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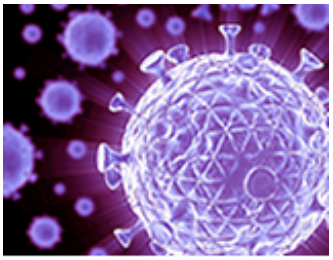

VOLUME 1, NUMBER 5

Bone Health, Vitamin D, and HIV

In this Issue...

The care of HIV-infected individuals has undergone a major transformation over the past 15 years, with increasing focus on the management of non-HIV comorbidities, particularly among older patients. Osteoporosis is a common condition associated with aging, and strong evidence suggests that the frequency of the disorder is higher than expected in HIV-infected patients compared with uninfected individuals. Vitamin D deficiency among the HIV-infected population may contribute to the high prevalence of bone disease and also to nonskeletal comorbidities such as cardiovascular disease (CVD).

In this issue, we review four studies that address important aspects of bone disease and vitamin D deficiency in HIV-infected individuals: Two of these studies focus on the relevant endpoint related to osteoporosis (osteoporotic fracture); another compares the bone effects of four commonly used antiretroviral regimens during the initiation of antiretroviral therapy; and the last study explores the association between vitamin D deficiency and subclinical CVD. All of these studies have important implications for decreasing the burden of comorbid disease among HIV-infected patients.

LEARNING OBJECTIVES

After completing this activity, the participant will demonstrate the ability to:

- Describe the pathophysiology of and risk factors for osteoporosis in HIV-infected patients
- Discuss strategies for the management of osteoporosis and vitamin D deficiency in HIV-infected individuals
- Identify gaps in our understanding of vitamin D deficiency and nonskeletal morbidities in HIV-infected persons

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- Clinicians caring for patients with HIV need current information about: appropriate treatment and maintenance of care…guidance for treating comorbidities…and information about emerging findings for treating HIV-associated neurocognitive disorders (HAND)
- The need for more information on HIV topics including updated guidelines for HIV, treating older patients with HIV, managing patients with comorbidities and coinfections, treatment and sequencing strategies for maximizing future therapeutic options, and new and emerging agents for HIV

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- Treating comorbidities in patients with HIV, especially among people older than age 50

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THIS ISSUE

- COMMENTARY from our Guest Authors
- FRACTURE INCIDENCE AMONG HIV-INFECTED AND HIV-UNINFECTED INDIVIDUALS

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- RISK FACTORS FOR FRAGILITY FRACTURE AMONG HIV-INFECTED INDIVIDUALS: EFFECT OF CD4 CELL COUNTS
- EFFECT OF SPECIFIC ANTIRETROVIRAL MEDICATIONS ON BONE MINERAL DENSITY AND FRACTURES
- VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

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Todd Brown, MD, PhD, has disclosed that he has received grants/research support from Glaxo/Smith/Kline and Merck. He has also served as a consultant for EMD Serono, Gilead, Tibotec, and ViiV Healthcare, and is a member of the Bristol-Myers Squibb Steering Committee.

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COMMENTARY

As the population of HIV-infected persons over the age of 50 years grows, the evaluation and management of non-AIDS comorbidities are becoming increasingly important parts of clinical care. Osteoporosis is a common condition associated with aging, with osteoporotic fracture a major source of morbidity and mortality among older persons in the general population.

Osteoporosis is more common among the HIV-infected population than in their uninfected peers. Mounting evidence, including the results of a recent study by Hansen and colleagues (reviewed in this issue), suggests that the higher prevalence of osteoporosis translates into a higher risk for fragility fracture—the only clinically relevant endpoint related to osteoporosis. Multiple subpopulations of HIV-infected individuals may be at increased risk for fracture and therefore represent important targets for interventions. As described in the Hansen study, those with HIV and hepatitis C virus (HCV) coinfection have a higher risk for fracture compared with those with HIV monoinfection. As discussed by Yong and collaborators in this issue, another at-risk population comprises individuals with CD4 cell counts <200 cells/mm3 despite virologic suppression with antiretroviral therapy (ART)—a condition that may be related to chronic immune activation. This finding has implications for therapies geared toward decreasing immune activation in those with suboptimal CD4 recovery on treatment.

Another risk factor for fracture is the use of ART. Although bone loss is invariably reported with ART initiation regardless of the regimen, suggesting an effect of immune reconstitution, certain ART regimens may have a more profound effect than others. A recent randomized trial by McComsey and associates (described herein) shows that tenofovir and atazanavir plus ritonavir have independent effects on bone loss. Many questions, including the mechanisms and the clinical implications, remain answered.

Although vitamin D deficiency may compromise skeletal health, an increasing number of observational studies[1-4] have described associations between vitamin D deficiency and nonskeletal outcomes, including subclinical cardiovascular disease (see Lai and collaborators, reviewed in this issue). While these types of associations are important to delineate, a vitamin D supplementation trial is warranted to fully understand the effect of vitamin D deficiency on health outcomes. Research is moving quickly toward a better understanding of issues related to bone metabolism and vitamin D deficiency among HIV-infected individuals. This knowledge will hopefully be translated quickly into changes in clinical practice that will improve and preserve the health of our patients.

Commentary References

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3. Mehta S, Mugusi FM, Spiegelman D, et al. Vitamin D status and its association with morbidity including wasting and opportunistic illnesses in HIV-infected women in Tanzania. *AIDS Patient Care STDS*. 2011;25(10):579-585.
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FRACTURE INCIDENCE AMONG HIV-INFECTED AND HIV-UNINFECTED INDIVIDUALS

Hansen AB, Gerstoft J, Kronborg G, et al. **Incidence of low and high-energy fractures in persons with and without HIV infection: a Danish population-based cohort study.** *AIDS*. 2012;26(3):285-293.

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Although cross-sectional studies have clearly demonstrated a higher prevalence of osteoporosis in HIV-infected persons compared with uninfected controls, the more clinically relevant question is whether the risk for fracture differs according to HIV status. Hansen and colleagues examined the incidence of fracture in HIV-infected and uninfected persons by using several national databases in Denmark, including the Danish HIV Cohort Study. A single-payer health system and multiple linkable databases allow for very complete capture of administrative data in both groups. In this study, 5306 HIV-infected individuals were age- and sex-matched in a 1:5 ratio to HIV-uninfected persons during the 1995 to 2009 study period and followed for incident fractures.

The major finding was that HIV-infected persons had an increased risk for fracture (incidence rate ratio [IRR], 1.5; 95% confidence interval [CI], 1.4 to 1.7) compared with population controls. This was observed particularly among HIV or HCV coinfected persons (IRR, 2.9; 95% CI, 2.5 to 3.4) vs uninfected persons.

Another noteworthy finding was that when the HIV-monoinfected group was stratified by use of ART, ART-treated, but not ART-naïve, persons were at higher risk for fracture compared with the uninfected control population. No increased risk for fracture was reported with tenofovir or efavirenz exposure. The major limitation of this study was the lack of availability of other important data, including body mass index (BMI), alcohol exposure, and use of concomitant medications such as corticosteroids.

Nevertheless, this study makes an important contribution to our understanding of fracture risk among HIV-infected persons. As in other studies[1-3] that have compared fracture risk in HIV-infected and uninfected individuals, the magnitude of the effect was in the moderate range, but it is nonetheless concerning for bone health in our patients. It should be noted that the relative risk for fracture in HIV-infected persons is likely to increase with the increasing age of the population, so it will be important to update these analyses as the HIV populations enter their eighth and ninth decades of life.

Particularly noteworthy was the higher risk for fracture among HIV and HCV coinfected persons. The reasons for this higher risk is unclear but may be related to hypogonadism, inadequate nutrition, low physical activity, or other factors. One intriguing possibility is that part of the risk is attributable to chronic HCV infection itself, and effective HCV treatment, which is becoming increasingly available, may reduce this risk. The finding of an increased fracture risk in ART-treated vs ART-naïve patients is consistent with the known decrease in bone mineral density (BMD) associated with ART initiation (see article by McComsey and coworkers, below). Given the established relationship between inflammation and bone loss in other disease populations (eg, rheumatoid arthritis, inflammatory bowel disease), the lack of an increased risk for fracture among ART-naïve persons is interesting, and the mechanisms that serve to protect bone from the negative effects of inflammation in persons with untreated HIV require investigation.

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RISK FACTORS FOR FRAGILITY FRACTURE AMONG HIV-INFECTED INDIVIDUALS: EFFECT OF CD4 CELL COUNTS

Yong MK, Elliott JH, Woolley IJ, Hoy JF. **Low CD4 count is associated with an increased risk of fragility fracture in HIV-infected patients.** *J Acquir Immune Defic Syndr*. 2011;57(3):205-210.

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HIV-infected persons have a higher prevalence of traditional risk factors for osteoporosis and fragility fracture, including high rates of smoking, alcohol abuse, low BMI, and low testosterone levels. Other HIV-specific risk factors, however, are also likely to increase fracture risk. Although chronic immune activation and systemic inflammation are thought to be major contributors to bone loss in patients with other inflammatory diseases, these associations are less clear in HIV infected individuals.

A potential marker of chronic immune activation among HIV-infected persons is inadequate CD4 cell recovery while on ART. In a case-control study, Yong and associates demonstrated that CD4 cell counts are also associated with fracture. In this study, 61 patients with low-trauma fracture over an 11-year period were matched in a 1:2 ratio with HIV-infected controls of the same gender, age, and HIV duration. The fracture endpoints and clinical information were obtained through clinical and administrative databases, and high-trauma fractures (eg, from a motor vehicle accident) were excluded from the study. The median CD4 cell count in cases was significantly lower than in controls (283 vs 448 cells/mm3, respectively), and the proportion of those with CD4 cell counts <200 cells/mm3 was higher in cases than in controls (36% vs 14%, respectively). After multivariable adjustment, those with CD4 cell counts <200 cells/mm3 were at a 4.9-fold higher risk for experiencing an incident fracture compared with those with CD4 cell counts >500 cells/mm3. Those with CD4 cell counts in the 200 to 500 cells/mm3 range were at intermediate risk for an incident fracture (odds ratio [OR], 2.4). This finding was unrelated to having a fully suppressed HIV viral load, suggesting that low CD4 cell counts were not associated with inadequate HIV treatment. Additional studies are warranted to better understand the mechanisms underlying this finding. The subpopulation of those with chronically low CD4 cell counts may have more immune activation and therefore may be

an important target group for interventions aimed at reducing inflammation. Furthermore, this finding also suggests that initiating HIV therapy at a higher CD4 cell count (ie, not letting patients' CD4 cell counts fall below 200 cells/mm3) may mitigate fracture risk.

Finally, it is important to point out the effect of various medications on fracture risk. Although this study showed no association between specific HIV medications (tenofovir, protease inhibitors [PIs], and efavirenz) and fracture, an increased risk was demonstrated with two non-HIV medications (corticosteroids and antiepileptic drugs). Although neither of these findings is unexpected, it is worthwhile to highlight these associations in HIV-infected populations.

In particular, the association between antiepileptic drugs and fracture risk was notable, as these agents generally were not prescribed for epilepsy, but for peripheral neuropathy — a condition with a high prevalence among HIV-infected populations, particularly those exposed to older nucleoside reverse transcriptase inhibitors (NRTIs). Although some anti-epileptic drugs have known effects on bone metabolism, mediated in part by their effect on vitamin D, it is also possible that peripheral neuropathy itself, rather than the agents used to treat it, contributed to this increased risk for fracture, given the established association between lower extremity peripheral neuropathy and falls in the general population. Further investigation is needed to unravel these complex associations.

In summary, this study highlights several potentially modifiable risk factors associated with the clinically relevant endpoint of fracture in HIV-infected persons and has important implications for fracture risk reduction.

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EFFECT OF SPECIFIC ANTIRETROVIRAL MEDICATIONS ON BONE MINERAL DENSITY AND FRACTURES

McComsey GA, Kitch D, Daar ES, et al. **Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG A5202**. J Infect Dis. 2011;203(12):1791-1801.

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The initiation of ART has consistently been associated with a ~2-6% loss in BMD, marked by a rapid acceleration of bone turnover. The mechanisms underlying this effect still have to be clarified but are likely attributable to immune reconstitution. Although this bone loss appears to be independent of the ART medications studied, certain ART agents appear to have a greater impact than others. For example, tenofovir (TDF) has been associated with a 1% to 2% increase in bone loss compared with abacavir (ABC) or stavudine (d4T). Certain[1-2] PIs have also been associated with enhanced bone loss, although the effects of specific PIs have not been well described.[3]

In a substudy of a large ART-naïve AIDS Clinical Trials Group (ACTG) trial, McComsey and colleagues reported the bone effects of four different regimens that are commonly used in HIV clinical practice: (1) efavirenz (EFV) + ABC/ lamivudine (3TC); (2) atazanavir/ritonavir (ATV/RTV) + ABC/3TC; (3) EFV + TDF/emtricitabine (FTC); and (4) ATV/RTV + TDF/FTC. In these 269 HIV-infected individuals initiating ART (85% male), those receiving TDF/FTC had a greater loss in spine BMD and hip BMD over 96 weeks than did those treated with ABC/3TC (-3.3% vs -1.3%, respectively; *P*=.004 for spine BMD and -4.0% vs -2.6%, respectively; *P*=.024 for hip BMD). In addition, those who were randomized to ATV/RTV experienced greater bone loss at the spine compared with EFV-treated patients (-3.1% vs. -1.7%, respectively; *P*=.035), but bone loss at the hip was similar and not statistically significant (-3.4% vs -3.1%, respectively; *P*=.61). Although bone loss was nominally greatest in the TDF/FTC + ATV/RTV arm, the test of interaction between the NRTI and the third agent was not statistically significant, arguing against a synergistic effect.

These data add to the growing evidence that TDF has specific negative effects on BMD. Similar to the findings of other studies[1-2], these effects were greatest in the first 48 weeks of treatment and leveled out thereafter. Many questions still remain about the effects of TDF on bone, including:

1. The mechanism: Although abnormalities in phosphate homeostasis have been reported among TDF-treated patients, their link to bone loss has not yet been established.
2. The effect on fracture: While this study showed no difference in fracture risk among the treatment arms, it was not powered to be able to demonstrate a significant effect. The recent Veterans Affairs (VA) study by Bedimo and associates demonstrated a higher risk for fracture in those receiving TDF.[4]
3. Clinical implications: Should TDF be avoided as an initial agent in certain populations at higher risk for fracture? Should treatment with TDF be discontinued in persons with osteoporosis (or other fracture risk factors)? Can the population who will have more pronounced bone loss with TDF be identified by demographic, clinical, biochemical, or genetic markers?

The ATV/RTV versus EFV comparison is novel and noteworthy. Again, questions about the mechanisms, effect on fracture, and clinical implications remain and require elucidation. Also unclear is the extent to which the effect of ATV/RTV is a PI class effect vs a medication-specific effect. Of the PIs examined in the VA study[4], lopinavir (LPV)/RTV was associated with an increased risk for fracture, but exposure to the newer PIs, including ATV/RTV, was relatively limited, so it is difficult to draw firm conclusions. Clearly, additional work is warranted to address the important clinical implications of these findings.

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4. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS*. 2012;26(7):825-831.

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VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

Lai H, Gerstenblith G, Fishman EK, et al. **Vitamin D deficiency is associated with silent coronary artery disease in cardiovascularly asymptomatic African Americans with HIV infection**. *Clin Infect* Dis. 2012; 54(12):1747-1755.

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As in the general population, vitamin D deficiency is common among HIV-infected patients. The health consequences associated with vitamin D deficiency, however, are incompletely understood. Although low vitamin D levels likely contribute to bone loss and fracture risk (at least among the Caucasian, postmenopausal women who represent the bulk of those who have been studied[1-2]), their impact on nonskeletal outcomes is much less clear.

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Vitamin D deficiency has been associated with subclinical cardiovascular disease (CVD) and endothelial dysfunction in the general population. Lai and collaborators investigated the relationship between subclinical CVD (coronary artery stenosis ≥50% by computed tomography angiography) among 674 HIV-infected, African American patients in Baltimore, Maryland. Not surprisingly, a very high prevalence of vitamin D deficiency was reported, with 20% of the participants having 25-hydroxy [25-OH] vitamin D levels <10 ng/mL. Interestingly, those with vitamin D deficiency were more than two-fold more likely to have significant subclinical CVD (OR, 2.28; 95% CI; 1.23 to 4.21) independent of traditional CVD risk factors. The importance of nontypical CVD risk factors in this population was suggested by the finding that almost 80% of those with significant CVD had a Framingham Risk Score of <10% (ie, low risk).

The results from this study suggest that vitamin D deficiency may be a modifiable risk factor for CVD. The study joins a series of others that implicate vitamin D deficiency as a contributor to other adverse health outcomes in HIV-infected patients, including renal disease, diabetes, and mortality.[3-6] Although all of these findings are intriguing, it is quite possible that vitamin D deficiency is a marker of poor health or other factors related to poor health outcomes, rather than an underlying cause. The only way to assess the potential causality of vitamin D in these outcomes is to conduct a vitamin D supplementation trial; the results of the Lai study provide the rationale for this type of vitamin D supplementation study among HIV-infected persons.

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5. Mehta S, Mugusi FM, Spiegelman D, et al. Vitamin D status and its association with morbidity including wasting and opportunistic illnesses in HIV-infected women in Tanzania. *AIDS Patient Care STDS*. 2011;25(10):579-585.

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