HIV and ART: Bad to the Bone?

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Not only does the welcome long-term survival of HIV-infected patients put them at risk of ordinary age-related bone loss, antiretroviral therapy leads to a decline in bone mineral density. What can be done?

With the graying of the world’s population, HIV-infected individuals are confronting the same age-related problems as everyone else—including cardiovascular disease, neurocognitive problems, and bone loss and fracture risk. Since the advent of highly active antiretroviral therapy (HAART) 15 years ago, HIV-positive men and women face a related and critical problem: Some of the same drugs that prolong their lives also contribute to a decline in bone mineral density (BMD) and an increase in fractures.

Large population-based studies comparing HIV-infected and non-infected individuals in Spain, Denmark, the United States, and elsewhere show a strong association between osteoporosis and HIV, and implicate HAART as one of the factors involved in bone loss among HIV-infected individuals.

Yet it was only this year that the National Osteoporosis Foundation included HIV among the risk factors that should prompt bone density testing for postmenopausal women younger than 65 and men ages 50 to 69, remarks Todd T. Brown, MD, PhD, Associate Professor of Medicine and Epidemiology at Johns Hopkins University.

The US Preventive Services Task Force guidelines on osteoporosis screening do not specifically mention HIV-positive people, but most experts now say this population is at increased risk and could benefit from earlier or more frequent screening.

What's the Link?

The most recent large-population study linking HIV and fractures comes from Spain, where the country’s public health system covers practically the entire population and offers extensive databases of electronic health records.

The 2013 analysis of a large database called SIDIAPQ (Sistema d’Informacio´ per al Desenvolupament de l’Investigacio´ en Atencio´ Primria-Q), containing clinical information for more than 2 million patients in the Catalonia region, finds an almost 5-fold increase in the risk of incident hip fractures among HIV-positive individuals over age 40 compared with the uninfected. The data, spanning 2007 to 2009 among 1,118,156 people (2489 of whom were HIV-positive) support the association between HIV and hip fracture risk—regardless of sex, age, body mass index (BMI), smoking, alcohol consumption, and comorbid conditions.

The same analysis reveals a 75% higher risk of all clinical fractures and a 60% increase in risk of non-hip clinical fractures among HIV-positive patients. But when stratified by age, the increase in major non-hip fractures was significant only among patients older than 59.

“You cannot underestimate the role of traditional risk factors like age in all populations including HIV-positive patients, particularly among those on antiretroviral therapy,” comments Brown. Risk factors more common among HIV-infected individuals than in the general population include lower BMI, higher smoking rates, heavy alcohol use, liver disease, and hepatitis C virus infection, he adds.

As for mechanisms that might cause bone loss directly, some studies suggest that systemic inflammation plays a role. Other reports implicate the T cells that the HIV virus targets.

In the general population, systemic inflammation is associated with loss of BMD and fracture, Brown
notes. And a 2013 meta-analysis finds that having lower CD4 T-cell counts before starting antiretroviral therapy (ART) predicts increases in bone turnover and fracture risk. “This may be related to T-cell recovery, not only recovery of numbers but recovery of function,” he speculates.

The ART-Fracture Connection

Over the first 1 to 2 years of ART therapy, BMD drops approximately 2% to 6%. It remains stable thereafter and generally does not return to baseline, Brown notes in a report just published online in the Journal of Bone Mineral Density. This finding is consistent across studies and is independent of the specific ART regimen used.

Bone loss is associated with marked increases in bone turnover in the first 6 months of ART, with markers of bone resorption rising earlier and higher than markers of bone formation, creating a “catabolic window,” Brown writes.

Some therapies have a worse effect on BMD than others. One of the most popular HIV medications, tenofovir, decreased BMD by about 1% to 2% versus comparator drugs in randomized controlled trials and increased the risk of fracture in a large observational study.

“It’s believed that tenofovir impairs the function of proximal tubules in the kidneys, such that the ability to reclaim phosphate is compromised and phosphate wasting develops,” explains Brown. “The body’s response to a loss of phosphate in the urine is to go to its reservoir of phosphate, which is bone. But whether or not phosphate wasting is the specific mechanism related to tenofovir and bone loss is unclear.”

Certain protease inhibitors (atazanavir, ritonavir) decrease BMD and others (lopinavir, ritonavir) are associated with an increased risk of fracture. Combining protease inhibitors and tenofovir appears to be particularly damaging, possibly by raising tenofovir levels and amplifying its effects, he adds. In some studies, switching to the nucleoside analog abacavir can help stabilize BMD, while other studies show that changing to raltegravir or substituting an integrase inhibitor for a protease inhibitor may improve BMD.

While a randomized clinical trial finds that halting HAART altogether decreases bone turnover markers and boosts BMD, it’s just too risky for patients. Stopping therapy not only raises CD4 cell counts but also increases non-AIDS events such as cardiovascular disease.

What to Do Now?

With so many unanswered questions, the main challenge is managing the care of HIV-positive patients to prevent osteoporosis or reduce fracture risk while balancing the benefits of antiretroviral therapy with the risks.

Right now, Brown advises clinicians to be aware of the increased fracture risk in HIV-infected populations and to implement measures for primary prevention of osteoporosis among older HIV-positive patients.

One such measure he suggests is giving a long-acting bisphosphonate, such as zoledronic acid, at the time ART is initiated in patients who have had previous fragility fractures or are at high risk. Estrogen might even be considered for HIV-positive postmenopausal women (who appear to lose bone at a faster rate than uninfected women) if they have severe hot flashes, he says, because it prevents bone loss and lessens hot flashes.

Brown advises clinicians to consider switching HIV-infected patients with established osteoporosis to an ART regimen with the least known bone toxicity.

Other preventive measures include behavioral changes (smoking cessation, alcohol reduction, increased weight-bearing exercise), identifying contributing comorbid conditions (eg, hypogonadism), assessing risk of falls, and regular BMD screening (optimally every 1 to 2 years, as suggested by one study).
Brown is currently studying calcium and vitamin D supplementation to prevent bone loss in
HIV-infected patients.
As for screening, he recommends using dual-energy x-ray absorptiometry (DEXA). He is currently
studying the use of quantitative CT (Q-CT) to measure effects of HIV and ART on bone strength
parameters that may not be picked up by DEXA.

Learning the factors that lead to bone loss during ART and those associated with stabilization of BMD
when someone discontinues therapy, Brown suggests, might "provide insights into this
osteo-immunologic interaction." In the meantime, until research teases out the factors involved in
bone loss, HIV, and HAART, he concludes, osteoporosis treatment should follow the guidelines set for
the general population.

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