

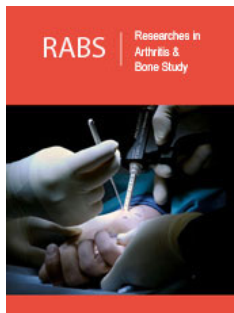
Bone Health in People Living with HIV (PLWHIV): A Growing Concern

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Opinion

One of the biggest successes in HIV medicine over the past 30 years is the significant advancements and safety in Combined Antiretroviral Therapy (cART) which in turn has led to a significant increase in the life expectancy of people living with PLWHIV. However, this in turn has led to an increased risk of other co-morbidities like diabetes, hypertension and osteoporosis which is increasingly important to further manage as this cohort ages. Fracture and osteoporosis in PLWHIV is associated with distinctive features. It can and does occur approximately ten years earlier than in HIV-negative counterparts whereby HIV itself is now recognized as an independent risk factor for bone loss. In addition, certain cART medications may increase the risk of osteoporosis, particularly Tenofovir Disoproxil Fumarate (TDF), and by the presence of co-infections such as Hepatitis B (HBV) Hepatitis C Virus (HCV) which in turn significantly increase the likelihood of osteoporosis and bone fractures [1,2].

The pathophysiology of osteoporosis is complex and involves different factors. HIV infection has a state of increased immune activation and inflammation which can lead to impaired bone formation and enhanced resorption. Moreover, cART, whilst clearly lifesaving can contribute to bone demineralization, especially regimens involving TDF. Endocrine and metabolic disturbances are also more prevalent in this population. Women living with HIV often experience early menopause, a condition strongly linked to bone density reduction [3]. The risk of developing diabetes, metabolic syndrome and lipodystrophy is high in HIV infection and these can also increase risk of osteoporosis. These conditions may also increase the risk of developing hypogonadism, or this can be risk due to HIV per se. Furthermore, HIV can also negatively affect the function of the thyroid, adrenal, and pituitary glands, all of which play roles in bone metabolism [4].

Traditional risk factors are important, including low Body Mass Index (BMI), malnutrition, aging, low physical activity levels, and smoking also remain relevant. These are potentially modifiable risk factors and a dedicated metabolic clinic may help PLWHIV to deal with these issues [5]. Additionally, co-infection with HCV is a major concern, as it is associated with compounded risk factors such as liver dysfunction and systemic inflammation, both of which further impair bone health [6]. These overlapping risk elements underscore the need and facilitation for tailored assessment and management strategies in PLWHIV. Assessment of osteoporosis in PLWHIV involves measurement of Bone Mineral Density (BMD) using Dual-Energy X-ray Absorptiometry (DEXA) scans. The Fracture Risk Assessment Tool (FRAX) is also commonly used to estimate fracture risk, although it may underpredict risk in PLWHIV due

to its lack of consideration for HIV- specific factors. Management of osteoporosis in PLWHIV is centered around bisphosphonates, which are the current recommended first-line therapies. Among these compounds, intravenous Zoledronic Acid is particularly effective, demonstrating sustained improvements in BMD at both the lumbar spine and hip for up to five years after administration. The safety profile of bisphosphonates in PLWHIV is comparable to that in the general population, with no evidence of increased risk for osteonecrosis of the jaw or atypical femoral fractures. Calcium and vitamin D supplementation is a routine part of monitoring, treatment and prevention protocols [1,2].

Alternative therapies such as denosumab and teriparatide have shown some promise in case reports and small cohort studies but require further validation in larger clinical trials. There is currently no robust data supporting the use of newer agents such as abaloparatide and romosozumab in PLWHIV. In terms of cART, switching from TDF to less bone-toxic alternatives like Tenofovir Alafenamide (TAF) may mitigate bone loss; however, combining such switches with bisphosphonate therapy may offer superior protection [1]. Osteoporosis and HIV is an area that need extensive research as research gaps remain. For instance, determining the optimal age for initiating osteoporosis screening in PLWHIV, assessing the efficacy and safety of newer anti-osteoporotic agents in PLWHIV and evaluating the impact of co-infections (e.g. HBV, HCV, and COVID-19) on bone health. Another important area for research potential is role of the gut microbiome and systemic inflammation in HIV-associated bone loss represents a promising

area for future research. Large-scale, well-designed clinical trials are needed to refine treatment strategies and improve outcomes for PLWHIV facing osteoporosis especially in low resource setting countries. Special attention is needed to address holistic need for elderly population LWHIV and osteoporosis [7].

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