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ANALYSIS OF RISK FACTORS ASSOCIATED WITH LOW BONE MINERAL DENSITY IN HIV PATIENTS: AN INTEGRATIVE LITERATURE REVIEW

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RESUMO

INTRODUÇÃO: As pessoas vivendo com HIV (PVHIV) possuem maior incidência de osteopenia, osteoporose e fraturas por fragilidade. A causa é provavelmente multifatorial e inclui interação entre fatores relacionados à infecção pelo vírus da imunodeficiência humana (HIV) e às terapias antirretrovirais (TARV), além dos fatores de risco tradicionais e comportamentais. Esta revisão integrativa de literatura tem o objetivo de identificar e analisar os fatores de risco relacionados à perda óssea nas PVHIV. **METODOLOGIA**: Foram utilizadas publicações dos últimos cinco anos nas bases de dados PubMed e Biblioteca Virtual em Saúde, com amostra final de 26 artigos. **RESULTADO**: A TARV leva ao aumento da perda óssea principalmente nos dois primeiros anos após o início do tratamento. O tenofovir e a duração de seu uso foram os mais relacionados à perda de densidade mineral óssea (DMO), seguidos dos inibidores de protease como atazanavir, lopinavir e darunavir. Outros fatores de risco associados à baixa DMO foram: índice de massa corporal baixo; menor massa corporal magra e gorda; síndrome metabólica; inatividade física e atividade física de baixa intensidade; coinfecção pelo vírus da hepatite C; uso de drogas; tabagismo; uso de álcool; idade avançada; sexo feminino; hipovitaminose D, hiperparatireoidismo secundário à hipovitaminose D; hipogonadismo e fraturas por fragilidade. A contagem de células TCD4+, carga viral, uso de corticosteroides e baixo consumo de cálcio e produtos lácteos não tiveram correlações significativas. **CONCLUSÃO**: A identificação e análise dos fatores de risco para baixa DMO pode facilitar uma melhor abordagem para intervenções clínicas e preventivas de PVHIV.

PALAVRAS-CHAVE: *Vírus da imunodeficiência humana (HIV); incidência; osteoporose; osteopenia; fatores de risco.*

ABSTRACT

INTRODUCTION: People living with HIV (PLHIV) exhibit an increased incidence of conditions like osteopenia, osteoporosis, and fragility fractures. The cause is likely multifactorial and includes interaction between factors related to human immunodeficiency virus (HIV) infection and antiretroviral therapies (ART), as well as traditional and behavioral risk factors. This integrative literature review aims to identify and analyze the risk factors contributing to reduced bone mass in PLHIV. **METHODOLOGY:** A collection of 26 articles published between 2017-2022, sourced from PubMed and Virtual Health Library databases, was employed for this purpose. **RESULTS:** ART use leads to increased bone loss, particularly during the first two

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years of treatment initiation. Tenofovir and the duration of its use were most closely associated with bone mineral density (BMD) loss, followed by protease inhibitors such as atazanavir, lopinavir, and darunavir. Additional risk factors associated with diminished BMD include: low body mass index; reduced lean and adipose body mass; metabolic syndrome; physical inactivity and low-intensity physical activity; co-infection with the hepatitis C virus; substance use; smoking; alcohol consumption; advanced age; female sex; hypovitaminosis D, hyperparathyroidism resulting from hypovitaminosis D; hypogonadism and fragility fractures. Conversely, no significant correlations were observed with CD4+ T cell counts, viral load, corticosteroid use, or insufficient intake of calcium and dairy products. **CONCLUSION:** Individuals living with HIV are at an elevated risk of experiencing low BMD, primarily due to the impact of ART. The identification and analysis of risk factors for reduced BMD could contribute to more effective approaches for clinical intervention and preventative measures for PLHIV.

KEYWORDS: *Human immunodeficiency virus (HIV); incidence; osteoporosis; osteopenia; risk factors.*

INTRODUCTION

The preservation of skeletal health throughout one's lifespan is governed by the process of bone remodeling, wherein compromised bone is replaced by osteoblasts with healthy bone tissue after its removal by osteoclasts[1]. When heightened osteoclastic activity coincides with suppressed osteoblastic activity, individuals become susceptible to low bone mineral density (BMD), leading to osteopenia or its more severe form, osteoporosis. Over time, these transformations can lead to potentially debilitating fractures[1].

In comparison to healthy individuals, people living with HIV (PLHIV) experience a swifter decline in bone mass. Although the exact mechanism linking HIV infection to bone loss remains unidentified, it is likely multifaceted, involving interactions between infection-related factors, HIV treatment, and both conventional and behavioral risk factors[1]. HIV infection itself is believed to induce an inflammatory state that contributes to bone loss through the promotion of osteoclastogenesis and bone resorption[2].

Enduring consequences of HIV infection and prolonged exposure to ART might further amplify the loss of bone mineral density (BMD)[3]. Certain antiretrovirals have been associated with low BMD, notably tenofovir disoproxil fumarate (TDF) and protease inhibitors (PIs), particularly during the first two years of treatment [1,3].

In addition, PLHIV also exhibit higher prevalence of traditional and behavioral risk factors linked to bone loss[1]. Consequently, the identification of these risk factors and the profiling of high-risk HIV patients susceptible to osteopenia, osteoporosis, and fractures assume significant importance. This information can facilitate clinical interventions for this population and enable the establishment of screening programs aimed at identifying candidates for preventive therapy[4,5]. Hence, this study aims to identify and analyze risk factors associated with bone loss in HIV-positive patients.

METHODS

This study employs an integrative literature review conducted through the following steps: 1) formulation of the research question; 2) literature search; 3) evaluation of data quality; 4) data analysis – categorization, exposition, and comparison; 5) presentation of outcomes[6]. The literature search was conducted between July 14 and August 18, 2022.

The central inquiry guiding this study was: "What are the risk factors associated with low bone mineral density in HIV-positive patients?" The databases consulted were PubMed and Virtual Health Library (VHL). The search terms included the following: osteoporosis, osteopenia, and risk factors, sourced from the Descriptors in Health Sciences (DeCS) and Medical Subject Headings (MeSH). The Boolean operator "AND" was employed to combine these terms.

According to the Oxford Centre for Evidence-Based Medicine[7], systematic literature reviews, meta-analyses, randomized clinical trials, and cohort studies comprise the top three tiers of scientific evidence (Figure 1). Therefore, only studies corresponding to these levels of evidence were included in the final selection.

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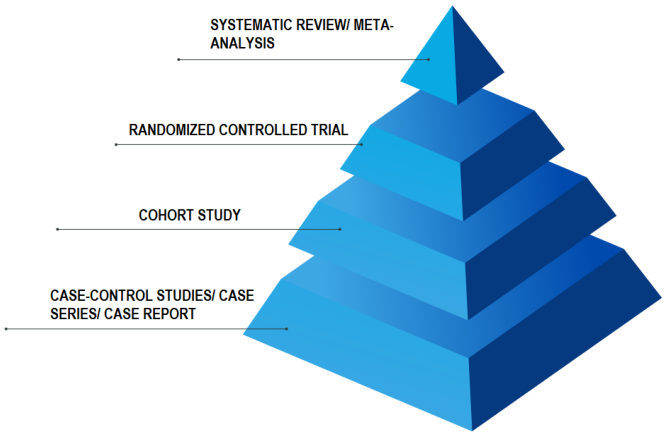
FIGURE 1. Hierachy of scientific evidence levels



Source: Adapted from Murad et al. (2016)[8].

The inclusion criteria were as follows: articles that addressed the research question and were published within the last five years (2017–2022), in Portuguese, English, or Spanish. Articles that were not primarily focused on risk factors related to osteoporosis in HIV-positive patients, as well as those with low levels of evidence (such as case-control studies, case series, case reports, animal studies, and in vitro studies), were excluded.

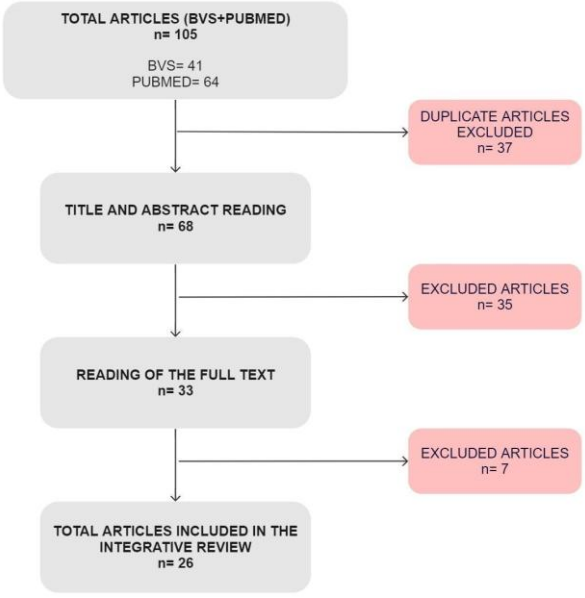
The process of article retrieval was conducted independently by the investigators. Initially, the titles and abstracts of the articles were reviewed, and a careful selection was made based on the predefined eligibility criteria. Subsequently, the selected articles were fully read to determine their suitability for inclusion in the final sample. Mendeley software was employed to facilitate the organization of the chosen articles.

RESULTS

The results of the article selection can be viewed in **Figure 2**. Table 1 provides a systematic presentation of the authors, publication years, countries of origin, journal sources, and methodologies employed in the selected articles.

The methodologies employed in these publications encompassed cross-sectional studies (n=15), cohort studies (n=7), and systematic reviews/meta-analyses (n=2).

FIGURE 2. Flowchart illustrating the process of article selection



Source: The authors, 2022.

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TABLE 1. Summary of Selected Articles

	AUTHOR/ YEAR/ COUNTRY	TITLE	JOURNAL	METHODOLOGY
1	Abreu *et al*/ 2022/ Brazil	Low bone mass and vitamin D in Brazilian people living with HIV under antiretroviral therapy	Archives of Osteoporosis	Cross-sectional study
2	Bregigeon *et al*/ 2017/ France	Frailty in HIV infected people: A new risk factor for bone mineral density loss	AIDS	Cross-sectional study
3	Cervero *et al*/ 2018/ Spain	Prevalence of and risk factors for low bone mineral density in Spanish treated HIV- infected patients	PLoS ONE	Cross-sectional study
4	Chaba *et al*/ 2017/ Brazil	Low bone mineral density among HIV-infected patients in Brazil	Revista do Instituto de Medicina Tropical de São Paulo	Cohort Study
5	Chen *et al*/ 2019/ Taiwan	Monitoring early developed low bone mineral density in HIV-infected patients by intact parathyroid hormone and circulating fibroblast growth factor 23	Journal of Microbiology, Immunology and Infection	Cross-sectional study
6	Chisati, Constantinou e Lampiao/ 2020/ Malawi	Reduced bone mineral density among HIV infected patients on antirretroviral therapy in Blantyre, Malawi: Prevalence and associated factors	PLoS ONE	Cross-sectional study
7	Davidson e Sowden/ 2019/ Australia	Evaluation of screening practices for low bone mass and prevalence of osteoporosis and fractures in people living with human immunodeficiency virus attending a sexual health clinic	Internal Medicine Journal	Retrospective Cohort Study
8	Erlandson *et al*/ 2018/ France	Bone Mineral Density Declines Twice as Quickly Among HIV-Infected Women Compared with Men	Journal of Acquired Immune Deficiency Syndromes	Secondary Longitudinal Study
9	Goh *et at*/ 2018/ Malaysia	Reduced bone mineral density in human immunodeficiency virus-infected individuals: a meta-analysis of its prevalence and risk factors: supplementary presentation	Osteoporosis International	Study Meta-analysis
10	Grant *et al*/ 2019/ USA	Effect of Testosterone Use on Bone Mineral Density in HIV- infected Men	AIDS Research and Human Retroviruses	Cohort Study
11	Kabore *et al*/ 2017/ Africa (Burkina Faso, Senegal, Camarões)	TDF and quantitative ultrasound bone quality in African patients on second line ART, ANRS 12169 2LADY sub-study	PLoS ONE	Cohort Study
12	Kalyan *et al*/ 2018/ Canada	Premature Spinal Bone Loss in Women Living with HIV is Associated with Shorter Leukocyte Telomere Length	International Journal of Environmental Research and Public Health	Cross-sectional study

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13	Komatsu *et al*/ 2018/ Japan	Osteoporosis-Related Fractures in HIV-Infected Patients Receiving Long-Term Tenofovir Disoproxil Fumarate: An Observational Cohort Study	Drug Safety	Cohort Study
14	Mata-Marín *et al*/ 2018/ Mexico	Mexican patients with HIV have a high prevalence of vertebral fractures	Infectious Disease Reports	Cross-sectional study
15	Mazzitelli *et al*/ 2022/ UK	FRAX assessment in people ageing with HIV Maria	HIV Medicine	Cross-sectional study
16	Meng *et al*/ 2022/ China	Prevalence and Risk Factors of Low Bone Mineral Density in HIV/AIDS Patients: A Chinese Cross-Sectional Study	Journal of Acquired Immune Deficiency Syndromes	Cross-sectional study
17	Negredo *et al*/ 2018/ Spain	High risk and probability of progression to osteoporosis at 10 years in HIV-infected individuals: the role of PIs	Journal of Antimicrobial Chemotherapy	Retrospective cohort study
18	Oursler *et al*/ 2020/ USA	Low Muscle Mass Is Associated with Osteoporosis in Older Adults Living with HIV	AIDS Research and Human Retroviruses	Retrospective cross-sectional study
19	Ozcan *et al*/ 2021/ Türkiye	The Prevalence and Associated Factors of Reduced Bone Mineral Density (BMD) Among Men with Suppressed Viral Load Taking Antiretroviral Therapy	Current HIV Research	Cross-sectional study
20	Perazzo *et al*/ 2018/ USA	Relationships Between Physical Activity and Bone Density in People Living with HIV: Results from the SATURN-HIV Study	Journal of the Association of Nurses in AIDS Care	Secondary cross-sectional study
21	Pezzaioli *et al*/ 2022/ Italy	Impact of hypogonadism on bone mineral density and vertebral fractures in HIV-infected men	Journal of Endocrinological Investigation	Retrospective cross-sectional study
22	Pramukti *et al*/ 2020/ USA	Bone fracture among people living with HIV: A systematic review and meta-regression of prevalence, incidence, and risk factors	PLoS ONE	Systematic review and meta-analysis
23	Ruiz *et al*/ 2017/ Colombia	Trastornos de la densidad mineral ósea en personas con VIH en tratamiento antirretroviral Pereira- Risaralda-Colombia	Infectio	Cross-sectional study
24	Shaiykova *et al*/ 2018/ France	Reduced bone mineral density among HIV-infected, virologically controlled young men: Prevalence and associated factors	Aids	Bicentric cross-sectional study
25	Ventura *et al*/ 2017/ USA	Lifetime and recent alcohol use and bone mineral density in adults with HIV infection and substance dependence	Medicine	Cohort Study
26	Zeng *et al*/ 2020/ China	Prevalence and risk factors for bone mineral density changes in antiretroviral therapy-naive human immunodeficiency virus-infected adults: A Chinese cohort study	Chinese Medical Journal	Cohort Study

**NA= Not applicable, as these are systematic reviews and/or meta-analyses.*

The participant count across the studies ranged from 31 to 3251 individuals, culminating in a total of 10,900 patients, excluding the two systematic reviews and/or meta-analyses from the calculation, as they did not accurately present the total number of enrolled patients. Table 2 summarizes the data presented and provides information concerning the inclusion criteria and patient profiles for each of the selected publications.

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TABLE 2. Summary of Sample Size, Gender, and Inclusion Criteria/Patient Profile

	AUTHOR/ YEAR/ COUNTRY	SAMPLE SIZE	SEX	INCLUSION CRITERIA / PATIENT PROFILE
1	Abreu *et al*/ 2022/ Brazil	187	Men (57,4%) and women (42,6%)	Adult patients (18-70 years old) diagnosed with HIV and on the same HAART therapy for at least 6 weeks.
2	Bregigeon *et al*/ 2017/ France	175	Men (69,2%) and women (30,8%)	Patients undergoing bone densitometry, for whom a frailty assessment was performed - CHS and SOF criteria.
3	Cervero *et al*/ 2018/ Spain	107	Men (69,2%) and women (30,8%)	Patients from the COMESEM cohort, aged over 18 years, using cART and undergoing bone densitometry during the follow-up period.
4	Chaba *et al*/ 2017/ Brazil	108	Men (73,1%) and women (26,9%)	HIV-infected patients ≥ 20 years of age who sought HIV-related care.
5	Chen *et al*/ 2019/ Taiwan	137	Men (92,7%) and women (7,3%)	20-year-old PLHIV seeking HIV-related care.
6	Chisati, Constantinou e Lampiao/ 2020/ Malawi	282	Men (36%) and women (64%)	Participants aged between 18 and 45 years were recruited from three primary and one tertiary healthcare facility. Patients without other comorbidities or conditions associated with low BMD and on ART > 12 months were included.
7	Davidson e Sowden/ 2019/ Australia	93	Men (89%) and women (11%)	All PLHIV attending the Sunshine Coast Health Service District Sexual Health Clinic.
8	Erlandson *et al*/ 2018/ France	2.598	Men (67,8%) and women (32,2%)	MHMC study patients. All participants with at least 2 DXA scans were included.
9	Goh *et at*/ 2018/ Malaysia	NA	Men and women (unspecified percentages)	Cross-sectional or longitudinal studies published in English, articles that used DXA and compared at least two groups, aged ≥ 18 years, and that used a conversion equation validated if BMD was measured using different DXA machines.
10	Grant *et al*/ 2019/ USA	403	Men (100%)	Data collected from BOSS - HIV-infected men on ART and HIV-uninfected men aged 50 to 69 years.
11	Kabore *et al*/ 2017/ Africa (Burkina Faso, Senegal, Camarões)	228	Men (26%) and women (74%)	All participants enrolled in the METABODY study and those who completed a baseline measure of bone quality using quantitative ultrasound (QUS) through 96 weeks of follow-up after initiation of second-line treatment.
12	Kalyan *et al*/ 2018/ Canada	73	Women (100%)	Study participants CAMos and CARMA.
13	Komatsu *et al*/ 2018/ Japan	3.251	Men (93,5%) and women (6,5%)	Japanese patients with HIV infection for more than 8 years receiving TDF.
14	Mata-Marín *et al*/ 2018/ Mexico	104	Men (87%) and women (13%)	PLWHA who attended the HIV outpatient clinic and were 40 years old and undergoing ART treatment.
15	Mazzitelli *et al*/ 2022/ UK	744	Men (92,9%) and women (7,1%)	All PLHIV DXA > 50 years between 2009 and 2018 from Chelsea and Westminster Hospital NHS Foundation Trust.
16	Meng *et al*/ 2022/ China	156	Men (100%)	Outpatient Chinese male PLWHA who had at least one DXA scan between October 2017 and August 2020 from the infectious disease department of Beijing Ditan Hospital of Capital Medical University.

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17	Negredo *et al*/ 2018/ Spain	875	Men (75,3%) and women (24,7%)	The analysis included 3,726 DXA scans of 875 patients with PLWHA, primarily before initiation of ART, men aged 50 years, menopausal women, people with a history of bone fractures, or patients using drugs or disease.
18	Oursler *et al*/ 2020/ USA	31	Men (93%) and women (7%)	Elderly PLWHA (≥ 50 years old), sedentary, using HAART, and enrolled in an exercise intervention study.
19	Ozcan *et al*/ 2021/ Türkiye	211	Men (100%)	PLWHA between 18 and 50 years old, on ART for at least 6 months, with at least one DXA dosage in the last six months, and virologically suppressed (HIV-1 RNA <50 copies/ml).
20	Perazzo *et al*/ 2018/ USA	147	Men (78%) and women (22%)	PLHA aged ≥ 18 years, on stable ART for at least 3 months with cumulative ART duration of at least 6 months, with HIV-1 RNA < 1,000 copies/mL, with LDL-C cholesterol ≤ 130 mg/dL, TG ≤ 500 mg/dL and (f) evidence of increased CD8+ T or hs-CRP of at least 2 mg/L.
21	Pezzaioli *et al*/ 2022/ Italy	168	Men (100%)	Patients aged > 18 years, with serologically documented HIV infection in a stable condition on ART, with no personal history of malabsorption or drugs with a potentially harmful effect on bone, blood samples taken in the laboratory of the central hospital, DXA and quantitative morphometric assay performed with the same densitometer.
22	Pramukti *et al*/ 2020/ USA	NA	Men and and women (unspecified percentages)	Studies with HIV-infected individuals aged ≥ 16 years reported data on the prevalence or incidence rate of fractures. Cross-sectional, cohort, and case-control studies were included with or without a control group..
23	Ruiz *et al*/ 2017/ Colombia	180	Men (76,5%) and women (23,5%)	PLWHA on unaltered ART for at least one year at any clinical stage.
24	Shaiykova *et al*/ 2018/ France	240	Men (100%)	Men aged between 18 and 50 years, on ART for more than 6 months, undetectable plasma HIV-1 RNA (<50 copies/ml), without opportunistic diseases, and without hepatitis B or hepatitis C.
25	Ventura *et al*/ 2017/ USA	246	Men (63%) and women (37%)	PLWHA, with alcohol, injecting, and non-injecting drug dependence in the past 12 months, who understand English, ≥ 18 years of age, willing to provide contact information ≥1 person- Boston ARCH Cohort survey participants.
26	Zeng *et al*/ 2020/ China	156	Men (100%)	ART-naïve PLWHA, Chinese, without hyperthyroidism, hyperparathyroidism, hypogonadism, diabetes mellitus, menopause, opportunistic infection, and do not use corticosteroids, or have previous calcium and vitamin D supplementation.

NA= Not applicable - Systematic reviews and/or meta-analyses; HAART= Highly Active Antiretroviral Therapy; DEXA/DXA= Dual-energy X-ray absorptiometry; CHS= Cardiovascular Health Study; SOF= Study of Osteoporotic Fractures; ART= Antiretroviral therapy; cART= Combination antiretroviral therapy; HC/FMUSP= Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo; MHMC= Modena HIV Metabolic Clinic; BOSS= Bone Strength Substudy; CAMos= Canadian Multicentre Osteoporosis Study; CARMA= Children and Women: AntiRetrovirals and Markers of Aging; LDL-C= Low-Density Lipoprotein; TG = Triglycerides; hs-CRP= High-sensitivity C-reactive protein.

The predominant and additional risk factors for low bone mineral density (BMD) in HIV-positive patients are summarized in Table 3. The category labeled as "Other" in Table 3 encompasses factors explored in individual studies.

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TABLE 3. Risk factors for Low Bone Mineral Density (BMD) in HIV-Positive Patients.

RISK FACTORS RELATED TO LOW BMD	QUANTITY OF ARTICLES THAT COVERED (%)	REFERENCES
FACTORS RELATED TO ART	50,00%	
Prior exposure to TDF	19,20%	Cervero *et al*, Davidson e Sowden, Kalyan *et al*, Komatsu *et al*, Ozcan *et al*
Current unspecified ART	11,50%	Cervero *et al*, Chisati, Constantinou e Lampiao, Goh *et al*
Prolonged exposure to TDF	11,50%	Komatsu *et al*, Mazzitelli *et al*, Ozcan *et al*
Prior exposure to IP	7,70%	Davidson e Sowden, Ozcan *et al*
Shorter duration of first-line treatment	7,70%	Kabore *et al*, Shaiykova *et al*
Current ART with IP and TDF	3,80%	Negredo *et al*
Current ART with IP/r and TDF	3,80%	Cervero *et al*
Current ART with PI (Atazanavir, Darunavir, Lopinavir)	3,80%	Negredo *et al*
Current ART with TDF/Emtricitabine	3,80%	Ruiz *et al*
Prior exposure to IP/r	3,80%	Cervero *et al*
Use of HAART	3,80%	Pramukti *et al*
Prolonged exposure to NNRTI	3,80%	Ruiz *et al*
Prolonged exposure to IP	3,80%	Mazzitelli *et al*
The prolonged time between HIV diagnosis and initiation of ART	3,80%	Cervero *et al*
OLDER AGE (AVERAGE OF ≥ 48 YEARS)	38,50%	Abreu *et al*, Cervero *et al*, Chen *et al*, Erlandson *et al*, Goh *et al*, Kalyan *et al*, Negredo *et al*, Pramukti *et al*, Ruiz *et al*, Ventura *et al*
LOW BMI (AVERAGE OF ≤ 21.6)	27,00%	Cervero *et al*, Chaba *et al*, Goh *et al*, Mazzitelli *et al*, Meng *et al*, Shaiykova *et al*, Zeng *et al*
HYPOGONADISM	15,40%	Abreu *et al*, Goh *et al*, Grant *et al*, Pezzaioli *et al*
SMOKING	15,30%	Cervero *et al*, Goh *et al*, Pramukti *et al*, Ventura *et al*
HCV/CHRONIC HEPATITIS C COINFECTION	15,30%	Cervero *et al*, Erlandson *et al*, Komatsu *et al*, Pramukti *et al*
SPECIFIC HIV-RELATED FACTORS (LOW CD4 COUNT, HIGH VIRAL LOAD))	15,30%	Cervero *et al*, Chaba *et al*, Goh *et al*, Ozcan *et al*
HYPERPARATHYROIDISM	11,50%	Abreu *et al*, Cervero *et al*, Chen *et al*

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USE OF ILLICIT DRUGS (INJECTABLE DRUGS, CANNABIS, AMPHETAMINES, COCAINE, METHADONE)	11,50%	Cervero *et al*, Pramukti *et al*, Ventura *et al*
DURATION OF HIV INFECTION	11,50%	Chaba *et al*, Ozcan *et al*, Pezzaioli *et al*
REDUCED PHYSICAL ACTIVITY	11,50%	Chisati, Constantinou e Lampiao, Erlandson *et al*, Perazzo *et al*
METABOLIC SYNDROME	7,70%	Abreu *et al*, Erlandson *et al*
HYPOVITAMINOSIS D	7,70%	Abreu *et al*, Cervero *et al*
NON-TRAUMATIC FRACTURES	7,70%	Cervero *et al*, Goh *et al*
WOMEN	7,70%	Abreu *et al*, Erlandson *et al*
MALE	7,70%	Cervero *et al*, Pramukti *et al*
ALCOHOL	7,70%	Cervero *et al*, Ventura *et al*
LOW LEAN BODY MASS	7,70%	Goh *et al*, Shaiykova *et al*
OTHERS*	42,30%	

PI/r= Ritonavir-boosted Protease Inhibitor; TDF=Tenofovir; ASMMI= Appendicular Skeletal Muscle Mass Index; HAART = Highly Active Antiretroviral Therapy. Others*: Low levels of FGF-23, menopause; fragility; low calcium intake; irregular intake of milk or dairy products; lipodystrophy; low-fat body mass; low body weight; Hispanic or Caucasian; women using medroxyprogesterone; leukocyte telomere shortening in women with HIV; use of corticosteroids; low ASMMI; low serum estradiol.

DISCUSSION

ANTIRETROVIRAL THERAPY

With the advent of antiretroviral therapy (ART), the life expectancy of individuals infected with HIV has gradually extended. Despite enhanced prognosis, PLHIV, even under successful treatment, remain susceptible to long-term complications. Notably, there is an elevated risk of diminished bone mineral density due to the impact of chronic HIV infection and ART. Presently, there is ample evidence showcasing a greater prevalence of bone fractures among HIV-infected patients in comparison to their non-infected counterparts, underscoring an evident correlation[4,9,10].

Untreated HIV infection is associated with reduced bone turnover, a pattern that transitions after the initial two years of ART commencement and immune restoration, ultimately stabilizing[11]. Nevertheless, certain studies suggest that the initiation of ART, irrespective of the drug regimen, contributes to heightened bone loss in PLHIV[12]. A number of randomized controlled trials have revealed that a rapid loss of bone mass primarily occurs between 6 and 12 months following the initiation of ART, followed by the stabilization of DMO[11,12,13].

In comparison to other regimens, the utilization of tenofovir disoproxil fumarate (TDF) is linked to heightened indicators of bone resorption, resulting in an approximate 1 to 3% greater decline in BMD during its administration[12]. TDF induces alterations in the transcriptional profile of osteoblasts, leading to modifications in genes associated with cell signaling, cell cycle, amino acid metabolism and the ability to induce isolated renal phosphate loss[9,11].

Furthermore, the duration of exposure to TDF is likely a paramount risk factor, with individuals subjected to the therapy for extended periods being more susceptible to low bone mass. The study conducted by Komatsu *et al* demonstrated an escalating cumulative probability of osteoporosis-related fractures after 5 years of TDF exposure, a finding that was similar in other studies[14,15].

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In contrast, the correlation was found to be insignificant among patients with pre-existing osteoporosis, likely due to prolonged HIV infection duration and ART exposure, which might correspond to the phase of "BMD stabilization"[11]. In the cohort studied by Davidson and Sowden, the link between the history of TDF exposure and osteoporosis was not established, possibly due to the substantial rate of drug exposure throughout the entire cohort[16].

Another category of antiretroviral regimen that closely associates with diminished bone mineral density (BMD) is Protease inhibitors (PIs) such as atazanavir, lopinavir, and darunavir. For instance, the investigation conducted by Mazzitelli *et al* identified a statistically significant correlation between the years of PI exposure and years of TDF exposure in the development of femoral osteoporosis[3]. The outcomes of studies by Negredo *et al* and Davidson and Sowden corroborate the impact of PIs on bone loss, which is manifested significantly in their investigations. However, these authors point out that it is uncertain whether this effect on low BMD applies across all PIs as a class or if it is a specific adverse impact of certain PIs. It was observed that darunavir was associated with the risk of bone loss in both men and women, whereas atazanavir was linked to this risk only in women[16,17]. In the ASSERT study highlighted by the work of Davidson and Sowden, notably greater declines in BMD and increases in bone turnover were discerned in the TDF group. Protease inhibitors were also implicated, albeit to a lesser extent[16].

Furthermore, another class that might contribute to decreased BMD is non-nucleoside reverse transcriptase inhibitors. Ruiz *et al* underscored the significant impact of this drug class on the reduction of bone mass [15].

Despite several studies implicating antiretroviral therapy in the etiology of low BMD, others have failed to corroborate this association[9,10,18,19].

Certain studies have emphasized the potential protective impacts of specific antiretroviral drugs on the integrity of bone mass. A protective effect associated with integrase strand transfer inhibitor (INSTI) therapy, predominantly using raltegravir, was evident in both men and women, as indicated by the research conducted by Erlandson *et al*[20]. Likewise, Ruiz *et al* demonstrated a protective effect on BMD in patients receiving Nevirapine[15]. Moreover, in the cohort examined by Shaiykova *et al*, the combination of TDF with other drugs, particularly efavirenz and emtricitabine, exhibited a protective effect against osteopenia during the initial year of usage. This effect became even more pronounced with durations exceeding 3 years[11].

METABOLIC SYNDROME

Metabolic syndrome (MS) encompasses a constellation of metabolic disturbances, including insulin resistance, atherogenic dyslipidemia, central obesity, and hypertension. The etiology of MS is intertwined with genetic alterations and lifestyle factors, culminating in insulin resistance and persistent low-grade inflammation[21].

Diagnosing MS involves several criteria, with the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) and the International Diabetes Federation (IDF) criteria being widely utilized. In the investigation conducted by Abreu *et al*, an association between MS and diminished BMD was identified in females, but not in males. Within this context, the primary variables that exhibited alterations were body weight and waist circumference (WC), surpassing the thresholds outlined by IDF and NCEP-ATPIII. The adverse impact of central obesity on bone mass is recognized, owing to its linkage with an ongoing inflammatory process characterized by cytokine release that fosters bone resorption. Additionally, central obesity serves as a risk factor for vitamin D deficiency[22].

BMI

Body mass index (BMI) is categorized by WHO into several classifications: underweight (BMI <18.5 kg/m²), normal weight (BMI 18.5- 24.9 kg/m²), overweight or pre-obese (BMI 25- 29.9 kg/m²), obesity grade I (BMI 30- 34.9 kg/m²), obesity grade II (BMI 35- 39.9 kg/m²) and obesity grade III (BMI ≥40.0 kg/m²)[23].

Low BMI, sedentary lifestyle, smoking, alcohol consumption, corticosteroid use, hypogonadism, HIV infection factors including infection duration, lowest CD4+ count, and ART are recognized as traditional risk factors for osteopenia/osteoporosis development in PLHIV. Thus, higher BMI acts as a protective factor against bone loss in both the general population and PLHIV[2-20].

This notion is supported by the work of Mazzitelli *et al*, which demonstrated a statistically significant link between spine osteoporosis and BMI <20 kg/m² (p = 0.02). Similarly, Cervero *et al* indicated that lower body weight significantly accounted for reduced BMD in treated PLHIV[9]. Comparable results emerged from studies by Meng *et al* and Zeng *et al,* in which patients with lower BMI were more likely to develop reduced BMD in both populations studied[3,4,24].

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Moreover, a cross-sectional study in Brazil involving 212 PLHIV undergoing antiretroviral therapy identified a positive correlation among BMI, waist circumference, and hypovitaminosis D. This connection can be attributed to obesity and central fat deposition, both of which lead to lower vitamin D levels due to storage within adipose tissue. This highlights an alternative mechanism for low BMD in this population[22].

However, despite the above findings, some articles exploring BMI as a potential risk factor did not establish it as a predictor of osteopenia or osteoporosis.

MUSCLE MASS AND PHYSICAL ACTIVITY

Muscle mass and physical activity were also noteworthy variables addressed in the research. Alterations in body composition resulting from HIV infection and the complexities of antiretroviral therapy mirror the natural aging process observed in older individuals. Consequently, individuals living with HIV are more prone to having diminished lean body mass and reduced fat mass, accompanied by atypical fat distribution. These factors can contribute to bone loss. Decreased lean body mass can result in weakened muscle strength, which can impact bone mineral density and bone structure[25].

For instance, the investigation led by Oursler *et al* examined clinically stable elderly individuals living with HIV, revealing a significant correlation between muscle mass and BMD[2,26].

Notably, although physical activity is a well-established intervention to attenuate bone loss related to aging, regular physical activity (except high intensity loads or endurance exercises) rarely reverses BMD loss, especially among postmenopausal women or hypogonadal men[20]. Numerous studies have examined the relationship between physical activity and BMD within their respective patient cohorts. For instance, Ozcan *et al* found no significant associations between physical activity and BMD among individuals reporting fewer than 150 minutes per week of physical activity. However, a positive and significant correlation emerged for those who engaged in at least 150 minutes per week of moderate to vigorous physical activity[27].

HEPATITIS C

The Hepatitis C virus (HCV) is increasingly recognized as an autonomous risk factor for low BMD, with rates of osteoporosis ranging from 14% to 28% among individuals solely infected with the virus. Moreover, more pronounced losses in BMD have been observed as the severity of liver disease associated with HCV increases. In the study conducted by Erlandson *et al*, the impact of HCV on BMD was found to be comparable to that of an additional five years of aging, with a more pronounced effect in women[14,20].

Furthermore, a systematic review and meta-analysis conducted by Pramukti e*t al* reached the conclusion that HCV coinfection posed an independent risk factor in relation to HIV[28].

SPECIFIC FACTORS RELATED TO HIV

Existing evidence indicates that individuals with HIV infection and low CD4+ cell counts (<50 cells/mm³) experience approximately 3% greater bone loss compared to those with higher CD4+ cell counts (>500 cells/mm³)[25]. A Brazilian study demonstrates that CD4 cell count <350 cells/µL, a known risk factor for low BMD, might suggest that the longer the duration of infection or the less successful ART, the more likely it is to develop low BMD[10]. On the other hand, studies including those by Abreu *et al*, Chen *et al*, Ozcan *et al*, Meng *et al*, and Zeng *et al*, did not establish a significant association between CD4+ T cell count and viral load with decreased BMD[4,18,22,24].

SMOKING, ALCOHOL, AND ILLICIT DRUG USE

Smoking is linked to low BMD, with its impact influenced by both the quantity and duration of smoking. A systematic review conducted by Pramukti et al identified a stronger association between alcohol use during the period before starting ART and a more pronounced decline in BMD[28].

The impact of alcohol use on BMD can vary across different periods of continuous HIV treatment, possibly due to interactions with HIV and its treatment. In the cohort study conducted by Ventura et al, the influence of alcohol on BMD was minimal, except for a potential negative effect of recent alcohol use between HIV testing and the initiation of antiretroviral therapy (ART), which aligns with findings from previous research[13].

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The results of Pramukti et al also emphasize that among people living with HIV/AIDS (PLHIV), those who use injection drugs had the highest prevalence of fractures among risk groups[28]. Similarly, the study by Cervero et al revealed an association between reduced BMD and the use of intravenous illicit drugs as a route of HIV transmission[9]. Consistent with this, the prevalence of low BMD and osteoporosis was high in an older cohort of PLHIV with substance dependence in the study by Ventura et al. This prevalence was similar to findings from other studies, highlighting the potential impact of substance use on bone health in this population[13].

AGE AND GENDER

Advanced age is a well-established risk factor for the development of primary osteoporosis[29] and it also plays a role in low BMD among PLHIV. Bone mass increases during growth and peaks between the ages of 25 and 30, after which it decreases, resulting in low bone mineral density[30]. After age 30, BMD is maintained for about 10 years before it begins to decline at a rate of about 0.3-0.5% per year in men and women[31,32]. Between ages 45 and 55, women experience greater bone mass loss than men. After that, the rate of bone loss becomes gradual and equalizes in both sexes[32].

Several studies within this review have highlighted advanced age as a risk factor for bone loss among PLHIV. For instance, Mazzitelli *et al* reported prevalence rates of 63.7% for osteopenia and 12.2% for osteoporosis among older PLHIV[3].

While many articles discussing advanced age as a risk factor present the condition as a cause of low BMD, some also underscore outcomes of bone mineral loss in men under 50 years of age who are receiving antiretroviral therapy (ART). This highlights early bone demineralization in treated young men with HIV, potentially indicating premature aging within this population[11,27].

HYPOGONADISM

Hypogonadism is characterized by diminished levels of total testosterone (≤350 ng/dL) and/or calculated free testosterone (≤65 pg/mL). The origins of this condition are multifaceted within HIV-infected males, as is the case with osteoporosis. However, existing information regarding the correlation between testosterone levels and BMD in HIV-infected men remains inconclusive[33,34].

Serum testosterone levels tend to be notably diminished among HIV-infected men, a factor that might contribute to reduced BMD[35]. Through a multivariate analysis, it has been revealed that men afflicted with hypogonadism possess a 5.9-fold higher likelihood of having low bone mass in comparison to those with normal levels of free testosterone[22]. In another analysis, the prevalence of hypogonadism in the low bone mass group was almost twice as high as in the overall cohort[16].

A robust correlation has been established between the use of testosterone and bone mineral density in individuals with HIV infection. These findings suggest that the use of testosterone could preserve BMD in HIV-infected males[35].

Abreu *et al* demonstrated that the frequency of testosterone deficiency is higher in the group of patients with low BMD. In this context, testosterone deficiency was observed in 60% of patients in the low BMD group. This finding suggests that men living with HIV who have low testosterone levels should have their bone mass carefully analyzed[22].

FRAGILITY FRACTURES

FRAX is a WHO-validated tool to establish the probability of severe osteoporotic fractures at 10 years and represents an inexpensive screening alternative that can be routinely used in clinical practice. FRAX is considered elevated when the risk of osteoporotic fractures at 10 years is greater than 10%. However, the tool has not been specifically validated in PLHIV and may underestimate the risk of fragility fractures.

The increased incidence of fractures is temporally aligned with the acute decline of 2-6% in BMD that has been reported in several studies in the first 2 years after ART[15]. Like other potential predictors of higher incidence of PLHIV fractures, HCV coinfection, smoking, the direct effect of HIV on immune homeostasis, and decreased muscle mass are observed in a small population, which may not represent all PLHIV[5,26,28,36]. A systematic review and meta-analysis revealed that males had a higher prevalence of fragility fractures than females (6.2% versus 4.9%, respectively).

CONCLUSÃO

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Based on the information presented, the conclusion can be drawn that individuals living with HIV are at an elevated risk of experiencing low BMD, primarily due to the impact of ART.

The findings provide substantial evidence that the initiation of ART, regardless of the specific drug regimen used, results in an increase in bone loss among PLHIV. This decline in BMD is particularly pronounced during the initial two years of treatment, after which it stabilizes and transitions into a protective effect against further bone loss.

Among the various drug regimens available for HIV treatment, significant emphasis has been placed on TDF, which has shown the strongest association with BMD reduction.

Additionally, certain drug regimens containing PIs such as atazanavir, lopinavir, and darunavir have also been closely linked to reductions in BMD.

In addition, the review identified other risk factors: Low BMI; reduced lean body mass and lower fat mass; presence of metabolic syndrome; physical inactivity and the practice of mild-intensity physical activity, except for moderate-to-vigorous intensity; co-infection with Hepatitis C virus (HCV); illicit drug use; smoking; alcohol consumption and its intensity during different periods of continuous HIV treatment; advanced age; particularly individuals with HIV over 40 years of age; female sex; hypovitaminosis D and secondary hyperparathyroidism due to hypovitaminosis D; hypogonadism and fragility fractures. Certain HIV-specific factors like CD4+ T cell count and viral load, as well as the use of corticosteroids and low calcium and dairy consumption, did not show significant correlations with low BMD according to the findings of the review.

Some studies were unable to definitively establish a causal link between low bone mineral density (BMD) and the identified risk factors. This could be attributed to the cross-sectional design of these studies, which inherently carries limitations. Moreover, each study had its own set of limitations that might have influenced the accuracy of their findings, leading to potential overestimations or underestimations.

The results reinforce the need for monitoring bone mineral density in HIV-positive patients due to the high likelihood of progression to osteopenia and/or osteoporosis and the increased risk of bone fractures, which reduces quality of life.

Therefore, the identification of the most prevalent and mainly modifiable risk factors, as well as the analysis of the profile of patients who are at high risk for BMD reduction, are of great relevance to healthcare professionals. This knowledge can both facilitate a better approach to PLHIV clinical interventions and serve as a basis for establishing screening programs designed to identify patients eligible for preventive therapies.

CONFLICTS OF INTEREST

There are no conflicts of interest related to the present article.

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