Osteoporosis in HIV and Aging

Aroonsiri Sangarlangkarn, MD, MPH, Jonathan S. Appelbaum, MD, FACP

Educational Objectives
By the end of the session, learners will be able to:

1. Describe two features that distinguish osteoporosis in HIV-infected patients from that in the general population.
2. Outline a factor for osteoporosis in HIV-infected patients and the strategy to minimize its effects on bone health.
3. Apply an evidence-based approach to the evaluation and management of osteoporosis in HIV-infected patients.

Suggested reading:

CASE ONE:

Ms. Fracture is a 50-year-old woman with past intravenous drug abuse, chronic obstructive pulmonary disease (COPD) from tobacco abuse, HIV well-controlled on ART who presents to your clinic to establish care. Her current medications include prednisone 10mg daily, methadone 100mg daily, ritonavir, atazanavir, tenofovir and emtricitabine daily. Her last CD4 count is 200 cells/mm³, and her viral load is undetectable.

As part of the initial intake, you ask whether she has had a bone density scan in the past to screen for osteoporosis, to which Ms. Fracture replies, “Doctor, what is osteoporosis?”

Questions:

1. What is osteoporosis? How does it differ from osteopenia?
   - Osteoporosis is a skeletal disorder characterized by low bone mass, micro-architectural disruption and increased risk of fractures.
   - Osteopenia, a precursor to osteoporosis, is a skeletal disorder characterized by lower than normal bone density, but not as low as osteoporosis.
2. How does the prevalence rate among HIV-infected patients differ than that in the general population?
   - Based on a meta-analysis by Brown et al (1), the prevalence rate for osteoporosis in HIV-infected patients was 15%. However, due to heterogeneity, the prevalence rate of osteopenia was not reported. Another study by Bonjoch et al (2) following 671 patients over 2.5 years found the prevalence rate to be 23% for osteoporosis, 47.5% for osteopenia.
   - Several studies have shown that the prevalence rates of osteoporosis and fragility fractures are higher in the HIV-infected. The meta-analysis by Brown et al (1) reported 6.4-fold increased risk of reduced bone mass density (BMD) (95% CI 3.7, 11.3) and a 3.7-fold increased risk of osteoporosis (95% CI 2.3, 5.9). However, a retrospective analysis by Triant et al (3) showed only a slightly increased risk of fractures in HIV-infected patients (2.9 vs 1.9 per 100 persons, p<0.0001).

3. Why does the prevalence for osteoporosis differ in HIV-infected patients compared to the general population? What are the effects of HIV on bone metabolism?
   - HIV-infected patients have HIV-associated risk factors for bone loss that increase the risk for osteoporosis compared to the general population. Moreover, studies have shown altered bone and calcium metabolism in HIV-infected patients, although the significance of these alterations is unclear, since current research did not report on clinically important outcomes such as osteoporotic bone fracture.
   - Altered bone remodeling: According to a cross-sectional analysis of 73 HIV-infected patients, those with advanced HIV demonstrated low levels of osteocalcin (a marker of bone formation) and high levels of C-telopeptide (a marker of bone resorption), likely driven by activation of the tumor necrosis factor (TNF) system (negatively correlated with osteocalcin, positively correlated with C-telopeptide). Osteocalcin levels rose in 16 of the patients after starting ART, potentially suggesting a beneficial effect of ART on bone remodeling (4).
   - Decreased parathyroid hormone (PTH): Research has also shown decreased PTH levels and response in HIV-infected patients, even in the absence of parathyroid infiltrative disease (5) and at all levels of calcium concentration (6). Although decreased PTH action theoretically increases bone mineral density, existing studies did not report on clinically important outcomes.

4. What are risk factors for bone loss? Your answer should address traditional risk factors and HIV-associated risk factors.
   - Risk factors for bone loss can be categorized into traditional risk factors and HIV-associated risk factors:
     o Traditional risk factors: can act in concert with HIV-associated risk factors
       ▪ Female gender
- Advanced age
- Personal history of fracture as an adult
- Family history of fragility fracture in a first-degree relative
- Low body mass index (BMI)
- Physical inactivity
- Early onset and duration of menopause
- Hypogonadism
- Smoking
- Excessive alcohol consumption
- Injection drug use
- Vitamin D deficiency
- Hepatitis C infection: increases fracture risk independently from HIV infection, possibly through alterations in calcitropic and gonadotropic hormone levels and weight loss (7).
- Chronic medical disease: rheumatoid arthritis, inflammatory bowel disease, celiac disease, cystic fibrosis, hyperthyroidism, type 1 and 2 diabetes, renal disease
- Medication: corticosteroids, heparin, cyclosporine, vitamin A and synthetic retinoids, loop diuretics, chemotherapeutic agents, antiepileptics, proton pump inhibitors, antidepressants, thiazolidinediones.
  - HIV-associated risk factors: HIV infection and medications used to treat it can act as risk factors for bone loss
    - HIV infection: Uncontrolled viremia or nadir CD4 cell count <200 cells/mm^3 have been shown to reduce BMD (1,8), possibly through chronic T cell activation, increased production of pro-inflammatory cytokines that enhance osteoclast activity (9), decrease in bone formation by promoting osteoblast apoptosis through HIV proteins (10).
    - ART: Overall, evidence is inconclusive whether ART (especially protease inhibitor) in general reduces BMD or increases fracture risks. However, tenofovir has been shown to cause initial, modest BMD loss (2.2% in lumbar spine, 2.8% in hip) that subsequently stabilizes (occurring between 24-48 weeks after initiation of tenofovir and stabilizes through 144 weeks) (11). However, there was no evidence of increased fracture with tenofovir.
    - Other medications related to complications of HIV: Ketoconazole can accelerate bone loss. Hypocalcemia is a side effect of foscarnet (15-30%) and pentamidine (<1%).

5. What questions would you ask Ms. Fracture to determine her risk factors? Would you order any lab tests?
   - To determine risk factors, investigate the following:
- **Weight changes:** Low BMI serves as a risk factor for bone loss, and weight loss may indicate malnutrition/malabsorption that lead of calcium and vitamin D deficiency.

- **Mobility:** Asking about how Ms. Fracture walks and manages her day-to-day life can reveal her level of physical activity as well as fall risks, both of which affect the incidence of fragility fractures.

- **Medication and substance use:** Focus on past use of steroids, ketoconazole, foscarnet or pentamidine, calcium/vitamin D intake, tenofovir exposure, smoking and recreational drug use.

- **Comorbidities:** Focus specifically on hepatitis C infection and signs of hypogonadism, such as early menopause or oligomenorrhea, both of which increases risk of bone loss.

  - After taking the above history, consider ordering 25-hydroxy vitamin D level and hepatitis C antibody screen.

**CASE ONE CONTINUED:**

After explaining to Ms. Fracture what osteoporosis is, you proceed to collect more information regarding her medical history.

Ms. Fracture was diagnosed with HIV 20 years ago during a period of heavy drinking and injection drug use, when she was found to have Pneumocystis jiroveci pneumonia (PCP) because her CD4 was “nonexistent.” Ms. Fracture underwent menopause when she was 46 years old. Although she has never broken any bones because she is sedentary, her mother broke her hip and wrist due to falls before she passed away.

When you review the medication bottles, you learn that she is also taking furosemide 20mg every other day for blood pressure and esomeprazole 40mg daily, which was started during a hospitalization many years ago. She is unsure what the esomeprazole is for.

On physical exam, her weight is 120 lbs, BMI 17.15. She is afebrile, BP 110/60, pulse 65, oxygen saturation 100% on room air. She is thin, but otherwise her exam is unremarkable.

6. What are Ms. Fracture’s risk factors for osteoporosis? Which ones can you potentially modify and how would you optimize them?

   - **Historical risk factors which cannot be modified:** nadir CD4 cell count <200 cells/mm³ at initial diagnosis, history of excessive alcohol consumption, early menopause, fragility fracture in first degree relatives.

   - **Current risk factors which are modifiable:**

      - **Cigarette smoking:** Counseling Ms. Fracture to stop smoking will help reduce her risk of osteoporosis, as well as multiple other diseases. It
likely will improve her COPD, hopefully to a point where she would not need to take chronic steroids, which also reduce her bone mass density.

- **Medication regimen:** While you try to reduce chronic steroid use as her COPD improves after smoking cessation, there are other potentially inappropriate prescriptions that can be optimized. In the elderly, goal blood pressure may not be as low as that in the younger population, so discontinuing the currently very low dose of furosemide, a risk factor for osteoporosis, will likely still leave her blood pressure within an acceptable range. It also seems that esomeprazole was started during an acute hospitalization in the past, and Ms. Fracture may not need this medication anymore. Stopping a proton pump inhibitor can also reduce the risk of osteoporosis, along with Clostridium difficile infection and aspiration pneumonia.

- **Sedentary lifestyle:** In addition to reducing her risk of osteoporosis, exercise can reduce frailty, falls, and increase muscle mass while decreasing fat mass.

- **Low body weight:** Apart from exercise, referring Ms. Fracture to a nutritionist might also help her increase weight and reduce her risk of osteoporosis.

**CASE ONE CONTINUED:**

Ms. Fracture is eager to make the changes you suggest, but she also wants to know if she has osteoporosis.

7. Would you screen Ms. Fracture for osteoporosis and why? What test would you order if you decide to screen her?

- Ms. Fracture should be screened with a bone densitometry (DXA) for 2 reasons:
  
  - Per guidelines by the Infectious Disease Society of America (IDSA), osteoporosis screening in HIV-infected patients should be performed in postmenopausal women and men >50 years old (strong recommendation, moderate quality evidence) (12).
  
  - Apart from the above guidelines, Ms. Fracture has multiple factors that increase her fracture risk compared to that of a 65-year-old white woman, which is the usual benchmark for screening in the general population. Her risk factors include glucocorticoid therapy, parental history of hip fracture, low body weight, current cigarette smoking, and premature menopause.
CASE ONE CONTINUED:

DXA results show the following T-scores: Hip total -2.8, femoral neck -2.4, L4 -2.5

8. Does Ms. Fracture have osteoporosis? What other tests would you order?
   - DXA is considered positive for osteoporosis if a T-score in the femoral neck or the lumbar spine is less than or equal to -2.5. As a result, it seems that Ms. Fracture has osteoporosis.
   - Currently it is controversial whether testing to identify secondary contributors to osteoporosis, such as vitamin D deficiency or hyperparathyroidism, is warranted. In addition, the most cost-effective approach has not been established. A review by Brown et al (13) recommended secondary screening based on a study in uninfected women (14) reporting 55 out of 173 patients (32%) with secondary causes of osteoporosis. The study also concluded that a testing strategy involving measurement of 24-hour urine calcium, serum calcium, and serum PTH for all women and serum thyroid-stimulating hormone (TSH) among women on thyroid replacement therapy would have been sufficient to diagnose 47 of these 55 women (85%) at an estimated cost of $75 per patient screened. However, the sample size in this study was small with questionable applicability to the HIV-infected population, no men were included, and no conclusions were made regarding evaluations for other conditions such as vitamin D deficiency or hypogonadism.
   - Because testing for secondary causes of osteoporosis is controversial, you may decide to forego further testing for Ms. Fracture. However, for other patients over the age of 65, in which screening for vitamin D deficiency is recommended regardless of HIV status, ordering a 25-hydroxyvitamin D level might be appropriate.

9. How would you treat Ms. Fracture?
   - Currently, data on the efficacy of bisphosphonates in HIV-infected patients is limited. A few, small randomized-controlled studies have shown increased BMD in HIV-infected patients on bisphosphonates. However, important clinical outcomes such as fracture reduction have not been investigated, compared to studies in the general population where fracture reduction with bisphosphonates has been validated. Moreover, long-term side effects of bisphosphonate in HIV-infected population are not known. This is an important issue because osteoporosis may occur at a much younger age in HIV-infected patients and therapy may be initiated sooner compared to the general population.
   - With the current lack of data, a reasonable approach would be to treat Ms. Fracture as you would a 55-year-old HIV-uninfected woman with the same risk profile. Because Ms. Fracture has multiple risk factors, it seems sensible to treat her with bisphosphonates, on top of recommending lifestyle changes.
and making sure she has sufficient intake of calcium (1200mg/day) and vitamin D (800 IU/day).

10. Would you switch Ms. Fracture’s ART regimen?
   - Because evidence is currently inconclusive whether tenofovir increases fracture risk, the best approach may be to continue the same ART regimen, especially since her viremia is currently well controlled. Switching regimen may result in loss of virologic control and new adverse effects/intolerance.

11. How would you monitor treatment?
   - Currently, there is limited data on optimal monitoring approach in HIV-infected patients, since data in the general population is still inconclusive. Most guidelines recommend DXA as a tool to monitor treatment, but there is no consensus on the frequency or the preferred sites to monitor. Most recommend monitoring every 2 years until BMD is stable, after which DXA can be performed less frequently.
   - Markers of bone turnovers, such as fasting urinary N-telopeptide (NTX) or serum carboxy-terminal collagen crosslinks (CTX), have been used in clinical research. However, their applicability to clinical practice is limited by cost and access.
Additional reference: