Recommendations for Evaluation and Management of Bone Disease in HIV

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Thirty-four human immunodeficiency virus (HIV) specialists from 16 countries contributed to this project, whose primary aim was to provide guidance on the screening, diagnosis, and monitoring of bone disease in HIV-infected patients. Four clinically important questions in bone disease management were identified, and recommendations, based on literature review and expert opinion, were agreed upon. 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. DXA should be performed in men aged ≥50 years, postmenopausal women, patients with a history of fragility fracture, patients receiving chronic glucocorticoid treatment, and patients at high risk of falls. In resource-limited settings, FRAX without bone mineral density can be substituted for DXA. Guidelines for antiretroviral therapy should be followed; adjustment should avoid tenofovir disoproxil fumarate or boosted protease inhibitors in at-risk patients. Dietary and lifestyle management strategies for high-risk patients should be employed and antiosteoporosis treatment initiated.

Keywords. bone disease; fragility fracture; human immunodeficiency virus; osteoporosis.

Patients with human immunodeficiency virus (HIV) infection have a higher risk of low bone mineral density (BMD) and fragility fracture than the general population [1] (Supplementary References 1–6). It is unclear whether HIV infection itself contributes to low BMD; however, individuals with HIV have a high prevalence of risk factors for low BMD, such as poor nutrition, low body weight, high rates of tobacco and alcohol use, and low vitamin D levels [1] (Supplementary References 7, 8). In addition, initiation of antiretroviral therapy (ART) is associated with a 2%–6% reduction in BMD during the first 2 years of treatment, which varies with the specific ART medications used [1] (Supplementary Reference 9). Osteoporosis in these patients may be associated with significant long-term morbidity, which is likely to increase as the HIV-infected population ages (Supplementary References 10, 11).

The Osteo Renal Exchange program (OREP) was established to provide guidance and recommendations on the screening, diagnosis, monitoring, and management of bone disease in patients with HIV. A complementary article on the management of renal disease will be published elsewhere.

METHODS

The OREP was conducted in several stages, described in detail in Supplementary Data, Appendix 1. In brief, 4 questions regarding screening and management of

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bone disease of key clinical importance to healthcare providers managing individuals with HIV infection were identified (Table 1). Following a comprehensive literature search, practical answers were drafted and agreement was reached through an established consensus process (Supplementary References 12, 13). Finally, a level of evidence and grade of recommendation (GOR) was assigned to each statement, in accordance with the Oxford Centre for Evidence-Based Medicine (CEBM) 2009 criteria (Supplementary Reference 14).

RESULTS

Screening and Monitoring Individuals With HIV Infection at Risk for Fragility Fracture

It is appropriate to assess the risk of fragility fracture and low BMD in all HIV-infected adults. Patients with major risk factors for fragility fracture, including (1) a previous history of fragility fracture, (2) receipt of glucocorticoid treatment for >3 months (≥5 mg of prednisone daily or equivalent), or (3) at high risk for falls, should be evaluated with dual-energy X-ray absorptiometry (DXA; see below) (CEBM 2a, GOR B) [2, 3]. In patients without major fracture risk factors, an age-specific evaluation is appropriate (Figure 1).

Fracture Risk Assessment by Fracture Risk Assessment Tool

Patients without a major risk factor for fragility fracture, men who are aged 40–49 years and premenopausal women aged ≥40 years should have their 10-year risk of fracture assessed using the Fracture Risk Assessment Tool FRAX score without BMD (Figure 1; Table 2) [4, 5], with risk assessment performed every 2–3 years or when a new clinical risk factor develops (CEBM 5) [2, 3]. FRAX gives a calculation of the 10-year probability of a major fracture (spine, forearm, proximal humerus, or hip) or hip fracture alone and can be used with or without BMD assessment (www.shef.ac.uk/FRAX/) (CEBM 2b, GOR B) [6, 7]. Risk factors used in the FRAX score are listed in Table 3 [6] (Supplementary References 15–26). As HIV infection and its treatment are associated with an increased risk for low BMD and fragility fracture (Supplementary References 1–6), some experts recommend the "secondary cause" of osteoporosis box should be checked when the FRAX calculator tool is used (CEBM 5) [1]. When calculating the FRAX score, country-specific algorithms should be used; however, if these are not available, another country with similar population characteristics should be chosen as a surrogate (CEBM 1a, GOR A) (Supplementary References 15, 16). FRAX can also be used to identify HIV-infected patients who should be assessed with DXA scanning for low BMD (CEBM 1a, GOR A) [6, 7].

Table 1. Key Clinical Questions Relating to Bone Disease That Were Identified and Addressed During the Osteo Renal Exchange Program

1 + 3[a]	To identify HIV-infected patients at risk for fragility fracture, what are the ideal screening, workup, and monitoring strategies?
2	How should ART be managed in ART-naive and -experienced patients at risk of bone disease?
4	What is the optimal strategy for the management of patients at risk for fragility fracture?

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

[a] Questions 1 and 3 were combined.

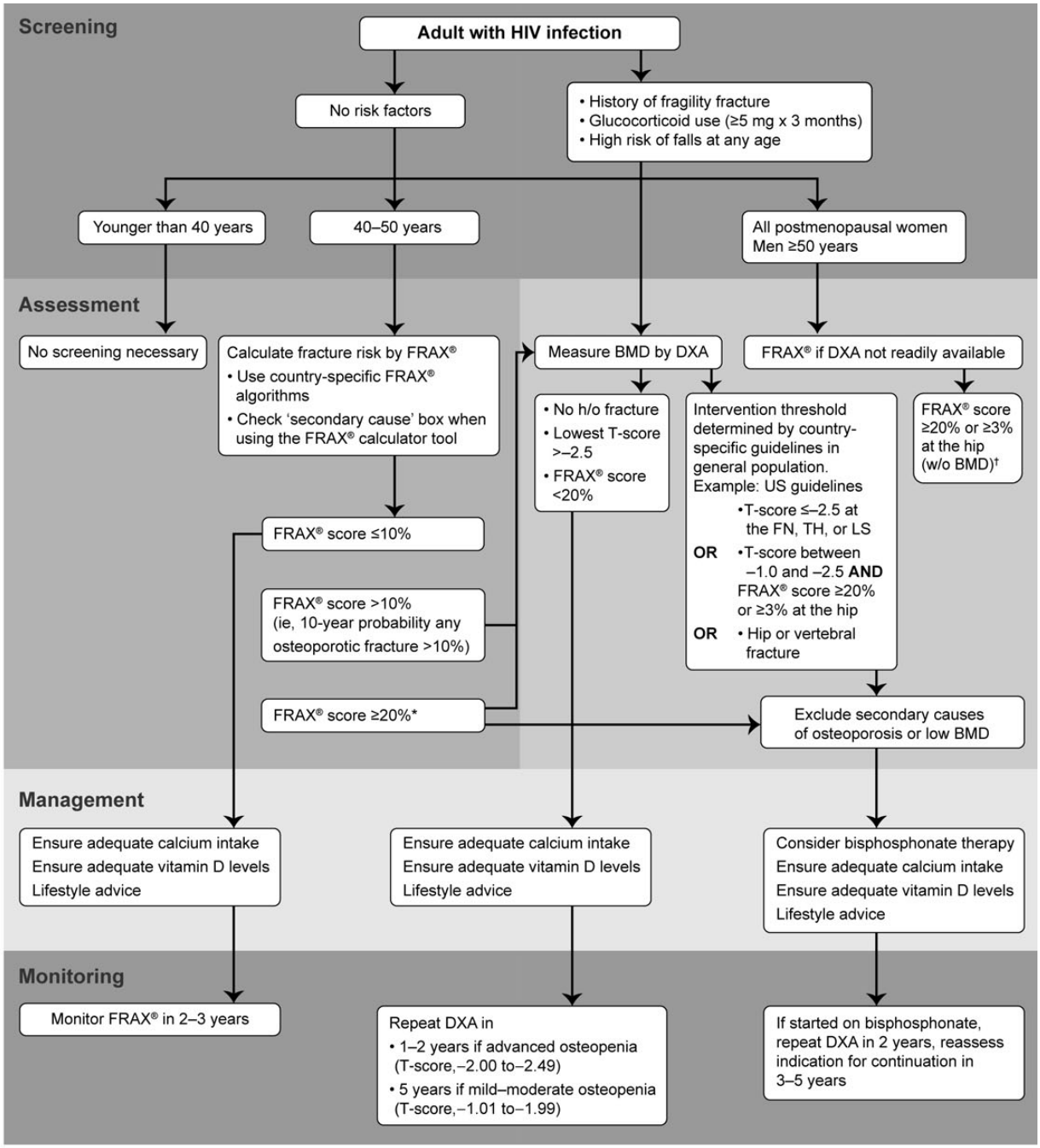
DXA Screening

It is reasonable to assess BMD by DXA scans in (1) men aged 40–49 years or premenopausal women aged ≥40 years, who have an intermediate- or high-risk stratification by FRAX (>10% 10-year risk of major osteoporotic fracture), (2) all postmenopausal women, (3) all men ≥50 years of age, and (4) adults with major fragility fracture risk factors regardless of age (CEBM 1a, GOR A) [2]. In countries in which DXA scans are not easily obtained, a DXA scan is not required to make treatment decisions for patients with a high risk of fracture (eg, FRAX score ≥20% for a 10-year risk of all osteoporotic fracture). Routine DXA screening of all HIV-infected patients on ART is not recommended.

When interpreting DXA scan results, T-scores should be used for postmenopausal women and men ≥50 years of age, and *z* scores used for those <50 years of age (CEBM 1a, GOR A) [8, 9]. The T-score thresholds for diagnosis of osteopenia and osteoporosis are shown in Table 4 [4, 8]; note that Z-scores are not used to diagnose osteoporosis. The optimal interval between DXA scan screening (or FRAX assessment) is unknown. Repeat DXA scanning should be considered after 1–2 years for those with baseline advanced osteopenia (T-score, −2.00 to −2.49) and after 5 years for mild to moderate osteopenia (T-score, −1.01 to −1.99) (CEBM 2b, GOR B) [10, 11]. The optimal interval for rescreening is also unclear for patients with normal BMD (T-score > −1) by DXA screening, although data from the general population suggest an interval of up to 15 years [10]. Rescreening should be considered earlier in those who have a new fragility fracture or develop a new major osteoporosis risk factor (CEBM 5).

Vertebral Fracture Screening and Assessment

Subclinical vertebral fractures are common in HIV-infected individuals (prevalence of approximately 25%) (Supplementary References 27, 28) and are a strong risk factor for future fractures. Therefore, height should be measured every 1–2 years in adults ≥50 years of age (CEBM 5) [4]. Assessment for subclinical vertebral fractures using lateral radiographs of the lumbar and thoracic spine or DXA-based vertebral fracture assessment is indicated for women aged ≥70 years and all men aged ≥80 years if



*In some countries, persons at high risk of fracture by FRAX® are eligible for further workup/osteoporosis treatment without DXA

†Based on US guidelines (National Osteoporosis Foundation). Country-specific intervention thresholds are preferred

T-scores should use the Caucasian young female reference for men and women regardless of ethnicity according to International Society of Clinical Densitometry (http://www.iscd.org/official-positions/2013-iscd-official-positions-adult/)

Figure 1. Algorithm for the screening, assessment, management, and monitoring of bone disease in human immunodeficiency virus (HIV)-infected patients. Abbreviations: BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; FN, femoral neck; FRAX, Fracture Risk Assessment Tool; LS, lumbar spine; TH, total hip.

BMD T-score is <−1.0 at the spine, total hip, or femoral neck; women aged 65–69 years, and men aged 75–79 years, if BMD T-score is –1.5 or less; and postmenopausal women aged 50–64 years and men aged 50–69 years with specific risk factors such as fragility fracture, historical height loss of ≥4 cm (≥1.5 inches), prospective height loss of ≥2 cm (≥0.8 inches), or recent or ongoing long-term glucocorticoid treatment (CEBM 5) [2, 4, 12–14] (Supplementary References 5, 27).

Table 2. Interpretation of Fracture Risk Assessment Tool Scores

Fracture Risk	Definition	Management
Low	<10% 10-year risk of major fracture	Reassure and reassess in ≤5 y depending on the clinical context
Moderate/intermediate	10%–20% 10-year risk of major osteoporotic fracture	Measure BMD and recalculate fracture risk to determine whether an individual's risk lies above or below the intervention threshold
High	10-year risk of major osteoporotic fracture ≥20% and/or hip fracture ≥3%	Can be considered for treatment without the need for BMD, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women

Source: [4, 5].

Abbreviation: BMD, bone mineral density.

Laboratory and Biomarker Assessments

Laboratory tests are not indicated to determine fracture risk or low BMD. Investigations for specific and reversible secondary causes of osteoporosis or low BMD should be performed (Table 5) [15]. Markers of bone turnover or inflammation should not be routinely measured in clinical practice for the assessment of bone disease or fracture risk, or at the time of initiation of ART (CEBM 2a, GOR D) [4, 16, 17].

Managing ART in ART-Naive and -Experienced Patients

As the benefits of ART far outweigh the potential negative long-term effects on bone mass and metabolism, and fracture risk, local or national guidelines for initiation and choice of ART regimen should be followed.

Table 3. Essential Components of Patient History and Examination Required for Fracture Risk Assessment Tool and Assessment for Low Bone Mineral Density

Risk factors required for FRAX [6] (Supplementary References 15–24)
Age
Race/geographic location
Female sex
BMI/height and weight
Prior fragility fracture
Parental history of hip fracture
Current tobacco smoking
Alcohol ≥3 standard drinks per day
Long-term use of glucocorticoids (≥5 mg prednisone per day or equivalent for >3 mo)
Rheumatoid arthritis
Secondary causes of osteoporosis[a]
Additional risk factors important for fracture risk assessment
Frailty/fall risk/physical inactivity (Supplementary Reference 25)
Vitamin D deficiency (Supplementary Reference 26)

Abbreviations: BMI, body mass index; FRAX, Fracture Risk Assessment Tool.

[a] Includes type I (insulin dependent) diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (<45 years of age), chronic malnutrition, or malabsorption and chronic liver disease.

A discussion about alternative ART regimens should occur in treatment-naive or -experienced individuals with low BMD or osteoporosis (Figure 2). This will primarily involve the avoidance of tenofovir disoproxil fumarate (TDF) or boosted protease inhibitors (PIs), as these regimens have been associated with a greater decrease in BMD compared with other nucleoside reverse transcriptase inhibitors and raltegravir (Figure 2) (CEBM 5) [1] (Supplementary References 29–32). Novel antiretroviral strategies such as a ritonavir-boosted PI plus raltegravir have been associated with significantly smaller changes in BMD than a ritonavir-boosted PI plus TDF/emtricitabine regimen (Supplementary References 29, 32, 33), but these strategies are not recommended for initial therapy except in patients in whom both TDF and abacavir are contraindicated (Supplementary References 34). Dolutegravir plus abacavir/lamivudine is a recommended regimen; however, there are no published data on the effects of dolutegravir on BMD.

Patients With Osteomalacia

Osteomalacia is defined as softening of the bone caused by defective bone mineralization due to inadequate amounts of available calcium and/or phosphorous and can lead to bone pain, muscle weakness, low BMD, and fragility fracture. Among HIV-infected patients, osteomalacia has been rarely associated with TDF or efavirenz treatment, due to effects on phosphorus homeostasis and vitamin D metabolism, respectively (Supplementary References 32, 37). Osteomalacia should be suspected in a patient with low BMD who has hypophosphatemia or phosphate wasting (fractional excretion of phosphorus >20%–30%) or severe vitamin D deficiency (generally a 25-hydroxy vitamin D level <10 ng/mL [25 nmol/L], accompanied by increases in parathyroid hormone and alkaline phosphatase), and the use of TDF and/or efavirenz should be avoided (CEBM 5).

Optimal Management Strategy for Patients at Risk for Fragility Fracture

Basic Recommendations for All HIV-Infected Patients

Management strategies for patients at high risk for fragility fracture (Figure 2) include dietary and lifestyle changes. An

Table 4. Bone Mineral Density T- and Z-Score Thresholds for Determination of Osteopenia and Osteoporosis

Population	Interpretation: Use of T-Score or Z-Score	Normal	Osteopenia	Osteoporosis
Postmenopausal women and men ≥50 y of age	T-score (compared with a young healthy adult)	≥ −1 SD	Between −2.5 and −1 SD	≤ −2.5 SD
All others	Z-score (age-, sex-, ethnicity-matched)	Low BMD for chronological age if ≤ −2 SD[a]		

Sources: [4, 8].

Abbreviations: BMD, bone mineral density; SD, standard deviation.

[a] In premenopausal women, men <50 years of age, and children, the diagnosis of osteoporosis should not be made by BMD criteria alone [4].

adequate daily intake of dietary calcium is recommended for postmenopausal women and men ≥50 years of age (CEBM 1, GOR B) [1, 4, 5]. Daily total calcium intake should be 1000 mg for men 50–70 years of age, or 1200 mg for women ≥51 years of age and men ≥71 years of age (CEBM 1, GOR B) [4]. Dietary calcium should be increased as a first-line approach, but calcium supplements may be appropriate if dietary calcium intake is insufficient (CEBM 2b, GOR B) [18, 19].

Table 5. Causes of Secondary Osteoporosis

Osteoporosis-Associated Condition	Laboratory Evaluation
Endocrine disorders	
Vitamin D deficiency[a]	25-hydroxy vitamin D
Hyperparathyroidism[a]	Intact parathyroid hormone, total calcium, phosphate, albumin, creatinine
Subclinical hyperthyroidism[a]	Thyroid-stimulating hormone, free thyroxine
Hypogonadism[a]	Men: free testosterone with morning measurement; women: menstrual history, estradiol, follicle-stimulating hormone, prolactin
Cushing syndrome	1 mg overnight dexamethasone suppression test or late-evening salivary cortisol levels
Renal disorders	
Phosphate wasting[a]	Simultaneous serum phosphate and creatinine and spot urine phosphate and creatinine to calculate fractional excretion of phosphate
Idiopathic hypercalcuria[a]	24-hour urinary calcium
Gastrointestinal disorders	
Celiac sprue	Immunoglobulin A tissue transglutaminase antibody
Hematologic disorders	
Multiple myeloma	Complete blood count, serum protein electrophoresis
Mastocytosis	Serum tryptase

Source: [15].

[a] First-line evaluations that should be investigated in all patients with a history of fracture, osteoporosis, or with 10-year risk of osteoporotic fracture by Fracture Risk Assessement Tool ≥20%. Other conditions should be investigated if other clinical factors suggest that these disorders are present.

As HIV-infected patients are at risk of vitamin D insufficiency or deficiency (CEBM 2b, GOR B) [20–24], vitamin D status should be determined by serum 25-hydroxy vitamin D levels in those with a history of low BMD and/or fracture (CEBM 1, GOR B). Determination of vitamin D status may also be considered in patients with any of the major risk factors for low vitamin D levels (eg, dark skin, dietary deficiency, avoidance of sun exposure, malabsorption, obesity, chronic kidney disease, or treatment with regimens containing efavirenz) (CEBM 2b, GOR C) [2, 25–27] (Supplementary Reference 37), although the health benefit of identification and correction of vitamin D deficiency in these groups is unclear (CEBM 4, GOR D) [2].

Supplementary vitamin D should be given to HIV-infected patients with vitamin D insufficiency (<20 ng/mL [<50 nmol/L]) or deficiency (<10 ng/mL [<25 nmol/L]), particularly if the deficiency is associated with compensatory hyperparathyroidism (CEBM 2b, GOR B) (Table 6) [1, 15, 28, 29] (Supplementary Reference 10). Vitamin D intake should be titrated to achieve a serum 25-hydroxy vitamin D level of approximately 30 ng/mL (75 nmol/L) and a suitable maintenance dose administered thereafter to sustain this level (CEBM 2a, GOR B) [4]. Vitamin D deficiency can blunt bone response to bisphosphonate treatment; therefore, the target serum 25-hydroxy vitamin D level of 30 ng/mL should be achieved before initiating therapy with an antiresorptive drug (CEBM 3a/b, GOR C) [30–32].

HIV-infected patients with osteopenia/osteoporosis should be reminded to increase regular weight-bearing and muscle-strengthening exercise, avoid tobacco use and excessive alcohol intake, and take steps to prevent falls (CEBM 5) [33–36] (Supplementary Reference 1).

Therapeutic Management of Osteoporosis in HIV-Infected Patients

Anti-osteoporosis treatment should be initiated for HIV-infected patients under the same criteria as those stated in country-/region-specific guidelines for the general population (Figure 2) (CEBM 2a, GOR C) [1, 28]. In the United States, for example, this would include all patients at high risk for fracture, including postmenopausal women and men ≥50 years of age presenting with a hip or vertebral (clinical or morphometric) fracture; or a

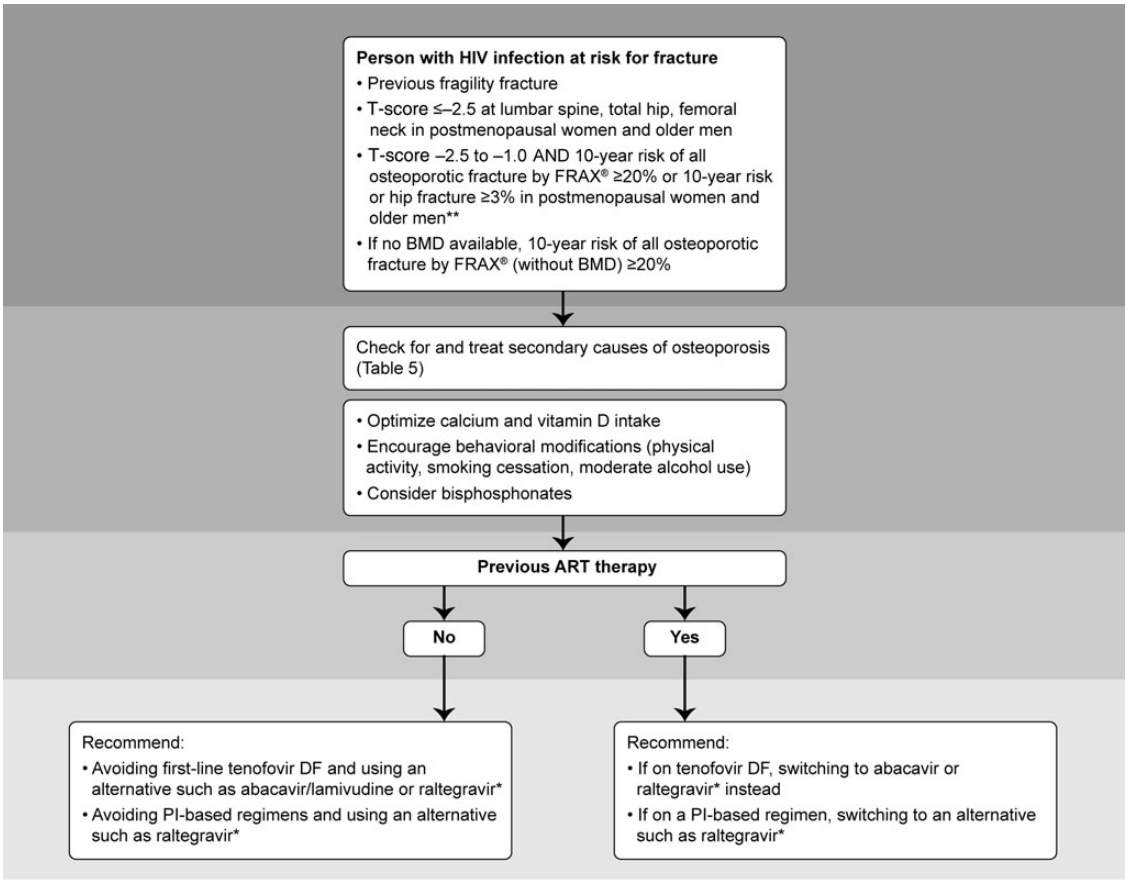


Figure 2. Algorithm for the management of antiretroviral therapy in HIV-infected patients at risk of bone disease. Abbreviations: ART, antiretroviral therapy; BMD, bone mineral density; DF, disoproxil fumarate; FRAX, Fracture Risk Assessment Tool; HIV, human immunodeficiency virus; PI, protease inhibitor.

T-score ≤−2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes of osteoporosis; or low bone mass (T-score between −1.0 and −2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥3% or major osteoporosis-related fracture ≥20% based on FRAX (CEBM 1, GOR B) [4]. Treatment thresholds may vary by country depending on multiple factors, including differences in the cost and availability of anti-osteoporosis treatment, the diagnostic resources available, and the costs associated with treating fracture. Before initiating anti-osteoporosis treatment, secondary causes of low BMD should be evaluated (Table 5) (CEBM 2a, GOR C) [1, 15, 29, 37] (Supplementary Reference 10). Avoidance or discontinuation of medications associated with bone loss (eg, antiepileptic drugs, proton pump inhibitors, thiazolidinediones, and corticosteroids) should be considered if appropriate alternatives are available (CEBM 5).

Alendronate or zoledronic acid is recommended for HIV-infected patients with osteoporosis (CEBM 2b, GOR A) [37–44] (Supplementary Reference 10). Other bisphosphonates have not been evaluated in this patient group. Patients with HIV infection should receive alendronate 70 mg once weekly (with calcium carbonate 1000 mg/vitamin D 400 IU per day) (CEBM 2a, GOR B) [37]. Intravenous zoledronic acid 5 mg yearly can be given as an alternative to alendronate.

Treatment duration should be individualized [4]. Bisphosphonate treatment should be reviewed after an initial 3- to 5-year period, because of concerns about the negative effects of long-term suppression of bone turnover (such as osteonecrosis of the jaw and atypical femoral fractures) (CEBM 1, GOR B) [4, 10]. Several outcomes have been used in the general population to judge the success of anti-osteoporosis treatment, including the lack of definite fractures, or symptoms or signs of possible fracture; maintenance of height (<1 cm of loss) (CEBM 2b, GOR C) [45]; no change or an increase in BMD measured by central DXA of hip and spine (CEBM 1, GOR B) [46]; reduction in serum or urine markers of bone resorption of ≥30% (CEBM 2b, GOR B) [47–50]; and therapy adherence (CEBM 2b, GOR B) [47, 51–55].

Table 6. Vitamin D Supplementation Regimens[a]

Vitamin D Level	Supplementation Regimen
>30 ng/mL (75 nmol/L)	1000 IU/day vitamin D3 (cholecalciferol)
20–30 ng/mL (50–75 nmol/L) (insufficiency)	2000 IU/day vitamin D3
15–19 ng/mL (37.5–50 nmol/L) (deficiency)	Vitamin D2 (ergocalciferol) or D3 50 000 IU/week × 8 weeks (or equivalent of 6000 IU/day vitamin D3)[b]
	Maintenance: vitamin D3 2000 IU/day[c]
<15 ng/mL (37.5 mmol/L) (severe deficiency)	Vitamin D2 or D3 50 000 IU once weekly × 8–12 wk (or equivalent of 6000 IU/day vitamin D3)[b]
	Maintenance: vitamin D3 2000 IU/day[c]

Source: [15].

[a] Well-designed trials investigating the effects of calcium and vitamin D on bone mineral density in human immunodeficiency virus–positive individuals are still lacking.

[b] Consider a more aggressive replacement strategy if patient has secondary hyperparathyroidism, osteomalacia, malabsorption syndrome, or obesity or is taking medications that affect vitamin D metabolism.

[c] Recheck 25-hydroxy vitamin D level after course of ergocalciferol, with a goal of >30 ng/mL. Consider monitoring urinary calcium in patients with a history of nephrolithiasis and concurrent calcium supplementation.

In HIV-infected patients, if BMD continues to decline on oral bisphosphonate therapy, a second-line approach can include intravenous zoledronic acid (CEBM 2b, GOR C) [40, 42, 43, 56]. Teriparatide may also be considered in this setting, but data are limited in HIV-infected populations (CEBM 4, GOR D) [57]. The safety and efficacy of denosumab has not been evaluated in HIV-infected individuals (CEBM 5). Referral to a specialist may be necessary in cases of treatment intolerance or failure or in cases of suspected osteomalacia (CEBM 2b, GOR C) [1].

DISCUSSION

This consensus-based, evidence-driven process was designed to develop and consolidate practical guidance for the screening, diagnosis, monitoring, and treatment of bone disease in HIV. The pathogenesis of bone disease in HIV infection has not been clearly defined, and is likely to be multifactorial. In addition to traditional osteoporosis risk factors, accumulating evidence supports the role of ART as an important factor associated with significant loss of BMD. Although the majority of randomized studies have reported reductions in BMD after initiation of ART, it appears that ART regimens that include TDF and/or ritonavir-boosted PIs are associated with a significantly greater loss of BMD, and these observations are reflected in our recommendations.

The optimal HIV-infected population to undergo DXA screening for low BMD has not been clearly established. Access to screening will also vary according to country-specific DXA screening guidelines for the general population. Alternative recommendations for DXA screening in HIV populations have been provided in this guidance, based on the ease of obtaining DXA.

The guidance provided in this publication differs from some of the other guidelines for the screening and management of bone disease in HIV infection, especially with regard to ART regimen choice and options for switching regimens [1, 2, 13]. Similar to the most recent 2014 European AIDS Clinical Society (EACS) guidelines [2], we make specific recommendations regarding the avoidance of ART therapies that have specific skeletal effects, including TDF and boosted PIs, in patients at risk for fragility fracture. Our recommendations are restricted to available evidence from clinical trials examining BMD changes; the findings of studies assessing the role of specific antiretroviral drugs in bone fractures have been inconsistent (Supplementary References 46, 47). Among integrase inhibitors, there are only limited data on the effect of dolutegravir and elvitegravir on bone, whereas there are data to support the use of raltegravir for its "bone-friendly" profile (Supplementary Reference 48). Well-designed trials are needed to fully determine the effect of integrase inhibitors when used as initial therapy or after a switch. Other knowledge gaps identified by this project are detailed in the Supplementary Data.

Our recommendations differ in several ways from the 2014 EACS guidelines. First, in our screening recommendations, we base the need for DXA evaluation on the results of the FRAX algorithm for those who are aged 40–49 years and do not meet other criteria for screening. This provides clear guidance to clinicians to assess fracture risk in persons in this younger age group, who are generally at low absolute risk of fracture. Also, in contrast to the EACS guidelines, men with clinical hypogonadism are not identified as a specific risk group in whom DXA screening should be targeted. The vast majority of these men will be eligible for screening based on their inclusion in other risk groups. Next, clinicians from 16 different countries participated in the program and provided input into these recommendations. Given the variation of practice around the world regarding osteoporosis screening and treatment in the general population, it is difficult to arrive at one set of recommendations for metabolic bone disease in HIV-infected persons that are applicable in all countries. With the use of FRAX without BMD, we emphasize that fracture risk can be assessed even in resource-limited settings. Finally, while we generally concur with the 2014 EACS guidelines, our recommendations are fully referenced with the underlying evidence base graded.

The OREP has several limitations. First, although literature searches were based on carefully constructed, formalized keyword strings, the review of the literature does not meet strict criteria for a systematic review. Second, the OREP did not address

all aspects of the management of bone diseases in HIV-infected patients. Instead, questions were prioritized to provide the most clinically useful guidance. Finally, the guidance does not take into account differing resource settings, and it may not be possible for all physicians to apply all aspects of the guidance within their practice.

Nonetheless, the OREP followed an academically rigorous process, supported by a group of leading physicians that represented a broad range of clinical opinion from diverse geographic regions and a variety of clinical practices. As such, it provides evidence-based guidance on the screening, monitoring, and treatment of bone disease in HIV-infected patients that is of practical use in clinical settings.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Acknowledgments. The Osteo Renal Exchange program (OREP) was conducted to provide guidance to assist human immunodeficiency virus (HIV) healthcare professionals in the identification and management of patients with bone and/or renal diseases based on evidence and/or expert opinion. The program involved 34 experts from 16 countries, predominantly infectious disease specialists with clinical experience in HIV, bone, or renal disease. The OREP also included nephrologists and endocrinologists with a special interest and experience in HIV. All were selected for participation by AbbVie with input from the Steering Committee (William Powderly [Chair], Todd Brown, Lynda Szczech, Carl Knud Schewe, Giovanni Guaraldi, Boris Renjifo). We acknowledge here the participation of Carl Knud Schewe, Lynda Szczech, Luis Soto-Ramirez, Mohamed Atta, Corinne Isnard-Bagnis, Frank Post, Gregory Kaminskiy, Lauro Pinto Neto, Alexandre Naime, Emmanuelle Plaisier, Lee Man-po, Paolo Maggi, Antonio Belasi, Toshio Naito, Joaquin Portilla, Chia-Jui Yang, Serhat Unal, Barry Peters, Eugenia Negredo, and Ansgar Rieke. This manuscript reports the bone disease outcomes of the OREP. This international survey and discussion program culminated in the agreement of statements relating to the screening, treatment, and monitoring of both renal and bone disease in HIV. The content of the program was developed by the Steering Committee and the participants. Boris Renjifo, a Medical Director at AbbVie, was a member of the Steering Committee and is cited as an author and, as such, was involved in the development and review of the manuscript. The authors thank Christina Chang, Vincenzo Colangeli, and Franco Grimaldi for conducting literature searches and providing a review of the supporting evidence.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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