Enferm Infecc Microbiol Clin. 2018;36(5):312–314

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Consensus statement

Executive summary of the consensus document on osteoporosis in HIV-infected individuals

Eugenia Negredo[a,b,c], Pere Domingo[d], Félix Gutiérrez[e], María José Galindo[f], Hernando Knobel[g], Fernando Lozano[h], Esteban Martínez[i], Mar Masiá[e], Rosa Polo[j], Vicente Estrada[k,*]

[a] *Lluita contra la Sida Foundation, Germans Trias i Pujol University Hospital, Badalona, Spain*
[b] *Universitat Autònoma de Barcelona, Barcelona, Spain*
[c] *Universitat de Vic-Universitat Central de Catalunya, Vic, Barcelona, Spain*
[d] *Hospitals Universitaris Arnau de Vilanova & Santa Maria, Universitat de Lleida, Institut de Recerca Biomédica (IRB) de Lleida, Lleida, Spain*
[e] *Hospital Universitario de Elche, Universidad Miguel Hernández, Alicante, Spain*
[f] *Hospital Clínico Universitario de Valencia, Spain*
[g] *Hospital del Mar, Barcelona, Spain*
[h] *Hospital Universitario de Valme, Sevilla, Spain*
[i] *Hospital Clínic de Barcelona, Barcelona, Spain*
[j] *Secretaría del Plan Nacional sobre el Sida, Ministerio de Sanidad, Servicios Sociales e Igualdad, Madrid, Spain*
[k] *Hospital Clínico San Carlos, IDISSC, Universidad Complutense, Madrid, Spain*

Keywords:
Osteoporosis
HIV infection
Antiretroviral therapy

A B S T R A C T

Osteoporosis has become an emerging comorbid condition in people living with HIV (PLWH). The increase in survival and the progressive aging of PLWH will make this complication more frequent in the near future. In addition to the traditional risk factors affecting the general population, factors directly or indirectly associated with HIV infection, including antiretroviral therapy, can increase the risk of osteoporosis. The present article is an executive summary of the document that updates the previous recommendations on the prevention and treatment of osteoporosis in PLWH. This document is intended for all professionals who work in clinical practice in the field of HIV infection.

Resumen ejecutivo del documento de consenso sobre la osteoporosis en las personas infectadas por VIH

Palabras clave:
Osteoporosis
Infección por el VIH
Tratamiento antirretroviral

R E S U M E N

La osteoporosis se ha convertido en una situación comórbida emergente en las personas infectadas por VIH. El incremento de la supervivencia y el envejecimiento progresivo de las personas infectadas por VIH harán que esta complicación sea más frecuente en un futuro cercano. Además de los factores de riesgo tradicionales, los factores directa o indirectamente asociados a la infección por VIH, incluyendo el tratamiento antirretroviral, pueden incrementar el riesgo de presentar osteoporosis. El presente artículo constituye un resumen ejecutivo del documento que actualiza las recomendaciones previas sobre la prevención y el tratamiento de la osteoporosis en las personas infectadas por VIH. Este documento va dirigido a todos los profesionales que ejercen la práctica clínica en el campo de la infección por VIH.

* Corresponding author.
E-mail address: Vicente.estrada@salud.madrid.org (V. Estrada).

The life expectancy of persons infected by the human immunodeficiency virus (HIV) has increased significantly. Consequently, osteoporosis has become an emerging comorbid condition. Aging of HIV-infected patients will undoubtedly lead this problem to become more frequent in the near future. In addition to the traditional risk factors affecting the general population, factors directly or indirectly associated with HIV infection, including antiretroviral therapy (ART), can increase the risk of osteoporosis.

Traditional risk factors for osteoporosis

The etiology and pathogenesis of osteoporosis in HIV-infected patients are multifactorial and are affected both by patient-related factors and by factors associated with HIV and ART. Many of the traditional risk factors affecting the general population have also been associated with low bone mineral density (BMD) in HIV-infected patients.

Recommendations:

1. Osteoporosis can be prevented by 30 min of physical exercise daily or on at least 3 days per week. Muscle strengthening exercises are also recommended (grade of recommendation, strong; level of evidence, low).
2. Patients should give up smoking and reduce alcohol consumption (grade of recommendation, strong; level of evidence, moderate).
3. Diet should include the intake of 1000–1500 mg of calcium per day; supplements should only be taken by patients who do not reach the recommended intake (grade of recommendation, strong; level of evidence, low).
4. Patients should take 800–1000 U/d of vitamin D. Patients with vitamin D insufficiency (25-OH vitamin D <20 ng/mL) or deficiency (25-OH vitamin D <10 ng/mL) should receive vitamin D supplements, particularly if they also have secondary hyperparathyroidism (grade of recommendation, strong; level of evidence, low).

Effects of HIV infection, associated inflammation, and ART

Abundant experimental data suggest that HIV infection *per se* and/or an associated pro-inflammatory state can favor the loss of BMD. Furthermore, loss of BMD in patients taking ART is noteworthy. It is most intense (decrease of 2–6%) during the first year after initiating ART and then gradually improves. This effect is independent of the regimen used.

Tenofovir disoproxil fumarate (TDF) is the antiretroviral drug most commonly associated with osteoporosis, especially at the beginning of treatment. In some studies, protease inhibitors have been associated with a greater loss of BMD than integrase inhibitors and non-nucleoside reverse transcriptase inhibitors, although their role in the pathogenesis of osteoporosis is controversial.

Recommendations:

1. TDF should be avoided in patients with osteoporosis or a high risk of fracture who have to initiate ART (grade of recommendation, strong; level of evidence, high).
2. TDF should be replaced by abacavir, tenofoviralafenamide, or raltegravir in patients with osteoporosis or a high risk of fracture (grade of recommendation, strong; level of evidence, moderate).

Diagnosis and screening

The objective should be to detect HIV-infected patients with a high risk of fragility fracture. The most frequent fractures affect the vertebrae, hip, and distal third of the radius and humerus. Fractures of the ankle, cranium, and facial bones are excluded from screening.

Recommendations:

1. The clinical evaluation should start with the identification of factors associated with a high risk of fragility fractures (grade of recommendation, strong; level of evidence, high).
2. Kyphosis and significant reductions in the patient's height over time are simple clinical findings that can point to reduced bone mass and, therefore, a greater risk of fracture. Plain lateral X-ray of the dorsal or lumbar spine is indicated for identification of asymptomatic fracture in patients with these conditions (grade of recommendation, strong; level of evidence, moderate).
3. The FRAX scale, a simple and accessible tool, is recommended in HIV-infected patients. HIV infection should be considered a secondary cause of osteoporosis in order to optimize the FRAX calculation (grade of recommendation, strong; level of evidence, low).
4. DXA is the standard procedure in the evaluation of BMD (grade of recommendation, strong; level of evidence, high).
5. HIV-infected patients should undergo DXA if they fulfill the following conditions (grade of recommendation, strong; level of evidence, moderate):
   a. Presence of major risk factors for fracture (long-term therapy with corticosteroids, history of fragility fractures, high risk of falling)
   b. Postmenopausal women or men with confirmed hypogonadism
   c. Men aged ≥50 years
   d. If the FRAX-España algorithm shows that the patient has a 10-year risk of hip fracture >3% and/or a risk of major osteoporotic fracture >10%
6. DXA should be repeated in patients without osteoporosis according to the following sequence (grade of recommendation, strong; level of evidence, moderate):

a. If the BMD value is normal or slightly reduced (*T*-score at any site ≤−1.5 SD), repeat at 10 years
b. If the patient has moderate osteopenia (*T*-score between −1.50 and −1.99 SD), repeat at 5 years
c. If the patient has advanced osteopenia (*T*-score between −2.00 and −2.49 SD), repeat every 1–2 years

7. In patients with osteoporosis, BMD should be monitored during the year following treatment and every 2–3 years thereafter (grade of recommendation, strong; level of evidence, moderate).
8. The prevalence of hypovitaminosis D is very high in HIV-infected persons, although no agreement has been reached on universal screening in this group. In general terms, levels of 25-hydroxy vitamin D and—eventually—parathyroid hormone (PTH) in plasma should be determined in patients with low BMD or disorders of renal tubular function, with a view to administering therapy with vitamin D supplements (grade of recommendation, weak; level of evidence, low).

General pharmacologic interventions

The ultimate objective of treatment of osteoporosis is to reduce the risk of fracture. However, few studies on the treatment of this condition treat the number and type of fractures as the main outcome measure, with changes in BMD being accepted as a surrogate marker of this risk. There are several secondary causes of loss of BMD in HIV-infected patients.

Recommendations:

1. Before considering pharmacological treatment, secondary osteoporosis should be ruled out. Patients with secondary osteoporosis should receive specific treatment (grade of recommendation, strong; level of evidence, high).

2. Patients should receive 1000–1500 mg/dof calcium as part of their diet and 800–1000 U/d of vitamin D. Vitamin D supplements should be administered to patients with insufficiency (25-OH vitamin D <20 ng/mL) and deficiency (25-OH vitamin D <10 ng/mL), particularly if it occurs alongside secondary hyperparathyroidism (grade of recommendation, strong; level of evidence, low).

Specific pharmacologic interventions for osteoporosis

Therapy with bisphosphonates, which inhibit reabsorption of bone, is the most common strategy for the treatment of osteoporosis in HIV-infected patients. However, prolonged use (>3–5 years) of these agents has been associated with severe—albeit uncommon—complications, including mandibular osteonecrosis and atypical sub-trochanteric fractures of the femur.

Recommendations:

1. The widest experience in the treatment of osteoporosis is with bisphosphonates, specifically, alendronate (weekly) and zoledronate (annually) (grade of recommendation, strong; level of evidence, moderate).
2. Treatment is recommended for the following groups (grade of recommendation, strong; level of evidence, moderate):
   a. Men aged ≥50 years or postmenopausal women with vertebral or hip fracture
   b. Men aged ≥50 years or postmenopausal women with densitometric evidence of osteoporosis (*T*-score <–2.5) or with a *T*-score between –1 and –2.5 and a FRAX index >10% for major osteoporotic fractures or >3% for hip fracture.
3. The indication for these drugs should be reviewed after 3–5 years of therapy. If BMD remains stable after an interruption of 2–3 years, therapy should not be reinitiated if the *T*-score falls below –2.5 or if new risk factors are added (grade of recommendation, strong; level of evidence, low).

Conflict of interest

Eugenia Negredo has carried out consultancy work and has received financial compensation from lectures by Abbvie, Boehringer Inggelheim, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag, Merck Sharp & Dohme and ViiVHealthcare; Has been receiving clinical research grants from Abbvie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, JanssenCilag and ViiVHealthcare.

Pere Domingo has carried out consultancy work for the laboratories Abbvie, BoehringerIngelheim, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag and ViiVHealthcare; Has been awarded clinical research grants from Abbvie, Boehringer-Inggelheim, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag and ViiVHealthcare, and has received financial compensation from Abbvie, BoehringerIngelheim, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag and ViiVHealthcare.

María José Galindo has done consulting work at Abbott Laboratories, Boehringer Inggelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and AbbVie; Has received grants for clinical research from Abbott Laboratories, Boehringer-Inggelheim, Glaxo, Janssen and received financial compensation from Abbott Laboratories, Boehringer-Ingheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck and Roche; Has collaborated in the development of educational materials for Janssen, Pfizer, ViiV, Glaxo and AbbVie.

Félix Gutiérrez has carried out consultancy work for the Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme and ViiVHealthcare laboratories; And has received financial compensation for lectures and/or preparation of teaching materials from Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme and ViiVHealthcare.

Hernando Knobel has done consulting work for the Abbvie, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag, Merck Sharp & Dohme and ViiVHealthcare laboratories; Has received financial compensation for lectures or educational presentations from Abbvie, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag, Merck Sharp & Dohme and ViiVHealthcare.

Fernando Lozano has carried out consultancy work for Abbvie, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag, Merck-Sharp & Dome and ViiVHealthcare and has received financial compensation for presentations and for educational purposes from Abbvie, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag, Merck-Sharp & Dome and ViiVHealthcare.

Esteban Martínez has carried out consultancy work for Gilead Sciences, JanssenCilag, Merck-Sharp & Dome and ViiVHealthcare; has enjoyed scholarships for clinical research from Merck-Sharp & Dome; And has received financial compensation for presentations and educational purposes from JanssenCilag and Merck-Sharp & Dome.

Mar Masiá has carried out consultancy work for the Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, ViiVHealthcare and Janssen laboratories; And has received financial compensation for lectures and/or preparation of teaching materials from Bristol-Myers Squibb, Janssen, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme and ViiVHealthcare.

Rosa Polo has received financial compensation for the development of educational presentations for Gilead Sciences, JanssenCilag and Merck Sharp & Dohme.

Vicente Estrada has carried out consultancy work for laboratories Abbvie, Gilead Sciences and JanssenCilag; Has received grants for clinical research from Abbvie, BoehringerIngelheim, Gilead Sciences and JanssenCilag, and has received financial compensation from Abbvie, BoehringerIngelheim, Bristol-Myers Squibb, Gilead Sciences, JanssenCilag, Merck Sharp & Dohme and ViiVHealthcare.