivir Ther* [Internet]. 2015;21(1):45–54. Available from: <http://www.intmedpress.com/journals/avt/abstract.cfm?id=2979&pid=48>
14. Bonjoch A, Figueras M, Estany C, Perez-Alvarez N, Rosales J, del Rio L, et al. High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort study. *AIDS* [Internet]. 2010 Nov;24(18):2827–33. Available from: <http://journals.lww.com/00002030-201011270-00009>

15. Bedimo R, Cutrell J, Zhang S, Drechsler H, Gao A, Brown G, et al. Mechanisms of bone disease in HIV and hepatitis C virus. *AIDS* [Internet]. 2016 Feb;30(4):601–8. Available from: <http://journals.lww.com/00002030-201602200-00008>
16. Brown TT, Hoy J, Borderi M, Guaraldi G, Renjifo B, Vescini F, et al. Recommendations for Evaluation and Management of Bone Disease in HIV. *Clin Infect Dis* [Internet]. 2015 Apr 15;60(8):1242–51. Available from: <https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/civ010>
17. Klassen KM, Fairley CK, Kimlin MG, Hocking J, Kelsall L, Ebeling PR. Vitamin D deficiency is common in HIV-infected southern Australian adults. *Antivir Ther* [Internet]. 2015;21(2):117–25. Available from: <http://www.intmedpress.com/journals/avt/abstract.cfm?id=2983&pid=48>
18. Jao J, Freimanis L, Mussi-Pinhata MM, Cohen RA, Monteiro JP, Cruz ML, et al. Low vitamin D status among pregnant Latin American and Caribbean women with HIV Infection. *Int J Gynecol Obstet* [Internet]. 2015 Jul;130(1):54–8. Available from: <http://doi.wiley.com/10.1016/j.ijgo.2015.01.017>
19. Cervero M, Agud J, García-Lacalle C, Alcázar V, Torres R, Jurdado J, et al. Prevalence of vitamin D deficiency and its related risk factor in a Spanish cohort of adult HIV-infected patients: Effects of antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2012;28:963–71.
20. Parfitt A. Dietary risk factors for age-related bone loss and fractures. *Lancet*. 1983;2:1181–5.
21. Mansueto P, Seidita A, Vitale G, Gangemi S, Iaria C, Cascio A. Vitamin D Deficiency in HIV Infection: Not Only a Bone Disorder. *Biomed Res Int* [Internet]. 2015;2015((Mansueto P; Seidita A; Vitale G.) Department of Internal Medicine and Biomedicine, University of Palermo, Palermo, Italy):1–18. Available from: <http://www.hindawi.com/journals/bmri/2015/735615/>
22. Trochoutsou A, Kloukina V, Samitas K, Xanthou G. Vitamin-D in the Immune System: Genomic and Non-Genomic Actions. *Mini-Reviews Med Chem* [Internet]. 2015 Jul 2;15(11):953–63. Available from: <http://www.eurekaselect.com/openurl/content.php?genre=article&issn=1389-5575&volume=15&issue=11&spage=953>
23. Mocanu V, Oboroceanu T, Zugun-Eloae F. Current status in vitamin D and regulatory T cells–immunological implications. *Rev medico-chirurgicală a Soc Medici Ții Nat din Iași*. 2013;117(4):965–73.
24. Overton E, Chan E, Brown T, Tebas P, McComsey G, Melbourne K, et al. High-Dose Vitamin D and Calcium Attenuates Bone Loss with Antiretroviral Therapy Initiation. *Ann Intern Med*. 2015;162(12):815–24.
25. Atteritano M, Mirarchi L, Venanzi-Rullo E, Santoro D, Iaria C, Catalano A, et al. Vitamin D Status and the Relationship with Bone Fragility Fractures in HIV-Infected Patients: A Case Control Study. *Int J Mol Sci* [Internet]. 2018 Jan 2;19(1):119. Available from: <http://www.mdpi.com/1422-0067/19/1/119>
26. Lozano F, Buzón M, Curran A, Estrada V, García F, Imaz A, et al. Grupo de Estudio de Sida de la Sociedad Española de Enfermedades Infecciosas. Documento consenso de GeSIDA sobre control y monitorización de la infección por el VIH (Actualización abril 2018). In 2018.
27. AIDSinfo. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV [Internet]. Department of Health and Human Services. 2018. p. 298. Available from: <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>
28. Mills A, Arribas JR, Andrade-Villanueva J, DiPerri G, Van Lunzen J, Koenig E, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis* [Internet]. 2016 Jan 1 [cited 2019 Nov 19];16(1):43–52. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1473309915003485>

29. Carr A, Grund B, Neuhaus J, Schwartz A, Bernardino J, White D, et al. Prevalence of and risk factors for low bone mineral density in untreated HIV infection: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment (START) trial. HIV Med [Internet]. 2015 Apr;16(S1):137–46. Available from: <http://doi.wiley.com/10.1111/hiv.12242>
30. Mascolini M. Modified FRAX tool underestimates fracture rates in older men with HIV. In: CROI Conference , Seattle, Washington.
31. Yin MT, Shiao S, Rimland D, Gibert CL, Bedimo RJ, Rodriguez-Barradas MC, et al. Fracture Prediction With Modified-FRAX in Older HIV-Infected and Uninfected Men. JAIDS J Acquir Immune Defic Syndr [Internet]. 2016 Aug 15 [cited 2019 Nov 19];72(5):513–20. Available from: <http://journals.lww.com/00126334-201608150-00007>

Tables

Table 1. Main characteristics of patients (p).

Baseline Characteristics	N = 245 patients
Sex	Male (100%)
Route of transmission	MSM (100%)
Age (mean)	34.7 (IQR: 30–40)
Race	Caucasian (68%) Spanish (87.7%) Latin American (29.3%)
Stage	A (91%) B (6%) C (3%)
High viral load (>100000 copies/ml)	32.62%
CD4 (median)	481cel/μL (IQR: 320–659)
CD4 < 200 cel/μL	10%
CD4 / CD8 ratio < 0.4	41%
Coinfection (HCV antibody/ HVB antigen)	2%
Time between HIV diagnosis and DXA scan (median)	3.3 months
Z-score	Normal (>-2): 77.2% (189 p) Low BMD (<-2.0): 22.8% (56 p)

Table 2. Comparative analysis of linear correlation between Z-Score in LS and baseline parameters studied in HIV patients. The following table summarizes the results of these models using the coefficient (coef.), their 95% confidence interval (95% CI), and the p-value. P<0.05=significant.

<i>Variable (vs Z-score CL)</i>	<i>Coef.</i>	<i>(95% CI)</i>	<i>P</i>
Age	-0.002	(-0.018, 0.015)	0.847
BMI	0.000	(-0.001, 0.000)	0.546
Ca	-0.110	(-0.463, 0.243)	0.539
P	-0.049	(-0.240, 0.142)	0.613
Vit. D	0.012	(-0.013, 0.036)	0.344
Albumin	-0.283	(-0.770, 0.205)	0.254
CD4	-0.012	(-0.063, 0.039)	0.644
CD8	0.030	(0.004, 0.055)	0.022
CD4/CD8 ratio	-0.588	(-1.092, -0.084)	0.022
Viral load	0.000	(-0.131, 0.131)	0.997
Tobacco			
Yes	0.140	(-0.179, 0.460)	0.387
Alcohol			
Yes	0.016	(-0.462, 0.495)	0.946
Drugs			
Yes	0.092	(-0.269, 0.452)	0.617
HIV Stage			
B	0.145	(-0.459, 0.749)	0.636
C	0.017	(-0.825, 0.858)	0.969
Dairy			
No	0.258	(-0.644, 1.161)	0.571
CD4			
<200	0.173	(-0.282, 0.629)	0.454
CD4/CD8 ratio			
<0.4	0.368	(0.084, 0.653)	0.011
Viral Load			
High	0.223	(-0.168, 0.613)	0.262

Table 3. Comparative analysis of linear correlation between Z-Score in FN and baseline parameters studied in HIV patients. The following table summarizes the results of these models using the coefficient (coef.), their 95% confidence interval (95% CI), and the p-value. P<0.05=significant.

<i>Variable (vs Z-score CF)</i>	<i>Coef.</i>	<i>(95% CI)</i>	<i>P</i>
Age	0.013	(-0.001, 0.026)	0.061
BMI	0.000	(-0.000, 0.001)	0.207
Ca	-0.098	(-0.394, 0.198)	0.515
P	-0.074	(-0.234, 0.087)	0.366
Vit. D	0.013	(-0.004, 0.030)	0.124
Albumin	0.110	(-0.301, 0.521)	0.599
CD4	-0.015	(-0.057, 0.028)	0.497
CD8	0.013	(-0.009, 0.034)	0.239
CD4/CD8 ratio	-0.385	(-0.808, 0.038)	0.074
Viral Load	-0.049	(-0.162, 0.065)	0.397
Tobacco			
Yes	0.249	(-0.020, 0.518)	0.069
Alcohol			
Yes	-0.561	(-0.957, -0.165)	0.006
Drugs			
Sí	-0.006	(-0.327, 0.315)	0.970
HIV Stage			
B	0.134	(-0.377, 0.644)	0.606
C	0.033	(-0.653, 0.719)	0.924
Dairy			
No	0.529	(-0.026, 1.084)	0.062
CD4			
<200	0.252	(-0.139, 0.644)	0.205
CD4/CD8 ratio			
<0.4	0.198	(-0.044, 0.440)	0.108
Viral load			
High	0.073	(-0.289, 0.434)	0.692

Table 4. Comparative analysis of logistic correlation between Z-Score (qualitative binary variable: normal range or non-normal range) and baseline parameters studied in HIV patients. The following table summarizes the results of these models using the odds ratio (OR), their 95% confidence interval (95% CI), and the p-value. P<0.05=significant.

Variable	OR	(95% CI)	P
Age	1.01	(0.97, 1.04)	0.764
BMI	1.00	(1.00, 1.00)	0.691
Ca	1.25	(0.58, 2.72)	0.578
P	1.26	(0.84, 1.91)	0.246
Vit. D	0.98	(0.93, 1.03)	0.345
Albumin	0.86	(0.30, 2.50)	0.776
CD4	1.01	(0.91, 1.13)	0.800
CD8	0.95	(0.89, 1.01)	0.123
CD4/CD8 ratio	3.41	(1.19, 9.9)	0.022
Viral Load	1.05	(0.74, 1.37)	0.726
Tobacco			
Yes	0.62	(0.30, 1.28)	0.204
Alcohol			
Yes	2.04	(0.66, 8.95)	0.265
Drugs			
Yes	0.71	(0.28, 1.65)	0.447
HIV Stage			
B	0.27	(0.01, 1.44)	0.218
C	0.55	(0.03, 3.30)	0.580
Dairy			
No	1.25	(0.17, 6.44)	0.801
CD4			
<200	0.92	(0.29, 2.44)	0.876
CD4/CD8 ratio			
<0.4	0.52	(0.26, 0.99)	0.050
Viral Load			
High	0.60	(0.23, 1.41)	0.256

Figures

Figure 1

Risk factors associated with bone comorbidity in HIV patients. The percentages of patients at risk are represented for each of the risk factors studied.

Figure 1

Risk factors associated with bone comorbidity in HIV patients. The percentages of patients at risk are represented for each of the risk factors studied.