Deciphering how HIV-1 weakens and cracks the bone

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Journal Title: Proceedings of the National Academy of Sciences
Volume: Volume 115, Number 11
Publisher: National Academy of Sciences | 2018-03-13, Pages 2551-2553
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1073/pnas.1801555115
Permanent URL: https://pid.emory.edu/ark:/25593/v160j

Final published version: http://dx.doi.org/10.1073/pnas.1801555115

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Accessed December 27, 2019 12:05 PM EST
Deciphering how HIV-1 weakens and cracks the bone

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Globally, life expectancy for HIV-infected individuals is increasing and many are living into their old age, largely due to the success and increased use of combination antiretroviral therapy (cART) (1). Among the debilitating features of aging are the development of osteoporosis and loss of immune competence (2). Notably, both osteoporosis and immune compromise are also features of HIV infection, fueling speculations that HIV may lead to a form of premature aging. In fact, over half of HIV-infected individuals exhibit some degree of clinically appreciable bone loss (3). The skeletal effects of HIV infection are further compounded by additional bone mineral density (BMD) loss at fracture-prone anatomical sites mostly within 48 wk of cART initiation (4). The clinical significance of HIV bone loss was for long unappreciated and evidence for a higher fracture rate in HIV-infected individuals relative to the general population has until recently been anecdotal. However, a series of large observational studies have now unambiguously shown a dramatic rise in fracture rate with HIV infection that is particularly pronounced with advancing age. Overall, fracture rate with HIV infection is two- to sixfold higher than the general population (5, 6), and hip fracture risk ninefold higher has been reported (7). These data forewarn of a looming epidemic of fragility fracture in the aging HIV population and provide a compelling rational to explore in greater depth the pathophysiology of this phenomenon, to inform the search for effective preventive and therapeutic strategies. In PNAS, Raynaud-Messina et al. (8) make significant inroads into this quest, adding to our current understanding of the mechanisms of HIV-induced bone loss. They demonstrate for the first time that HIV-1 is capable of infecting the bone resorbing cell, the osteoclast, thereby directly modifying the structure and the function of the osteoclasts bone resorption apparatus, known as the "sealing zone" (SZ), leading to enhanced adhesion and osteolytic activity.

To put these findings in context and to better appreciate the cellular and molecular events of bone homeostasis, one must recognize that the skeleton is a dynamic organ that is continually renewed by the coordinated removal of worn out bone by osteoclasts and the deposition of new bone by osteoblasts, the cells responsible for bone formation (9). While osteoblasts develop primarily from cells of mesenchymal origin, the precursors of osteoclasts derive from cells of the immune system, specifically those of monocytic lineage.

Under the influence of the key osteoclastogenic cytokine, receptor activator of NF-κB ligand (RANKL), and the presence of permissive amount of macrophage colony stimulating factor, monocytes differentiate into osteoclasts. The activity of RANKL is moderated by its physiological decoy receptor osteoprotegerin (OPG) (10). Thus, the ratio of RANKL to that of OPG in the bone microenvironment is the key determinant of the rate of osteoclast differentiation and consequently of bone resorption in the body. Of note, osteoclastogenesis is further potentiated by other inflammatory cytokines,
including TNF-α and IL-17 that amplify RANKL activity and promote its secretion (11).

It is now evident that skeletal health is strongly influenced by the immune system, a consequence of deep integration and centralization of common cell types and cytokine mediators, which is now referred to as the “immuno-skeletal interface” (ISI). Not only are osteoclast precursors derived from cells of mononuclear lineage, but under inflammatory conditions, such as rheumatoid arthritis, periodontitis, and during estrogen deficiency, activated B and T lymphocytes secrete osteoclastogenic cytokines, including RANKL, TNF-α, and the RANKL-independent osteoclastogenic factor, secreted osteoclastogenic factor of activated T cells (12).

Furthermore, B cells are a major source of OPG, the key regulator of RANKL, and B cell OPG production is sustained by interactions with T cells, in part via CD40:CD40 ligand (CD40L) costimulation (13, 14). Thus, under basal conditions, B cells act as critical stabilizers of peak BMD, and animal models of B cell deficiency, T cell deficiency, and CD40 and CD40L deficiency display diminished B cell OPG production and severe bone loss (15).

Although CD4 T cell depletion is the hallmark of HIV infection, the humoral immune response is also markedly denuded, with significant depletion in resting memory B cells, along with a concomitant increase in activated and exhausted memory B cell populations and an increase in the frequency of immature/transitional B cells (16).

Given these observations, it has been proposed that HIV infection could disrupt the ISI and adversely impact bone health. Consequently, our group recently investigated RANKL and OPG cellular kinetics in animals (using the HIV-transgenic rats) and in clinical studies in HIV-infected individuals. As predicted, we observed marked elevation in RANKL production concurrent with a marked depletion in OPG production by B cells in the setting of HIV infection. This alteration in B cell secretory function led to a significant elevation in RANKL/OPG ratio, resulting in enhanced bone resorption with marked reduction in BMD at key fracture-prone sites in both the animal model and human subjects (17, 18).

Chakravarti et al. (19) similarly reported that serum OPG concentrations are diminished in HIV-infected patients and speculated that human peripheral blood T cells may also be a potential source of OPG. Interestingly, they noted that treatment of peripheral blood CD4 T cells in vitro with the HIV-1 gp120 caused a decline in T cell OPG production. In subsequent studies, our group confirmed these findings in vivo in HIV-infected patients, demonstrating that similar to B cells, T cells are also a source of OPG in humans, and that HIV infection leads to a marked reduction in T cell OPG production and an increase in the T cell RANKL/OPG ratio that correlated significantly with BMD z-scores in the hip and lumbar spine in HIV-infected patients with CD4 T cell counts ≥ 200, concurrent with increases in T cell RANKL production (20). Another central cytokine involved in the ISI is IFN-γ. Under inflammatory conditions, IFN-γ promotes bone loss by up-regulating the activity of antigen-presenting cells (especially macrophages), leading to T cell activation and osteoclastogenic cytokine production (21). Taken together, these data suggest that

HIV-induced disruption of the ISI acts indirectly via alteration in immune cellular secretion of key osteoclastogenic regulatory factors to accelerate bone resorption and promote bone loss.

In addition to the indirect effects of ISI disruption on osteoclastogenesis described above, new findings by Raynaud-Messina et al. (8) in PNAS indicate that HIV-1 also mediates a direct disruptive effect on osteoclast structure and function. Using in vivo humanized mice and ex vivo human joint tissue, the authors demonstrate that osteoclast precursors can be directly infected with HIV-1 and that osteoclast precursor infection occurs at different stages of osteoclastogenesis, either via cell-free viruses or more efficiently by transfer from infected T cells.

Raynaud-Messina et al. provide the first direct evidence of osteoclasts as a reservoir for the HIV virus and of the direct damaging effects of HIV infection on the bone’s resorption machinery.

HIV-1-infected osteoclast precursors display enhanced migratory ability and thus have enhanced ability to recruit and concentrate in the bones. Importantly, the authors show that infection of osteoclasts by HIV-1 disrupts the structure and function of the SZ, the resorption apparatus of the osteoclast. Not only is the size of the SZ increased, their ability to secrete tartrate-resistant acidic phosphatase, demineralize, and degrade larger bone areas is enhanced. Furthermore, there is enlargement of the SZ podosomes, the structure involved in cell adhesion, mechanosensing, and cell migration. The net effects of these changes are enhanced adhesion and osteolytic activities of human osteoclasts with a consequent increase in bone degradation. These bone effects of HIV-1 were shown to be mediated by the viral protein, Nef, partly through the activation of Src, a regulator of the podosomes and of their assembly into the SZ.

Raynaud-Messina et al. provide the first direct evidence of osteoclasts as a reservoir for the HIV virus and of the direct damaging effects of HIV infection on the bone’s resorption machinery.

Although, the findings by Raynaud-Messina et al. (8) need to be validated in clinical studies involving HIV-infected participants, the significance of this and other related work cannot be overstated. With expanding uptake of CART, lifespan with HIV infection is expected to continue to increase and age-related comorbidities, including fragility bone disease (osteoporosis and fractures), will continue to rise. There are reasons to be concerned that age-related bone loss will synergize with HIV-induced skeletal assault to precipitate an epidemic of fracture in the aging HIV population. A clearer understanding of the pathophysiology of the HIV bone effects is therefore warranted to aid in constructing effective remedies. Based on emerging data, such efforts can now reasonably be targeted, either at mitigating the impact of HIV-1 on the ISI or purging/protecting osteoclasts from direct viral invasion and disruption. HIV-1 disruption of osteoclastogenesis either indirectly via alterations in the ISI or directly through infection of osteoclasts is represented in Fig. 1 (8, 18).

20 Titanji KVA, et al. (February 8, 2018) T cell RANKL/OPG imbalance is associated with HIV-induced bone loss in patients with higher CD4+ T cell counts. AIDS, 10.1097/QAD.0000000000001764.