

INTRODUCTION

Although the prevalence of HIV infection is gradually decreasing, the numbers of patients living with HIV are increasing which has been attained due to various government program and free antiretroviral therapy (ART).

In India, at present more than 1 million people are living with a various drug regimes provided through ART centers and private set up. Many patients are on ART since more than a decade, which poses typical problems due to longstanding HIV disease or drugs used for ART. This includes metabolic syndrome, lipodystrophy, bone marrow suppression, nephrotoxicity, cardiomyopathy, metabolic bone diseases and many more.

The major bone lesions detectable in these patients are due to demineralization which includes osteopenia, osteoporosis, osteomalacia, avascular necrosis of neck of femur and very rarely fractures. These bone abnormalities may occur because of HIV disease itself or as a side effect of ART drugs. Studies from western countries showed relation between ART drugs and abnormal bone lesions. However in India nutritional status may also play a role in abnormal bone lesions in addition to side effects of ART drugs. Thus in Indian population, ART may actually improve bone mineral density by improving appetite, decreasing the incidence of vitamin D deficiency.¹

Other risk factors for osteoporosis are gender (women are more susceptible for osteoporosis), age (risk of osteoporosis increases with age), body size (thin person are at greater risk), ethnicity (White and Asian are at highest risk), hormones (low estrogen at menopause and low testosterone in men), low calcium and vitamin D intake, lack of exercise, smoking and alcohol intake and prolong use of certain drugs like glucocorticoids, protease inhibitors, cyclosporine, tacrolimus, heparin, lithium, methotrexate, anticonvulsants and medroxyprogesterone.²

Osteoporosis is estimated to affect 200 million women worldwide and 1 in 3 women and 1 in 5 men over age of 50 years will experience osteoporotic fractures. In a study among Indian women aged 30-60 years from low income groups, BMD at all the skeletal sites were much lower than values reported from developed countries, with a high prevalence of osteopenia (52%) and osteoporosis (29%) thought to be due to inadequate nutrition.³

Meta-analysis showed that, the prevalence of osteoporosis

was 3 times higher among HIV infected patients compared to HIV negative controls. Several studies have shown that BMD decreases by 2% - 6% within the first 2 years of various ART regimens. In a Turkish study osteopenia and osteoporosis were diagnosed in 53.9% and 23.8%, in HIV positive patients. There is an increase in fracture rates in the HIV infected population and it is 30%-70% higher than those among matched uninfected control subjects.⁴

MECHANISMS OF HIV ASSOCIATED OSTEOPENIA/ OSTEOPOROSIS

The pathogenesis of reduced BMD in HIV infected patients is probably multifactorial. The sum of traditional risk factors with HIV infection, and HAART side effects can determine the onset of these bone lesions in HIV infected patients.

DIRECT EFFECT OF HIV ON BONE

Bone might be considered an HIV reservoir where limited blood flow and the particular anatomical structure may also induce a poor antiretroviral drug concentration to tackle the HIV infection. Moreover, the infection of osteoblasts may be closely related to the incomplete refilling of bone lacunae during bone remodelling with subsequent bone loss. The apoptosis process plays a major role in HIV pathogenesis. The loss of CD4 cell is also related to the apoptosis activated by the interaction between HIV gp120 and the CD4 receptor by causing an increase in TNF- α which has direct inhibitory effect on osteoblasts function.^{5,6}

ROLE OF VITAMIN D

Vitamin D deficiency is common in HIV infected patients. Hypovitaminosis D is due to poor dietary intake and effect of ART on vitamin D metabolism.

EFFECT OF ART

HAART has been suspected of influencing bone turnover independently of the bone loss associated with HIV-1 infection itself, although it has been suggested that this effect may be relatively modest in relation to the loss of BMD associated with other established osteoporosis risk factors. Initiation of HAART has been consistently associated with up to a 6% reduction in hip BMD, a common site of fracture, over the first 48-96 weeks of therapy. In a recent meta-analysis of cross-sectional studies, protease inhibitors (PI's) had a higher prevalence of osteoporosis compared to those receiving non protease inhibitor regimens.^{7,8}

In vitro studies have illustrated that protease inhibitors inhibit the 25-hydroxylase and 1- α hydroxylase. The net effect of PIs on vitamin D is a reduction in the production of the active form of vitamin D 1, 25(OH)₂D which causes decrease in calcium absorption and decrease in bone density. Also protease inhibitors increase osteoclast activity through the abrogation of a physiological block to RANKL signaling represented by interferon gamma mediated proteosomal degradation of TNF receptor associated factor 6 (TRAF – 6) and also inhibit osteoblastogenesis.⁹

NRTI's inhibit the DNA polymerase the enzyme involved in the replication of mitochondrial DNA, leading to mitochondrial damage and dysfunction, which in turn leads to lactic acidemia and causes osteopenia. There is a calcium hydroxyapatite loss as the bone tries to buffer chronic acidosis and hence osteoporosis.⁹

IN OUR STUDY AT KEM HOSPITAL:

120 subjects in 2 groups were studied (ART naïve, n=60 and ART experienced, N=60). Prevalence of low BMD in HIV positive subjects was 85% (osteopenia and osteoporosis found to be 75% and 10% respectively). The high prevalence of low BMD in our study can be attributed to lower socioeconomic status, malnutrition, vitamin D deficiency and delay in seeking medical care in Indian population.

In ART-naïve group prevalence of osteopenia was seen in 76.7% and osteoporosis in 3.3% whereas in ART-experienced group it was seen in 73.3% and 16.7% respectively. When ART-naïve and ART-experienced group were compared there was no statistically significant change seen in osteopenia (p= 0.12) but osteoporosis was significantly higher in ART-experienced group (p=0.014). Thus bone attrition is seen in HIV positive patients irrespective of ART or no ART. And ART doesn't significantly increase the rate of bone loss in HIV positive patients. This finding is similar to study by C Amiel et al in France which compared BMD in ART naïve and PI based ART experienced group in 81 subjects which concluded that there is no deleterious effect of the ART on BMD but does indicate a decrease in bone density in HIV patients irrespective of the treatment.¹⁰

CONCLUSION

In contrast to studies in western countries, our study demonstrated that bone attrition is seen in HIV positive patients but it is not altered by ART. This difference may be due to nutritional status of Indian population. ART increases appetite which may improve nutritional status hence there is improvement in bone health and ART may deteriorate it. Thus a balance in bone health is maintained in Indian population. Other reason may be the use of different ART regimes in Indian population (NRTI + NNRTI) compared to western countries (NRTI+PI). And as per literature PI is blamed for deterioration of bone health.

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