

Recommendations for Evaluation and Management of Bone Disease in HIV

**Todd T. Brown¹, Jennifer Hoy², Marco Borderi³, Giovanni Guaraldi⁴, Boris Renjifo⁵,
Fabio Vescini⁶, Michael T. Yin⁷, William G. Powderly⁸**

¹Division of Endocrinology, Diabetes & Metabolism, Johns Hopkins University School of Medicine, Baltimore, MD, USA

²Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia

³Infectious Diseases Unit, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, Bologna, Italy

⁴Department of Medical and Surgical Sciences for Children and Adults, University of Modena and Reggio Emilia, Modena, Italy

⁵Global Medical Affairs Virology, Global Pharmaceutical Research and Development, AbbVie, North Chicago, IL, USA

⁶Endocrinology and Metabolism Unit, University-Hospital "Santa Maria della Misericordia", Udine, Italy

⁷Department of Medicine, Columbia University Medical Center, New York, NY, USA

⁸Division of Infectious Diseases, Washington University School of Medicine, St Louis, MO, USA

Corresponding author: Todd T. Brown, MD, PhD, Division of Endocrinology, Diabetes & Metabolism, Johns Hopkins University, 1830 East Monument Street, Suite 333, Baltimore, MD 21287. Tel.:+1 410-502-6888, Fax:+1 410-955-8172, Email:tbrown27@jhmi.edu

Alternate author: William G. Powderly, MD, FRCPI, Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, Campus Box 8051, 660 South Euclid Ave, St. Louis, MO 63110. Tel.:+1 314-454-8215, Fax:+1 314 454-8294, Email: wpowderl@dom.wustl.edu

Summary

We provide guidance and recommendations on clinically relevant questions regarding the screening, monitoring and management of bone disease in HIV-infected patients using the best available data from a comprehensive literature search.

Abstract

Thirty-four 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. Risk of fragility fracture should be assessed primarily using FRAX[®] (without DXA) in all HIV-infected men aged 40–49 years and HIV-infected premenopausal women ≥ 40 years. DXA should be performed in: men ≥ 50 years; postmenopausal women; those with a history of fragility fracture; those receiving chronic glucocorticoid treatment; and those at high risk of falls. In resource-limited settings, FRAX[®] without bone mineral density can be substituted for DXA. Guidelines for ART 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 anti-osteoporosis treatment initiated.

Introduction

Patients with HIV infection have a higher risk of low bone mineral density (BMD) and fragility fracture than the general population [1, 1s–6s]. 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, 7s, 8s]. 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, 9s]. Osteoporosis in these patients may be associated with significant long-term morbidity, which is likely to increase as the HIV-infected population ages [10s, 11s].

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 paper on the management of renal disease will be published elsewhere.

Methods

The OREP was conducted in several stages, described in detail in Appendix One, Supplemental Materials. In brief, four questions regarding screening and management of 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 [12s, 13s]. 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 [14s].

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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 those without major fracture risk factors, an age-specific evaluation is appropriate (Figure 1).

Fracture Risk Assessment by FRAX[®]

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 FRAX[®] score without BMD (Table 2 [4, 5]) (Figure 1), 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, 15s–26s]. As HIV infection and its treatment are associated with an increased risk for low BMD and fragility fracture [1s–6s], 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) [15s,

16s].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].

Dual-Energy X-Ray Absorptiometry (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 (e.g., FRAX[®] score $\geq 20\%$ 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 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 approximately 25%) [27s, 28s] 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 X-rays of the lumbar and thoracic spine or DXA-based Vertebral Fracture Assessment is indicated for: women ≥ 70 years of age and all men ≥ 80 years of age if BMD T-score is < -1.0 at the spine, total hip or femoral neck; women 65–69 years of age, and men 75–79 years of age, if BMD T-score is -1.5 or below; and postmenopausal women 50–64 years of age and men 50–69 years of age 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, 5s, 27s].

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.

A discussion about alternative ART regimens should occur in treatment-naïve 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 (PI), 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, 29s–32s]. 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 [29s, 32s, 33s], but these strategies are not recommended for initial therapy except in patients in whom both TDF and abacavir are contraindicated [34s]. 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 [32s, 37s]. 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 OH vitamin D <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 of a fragility fracture (Figure 2) include dietary and lifestyle changes. An 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].

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(OH)D levels in those with a history of low bone mineral density 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 (e.g. dark skin, dietary deficiency, avoidance of sun exposure, malabsorption, obesity, chronic kidney disease, or treatment with regimens containing efavirenz) (CEBM 2b, GOR C) [2, 25–27,37s], 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, 28, 29,10s][15]. Vitamin D intake should be titrated to achieve a serum 25(OH)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(OH)D level of 30 ng/mL should be achieved before initiating therapy with an anti-resorptive 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, 1s].

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 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 $\geq 3\%$ or major osteoporosis-related fracture $\geq 20\%$ 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, 10s]. Avoidance or discontinuation of medications associated with bone loss (e.g. anti-epileptic 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, 10s]. 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 3–5 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% or more (CEBM 2b, GOR B) [47–50]; and therapy adherence (CEBM 2b, GOR B) [47, 51–55].

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 protease inhibitors 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 guidelines [2], we make specific recommendations regarding the avoidance 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 [46s, 47s]. Among integrase inhibitors, there are only limited data on the effect of dolutegravir and elvitegravir on bone, while there are data to support the use of raltegravir for its 'bone friendly' profile [48s]. 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 Supplemental Materials.

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 40-49 years and do not meet other criteria for screening. This provides clear guidance to clinicians to assess fracture risk 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.

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Potential conflict of interests

Dr Todd T. Brown has served as a consultant to AbbVie, ViiV Healthcare, Merck, Gilead, Theratechnologies, and EMD-Serono.

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Dr Giovanni Guaraldi has received consulting fees and honorarium from AbbVie, has served on advisory boards for Gilead and Merck, and has served as a speaker for AbbVie, Gilead, BMS, ViiV Healthcare and Merck.

Dr Boris Renjifo is an AbbVie employee and may hold Abbott or AbbVie stocks or options.

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Tables

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

1+3*	In order to identify HIV-infected patients at risk for fragility fracture, what are the ideal screening work-up, 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 of fragility fracture?

*Questions 1 and 3 were combined.

Table 2. Interpretation of FRAX® Scores [4, 5].

Fracture risk	Definition	Management
Low	<10% 10-year risk of major fracture	Reassure and reassess in 5 years or less 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 $\geq 20\%$ and/or hip fracture $\geq 3\%$	Can be considered for treatment without the need for BMD, although BMD measurement may sometimes be appropriate, particularly in younger postmenopausal women

BMD, bone mineral density.

Table 3. Essential Components of Patient History and Examination Required for FRAX[®] and Assessment for Low BMD.

Risk Factors Required For FRAX[®] [6, 15s–24s]
Age
Race/geographic location
Female gender
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 months)
Rheumatoid arthritis
Secondary causes of osteoporosis*
Additional Risk Factors Important for Fracture Risk Assessment
Frailty/fall risk/physical inactivity [25s]
Vitamin D deficiency [26s]

*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.

BMD, bone mineral density; BMI, body mass index.

Table 4. BMD T- and Z-Score Thresholds for Determination of Osteopenia and Osteoporosis[4, 8].

	Interpretation: use of T-score or Z-score	Normal	Osteopenia	Osteoporosis
Post-menopausal women and men ≥ 50 years 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-, gender-, ethnicity-matched)	Low bone mineral density for chronological age if ≤ -2 SD*		

BMD, bone mineral density; SD, standard deviation.

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

Table 5. Causes of Secondary Osteoporosis [15].

Osteoporosis-associated condition	Laboratory evaluation
<i>Endocrine disorders</i>	
Vitamin D deficiency*	25-OH vitamin D
Hyperparathyroidism*	Intact parathyroid hormone, total calcium, phosphate, albumin, creatinine
Subclinical hyperthyroidism*	Thyroid stimulating hormone, free thyroxine
Hypogonadism*	Males: Free testosterone with morning measurement Females: Menstrual history, estradiol, follicle-stimulating hormone, prolactin
Cushing's Syndrome	1 mg overnight dexamethasone suppression test or late evening salivary cortisol levels
<i>Renal disorders</i>	
Phosphate wasting*	Simultaneous serum phosphate and creatinine and spot urine phosphate and creatinine to calculate fractional excretion of phosphate
Idiopathic hypercalcuria*	24-hour urinary calcium
<i>Gastrointestinal disorders</i>	
Celiac sprue	IgA tissue transglutaminase antibody
<i>Hematologic disorders</i>	
Multiple myeloma	Complete blood count, serum protein electrophoresis
Mastocytosis	Serum tryptase

*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 FRAX[®] ≥20%. Other conditions should be investigated if other clinical factors suggest that these disorders are present.

Table 6. Vitamin D Supplementation Regimens* CEBM 3a [15].

Vitamin D Level	Supplementation Regimen
>30 ng/mL(75 nmol/L)1000 IU/day vitamin D3	1000 IU/day vitamin D3 (cholecalciferol)
20–30 ng/mL(50–75 nmol/L) (insufficiency)	2000 IU/day vitamin D3
15–19 ng/mL (deficiency) (37.5–50 nmol/L)	Vitamin D2(ergocalciferol) OR D3 50 000 IU/week x 8 weeks (or equivalent of 6000 IU/day vitamin D3) ^a
	Maintenance: vitamin D3 2000 IU/day ^b
<15 ng/mL (37.5 mmol/L) (severe deficiency)	Vitamin D2OR D350 000 IU once weekly x 8–12 weeks (or equivalent of 6000 IU/day vitamin D3) ^a
	Maintenance: vitamin D3 2000 IU/day ^b

HIV, human immunodeficiency virus.

*Well designed trials investigating the effects of calcium and vitamin D on BMD in HIV-positive individuals are still lacking.

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

^bRecheck 25(OH)D level after course of ergocalciferol, goal > 30 ng/mL. Consider monitoring urinary calcium in patients with a history of nephrolithiasis and concurrent calcium supplementation use.

Figure Legends

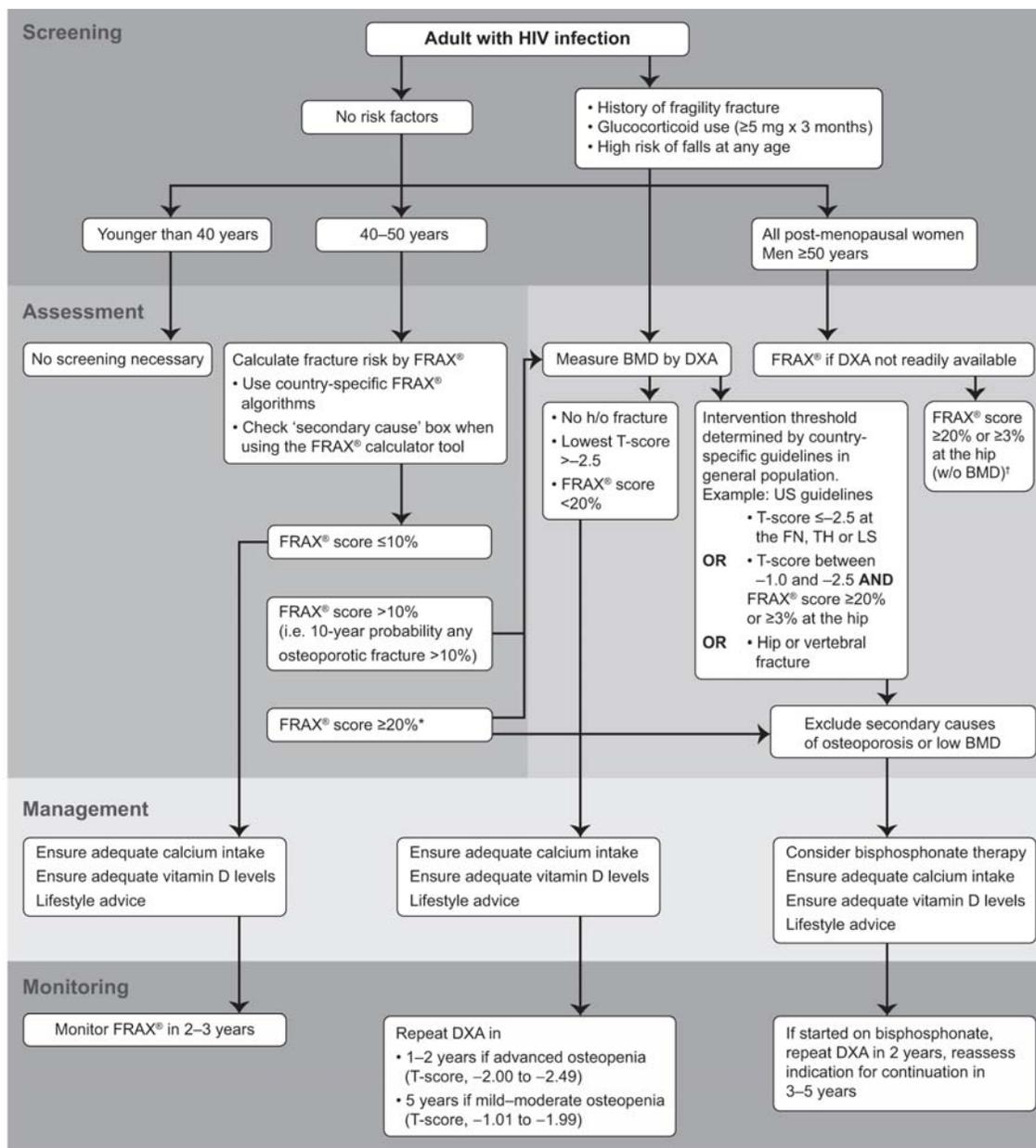
Figure 1. Algorithm for the Screening, Assessment, Management and Monitoring of Bone Disease in HIV-Infected Patients.

BMD, bone mineral density; DXA, dual energy x-ray absorptiometry; FRAX[®], Fracture Risk Assessment Tool.

Figure 2. Algorithm for the Management of Antiretroviral Therapy (ART) in HIV-Infected Patients at Risk of Bone Disease.

FRAX[®], Fracture Risk Assessment Tool.

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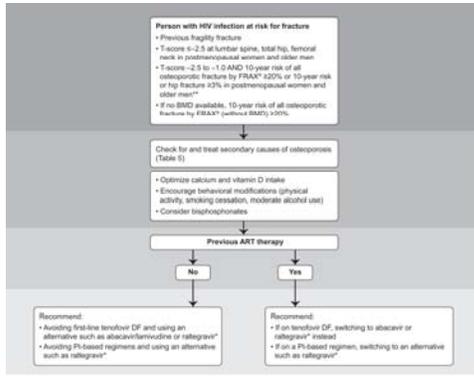


DXA = dual energy X-ray absorptiometry, FN = femoral neck, TH = total hip, LS = lumbar spine

^{*}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/>)



**There are limited to no data for the other integrase inhibitors. **Based on US intervention thresholds. Country-specific guidelines should apply.

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