Low Bone Mineral Density with Tenofovir: Does Statistically Significant Mean Clinically Significant?

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(See the article by Stellbrink et al, on pages 963–972.)

Adults with human immunodeficiency (HIV) infection appear to have a greater prevalence of low bone mineral density (BMD) and of fractures than do adults without HIV infection [1,2]. HIV infection itself may contribute to this greater prevalence. HIV induces inflammation (a known association with accelerated BMD loss), and low BMD has been reported in individuals with untreated HIV infection [1, 3]. The use of particular antiretroviral drugs appears to be a contributing factor. Of those drugs that are in common use today, the nucleotide reverse-transcriptase inhibitor tenofovir and various HIV protease inhibitors have been shown to lower BMD in randomized trials [4, 5]. Furthermore, BMD was found to increase initially with cessation of antiretroviral therapy, relative to BMD in patients with continuous therapy [6].

In a randomized, placebo-controlled trial, the ASSERT investigators assigned antiretroviral-naive adults to commence efavirenz therapy in combination with tenofovir-emtricitabine or abacavir-lamivudine. In this issue of Clinical Infectious Diseases, the ASSERT investigators present data regarding changes over a 48-week period in BMD and in markers of bone mineral turnover [7]. With use of the standard technique of dual-energy x-ray absorptiometry (DXA), it was found that BMD at both the hip and the spine decreased over 48 weeks. The decrease in hip BMD was ongoing through week 48, but the spine BMD decrease appeared maximal at week 24.

Given the data from 2 previous randomized trials [4, 5], it was not surprising that tenofovir was associated with a greater decrease in BMD than was abacavir. Surprisingly, abacavir was also associated with a decrease in BMD. In the Simplification with Tenofovir-Emtricitabine or Abacavir-Lamivudine (STEAL) study, in which patients who were receiving antiretroviral therapy and who had undetectable plasma HIV loads were randomly assigned to receive either tenofovir-emtricitabine or abacavir-lamivudine, tenofovir lowered BMD, but abacavir was associated with increased BMD [8].

No study has identified risk factors for BMD loss with any antiretroviral drug. The ASSERT study sheds some welcome light on this issue. Participants were significantly more likely to experience greater BMD loss at both hip and spine if they had lower baseline body mass index at baseline and were of non-Black race, and they were more likely to experience greater spine BMD loss if they were >45 years of age. Unfortunately, the relative risk associated with each of these parameters was not stated, so it is unclear whether statistically significant also means clinically significant.

Only data through week 48 were reported. Previous longer studies of tenofovir have found that BMD loss generally stabilized by week 48, but all of these studies had relatively high drop-out rates beyond week 48. In contrast, the SMART study [6] found that BMD loss appeared to continue beyond the first year of continuous antiretroviral therapy and at a rate that was higher (0.8% per year at the hip) than that in a healthy control population of similar age (0.19% per year at the hip), but similar to that observed among postmenopausal women (0.79%) [9]. Long-term BMD data from the ASSERT study are essential.

The ASSERT study provides the first prospective data on markers of bone mineral turnover in HIV-infected patients who initiate antiretroviral therapy. These markers all increased at week 12 of therapy, and their changes correlated significantly with BMD changes at week 48. It is unclear, however, whether identification of these changes in bone turnover markers
was clinically useful, because the authors do not report whether early change in any marker predicted BMD loss. All markers, both of bone formation and bone resorption, had increased significantly by week 12, so it remains unknown whether tenofovir increases bone resorption or bone formation (with a compensatory change in the other). Future studies of bone turnover markers should evaluate earlier time points to address this possibility. Of possible relevance, only bone formation was significantly different between the groups at week 48, which suggests but does not prove that tenofovir is primarily reducing new bone formation.

The ASSERT data have additional limitations. Only 20% of the patients were male, which limited the study's capacity to determine whether BMD loss differed between men and women. Second, ~30% of participants withdrew from the study (although this was mostly by week 24, which was before the first DXA assessment, and so it is unlikely that BMD differences contributed to these drop-outs). Third, the virological response rate in the ASSERT study, as in another comparative trial [5], was lower for those who received abacavir [10]. Given the results of the SMART study, it is possible that lower virological suppression with abacavir may have resulted in higher BMD, but the findings of the Gilead 903 study, in which stavudine had similar virologic activity to tenofovir but caused less BMD loss, argue against this possibility [4]. The investigators did not evaluate sex hormone or vitamin D deficiency as potential contributors to BMD loss, particularly because efavirenz was also used in the ASSERT study and has been associated with vitamin deficiency [11]. Of course, in addition, the study was too small and too brief to assess fracture rates.

The clinical value of the ASSERT data is uncertain. The authors report the proportion of participants in each group who experienced a BMD decrease >6%, which is the recognized between-test variability of DXA. However, the proportion of participants who developed osteopenia (BMD, 1.5–2.5 standard deviations [SDs] lower than the mean value for young adults of the same sex and race) or osteoporosis (at least 2.5 SDs lower) was not reported. Even more useful would have been to report the proportion in each group who, by virtue not only of BMD but also of other fracture risk factors (including age, sex, alcohol consumption, and smoking status), were at sufficient risk to merit antiresorptive therapy according to guidelines from the National Osteoporosis Foundation [12].

How should clinicians respond to the BMD data from the ASSERT study and other studies that implicate tenofovir in BMD loss? It is becoming our (unvalidated) practice to measure BMD before the initiation of tenofovir therapy and again ~12 months later; the ASSERT data suggest that older, non-Black, lean adults are at greater risk than others and, therefore, may particularly merit assessment. We also assess fracture risk, because some patients without osteoporosis but with multiple other fracture risk factors appear to merit antiresorptive therapy [13]: the FRAX tool has been developed by the World Health Organization to permit estimation of fracture risk on the basis of 9 readily determined clinical parameters (eg, age) and hip BMD—a Framingham equation for bones [14].

There are no data to suggest that patients who are at higher risk of fracture should not receive tenofovir, but alternatives should perhaps be considered for those with previous fractures after minimal trauma or with known osteoporosis. Lastly, markers of bone turnover should continue to be studied in clinical trials but cannot be recommended for clinical use at this time. Additional bone marker data may shed light on the pathogenesis of BMD loss associated with tenofovir use and lead to appropriate interventions to prevent BMD loss in tenofovir recipients at higher risk.

BMD and fractures are likely to become secondary end points of increasing interest in future clinical trials, especially with the trend to earlier initiation of antiretroviral therapy and the similar antiviral efficacy rates of current preferred antiretroviral regimens [15]. To generate clinically useful BMD and fracture data, such trials will need to be larger and longer, will need to enroll patients with intermediate or high risk for bone loss, and should report clinically relevant end points. Future randomized studies, such as the START trial (ClinicalTrials.gov identifier NCT00867048) will provide much needed BMD and fracture data as to whether earlier antiretroviral initiation—and consequent earlier suppression of HIV replication—accelerates BMD loss or increases fracture risk.

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