Research

HIV and Osteoporosis

By Samantha Reiss

Results from recently conducted research indicate the development of both osteopenia and osteoporosis in individuals living with Human Immunodeficiency Virus (HIV). Data suggesting this correlation are in the beginning stages of research, and the etiology of bone loss in patients living with HIV has only recently been studied along with potential origins in the medications used to treat the infection. Surveying the available data has allowed for the knowledge of various differential pathogenesis and the beginnings of more specified testing. The goal of such testing is to detect the causative agents of substantial bone loss in HIV patients.

Studies finding correlations between HIV-infection and bone mineral density (BMD) loss cumulatively support the connection. One study conducted by Triant et al. involved 8,525 HIV-infected individuals and 2,208,792 uninfected individuals and found a two to four times higher prevalence of bone fracture among those infected with HIV.[1] Other studies done by Young et al., using data from the HIV Outpatient Study (HOPS)[2], the Veterans Aging Cohort Study Virtual Cohort (VASC-VC)[3], and the Women's Interagency HIV Study (WIHS)[4], maintain this correlation. The WIHS study by Sharma et al. found that infected women (median age of 40) had a fracture rate of 2.19/100 person-years while women who were uninfected (median age of 35) had a rate of 1.54/100. Although data have established a definite correlation between HIV infection and bone mineral density loss, the causes of such correlation are multifactorial and indicate differential pathogenesis.

HIV, or Human Immunodeficiency Virus, is a retrovirus typically spread by the transference of bodily fluids from one infected person to another. The disease is commonly transmitted through sexual contact and the sharing of needles or drug injection equipment. The virus deteriorates the body's response to infection by attacking the immune system. The mechanism by which the virus attacks CD4 T-cells uses the enzyme reverse transcriptase to generate a complementary DNA of the virus's RNA and attaches it to the DNA of the host cell. The virus then spreads and kills the CD4 T-cells and impedes the body's ability to fight against infection. If left untreated, HIV progresses into the late stage of the virus, acquired immunodeficiency syndrome (AIDS). Since the beginning of the HIV/AIDS epidemic, 35 million people have died and 1.2 million people are living with the virus today[5,6].

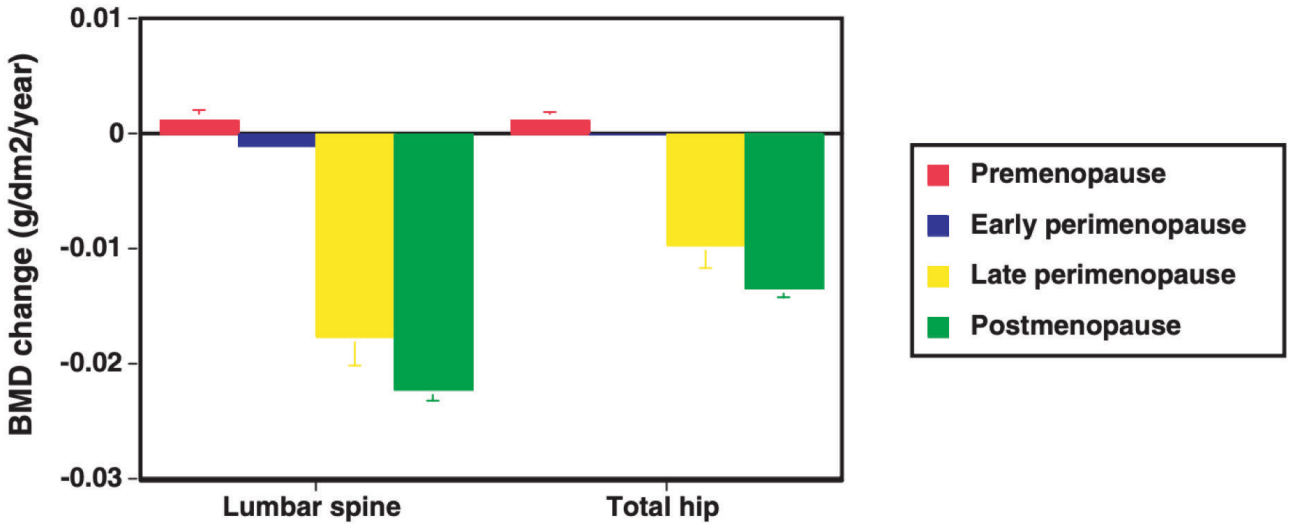
There is no cure for HIV, but combination antiretroviral therapy (cART) is recommended for individuals with detectable viremia regardless of CD4 cell count for reduction of possible transmission, progression of the disease, and improved overall health. These medications include a regimen of nucleoside reverse transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors (InSTI)[7]. Intervention by the specific cART medication, tenofovir disoproxil fumarate (TDF), has the most significant elevated ranges for bone mineral density loss when compared to other cART medications. TDF is commonly recommended for use as a preexposure prophylaxis to prevent infection. People living with HIV are at a higher risk of both osteoporosis and osteopenia due to viremia and cART medication side effects.

Osteoporosis and osteopenia are similar in that they are diseases defined by bone mineral density loss. Osteopenia is diagnosed by using a dual-energy X-ray absorptiometry (DEXA) to detect below-average T-scores of -1.0 to -2.5. Comparatively, osteoporosis is a more severe diagnosis indicating the weakening of bone strength due to bone mineral density loss and a low T-score of -2.5 or below. DEXA scans measure bone mineral density at the femoral neck or lumbar spine to assess the risk of osteopenia and osteoporosis using T-scores. The World Health Organization criteria then delegates the T-score resulting from these scans to a corresponding osteoporosis or osteopenia diagnosis. Bone mineral density loss is most often caused by a decrease in estrogen levels due to menopause, calcium deficiencies, and/or viremia. Postmenopausal women were reported to experience rates of 0.022 g/cm^2·yr (2.0%) bone mineral loss in the spine and 0.013 g/cm^2·yr (1.4%) in the hip (Figure 1). Using these data to compare rates of bone mineral loss in HIV patients during their first 1-2 years using cART, a rate of 2% to 6% bone mineral loss was found[9]. Further data correlating HIV as a pathogenesis factor for osteoporosis and osteopenia have been reported in studies, due to both viremia and mediation by cART medications.

Osteoporosis and osteopenia have an etiology in HIV patients due to both viremia as well as cART medications. HIV infection itself has significant effects on bone mineral density due to inflammation impeding bone formation and increasing osteoclastic activity. Bone remodeling is a process in which mineralized bone is removed by osteoclasts, cell-types responsible for bone resorption, and is replaced by bone matrices formed by osteoblasts.

Regulation of bone remodeling preserves skeletal integrity by ensuring proper function of osteoclasts and osteoblasts. Such regulators include "growth hormone, glucocorticoids, thyroid hormones, and sex hormones, [as well as] factors such as insulin-like growth factors (IGFs), prostaglandins, tumor growth factor-beta (TGF-beta), bone morphogenetic proteins (BMP), and cytokines."[10] HIV proteins have been found to increase osteoclastic resorption of bone and induce osteoblastic apoptosis. The GP120 molecule of HIV promotes bone loss by upregulating RANKL, a protein that supports the development and function of osteoclasts. The molecule has also been found to "increase the rate of apoptosis in primary osteoblasts."[11] HIV proteins also induce systemic inflammation by increasing levels of cytokines and tumor necrosis factor, both of which promote osteoclastic activity. Bone mineral density loss has a multifactorial etiology in HIV-infected individuals, and viremia itself contributes to this phenomenon.

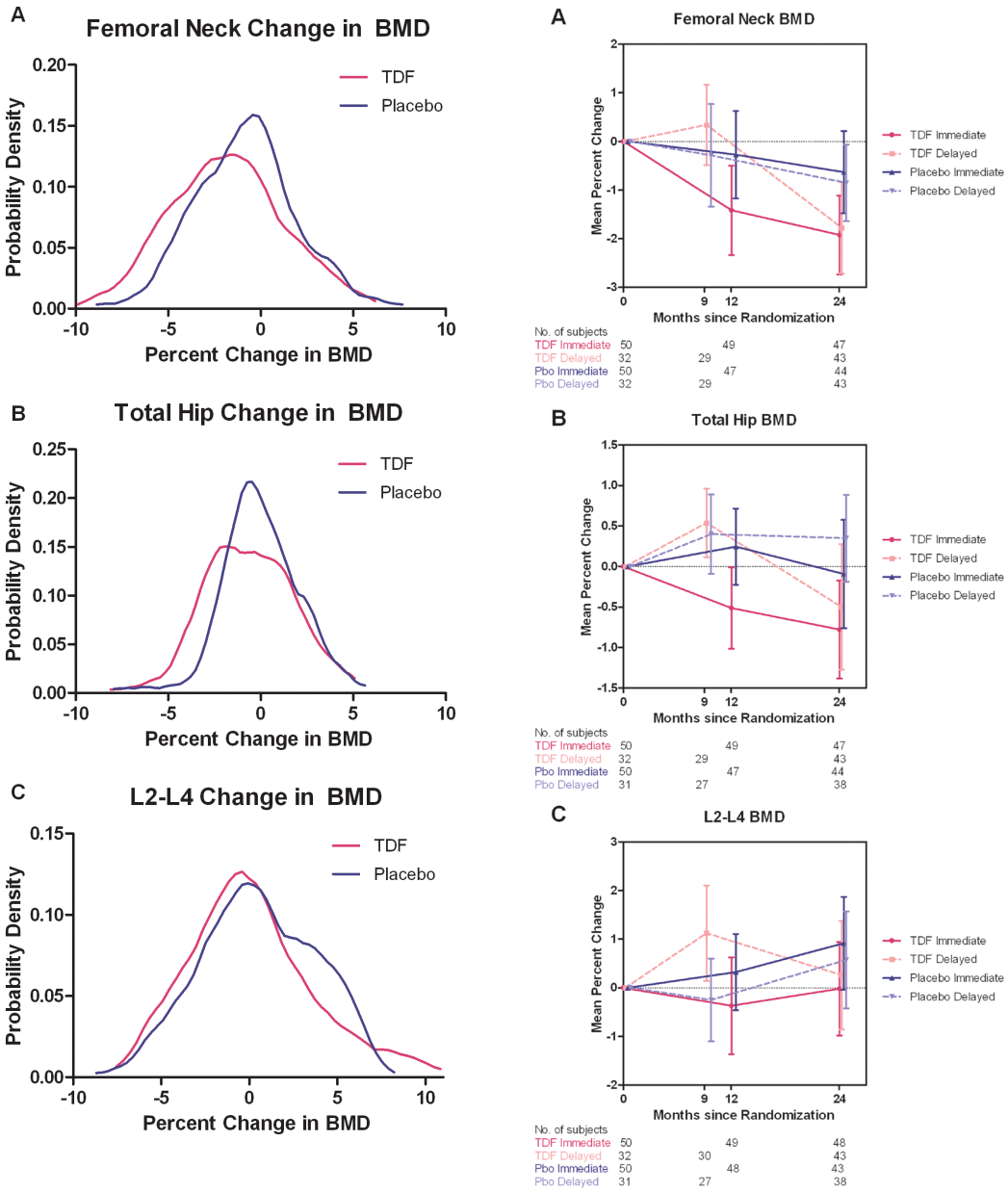
Figure 1



Source: Finkelstein, Joel S., et al. "Bone Mineral Density Changes during the Menopause Transition in a Multiethnic Cohort of Women." Obstetrical & Gynecological Survey, vol. 63, no. 7, 2008, pp. 442–444., https://doi.org/10.1097/01.ogx.0000325504.51681.10.

Figures 2 & 3

Source: Liu, Albert Y., et al. "Bone Mineral Density in HIV-Negative Men Participating in a Tenofovir Pre-Exposure Prophylaxis Randomized Clinical Trial in San Francisco." PLoS ONE, vol. 6, no. 8, 2011, https://doi.org/10.1371/journal.pone.0023688.



Antiretroviral therapies (ART) include a variety of medications and regimes enacted to treat HIV infection. Patients who use ART are given medications such as tenofovir disoproxil fumarate (TDF), protease inhibitors, and the more recently developed tenofovir alafenamide (TAF). TDF is most associated with significant bone mineral density loss in clinical trials. In a randomized control trial conducted in San Francisco by Liu et Al., 210 HIV-uninfected men were divided into two groups. The first group was given TDF, and the other control group was prescribed a placebo. Results of the trial found that 13% of the TDF group experienced >5% bone mineral density loss at the femoral neck compared to 6% loss within the placebo group. The study concluded that TDF use resulted in "a small but statistically significant decline in BMD at the total hip and femoral neck"[11] (figures 2 & 3). Another study conducted by Tiwari & Patel observed the effects of ART on 124 HIV-positive individuals and 64 HIV-negative individuals to ascertain the correlation of osteoporosis with CD4 counts (a clinical indicator of HIV). Among the HIV-infected individuals on ART, 45.7% showed normal bone mineral density, while the other 44.3% had reduced BMD12. Overall, the two studies indicate strong correlations between the presence of the cART medications (specifically TDF) and subsequent decreases in bone mineral density. There is evidence to suggest etiology of osteoporosis in HIV patients is derived from the intervention of antiretroviral therapy drugs.

Data from clinical trials and research studies conclude a strong correlation between HIV-infection and the onset of osteoporosis and osteopenia. Locating the etiology of such a correlation has been more difficult and needs more testing. Differential etiologies such as viremia and combined antiretroviral therapies are two accepted causative agents of bone mineral density loss in HIV-infected individuals. HIV protein molecules like GP120 initiate inflammation and excessive bone remodeling, demonstrating that viremia is one of these causative agents. Similarly, the onset of bone mineral density loss and the heightened rates of low DEXA scores by patients using TDF support cART medications as another possible etiology.

Scan to View Citations