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HIV and Bone

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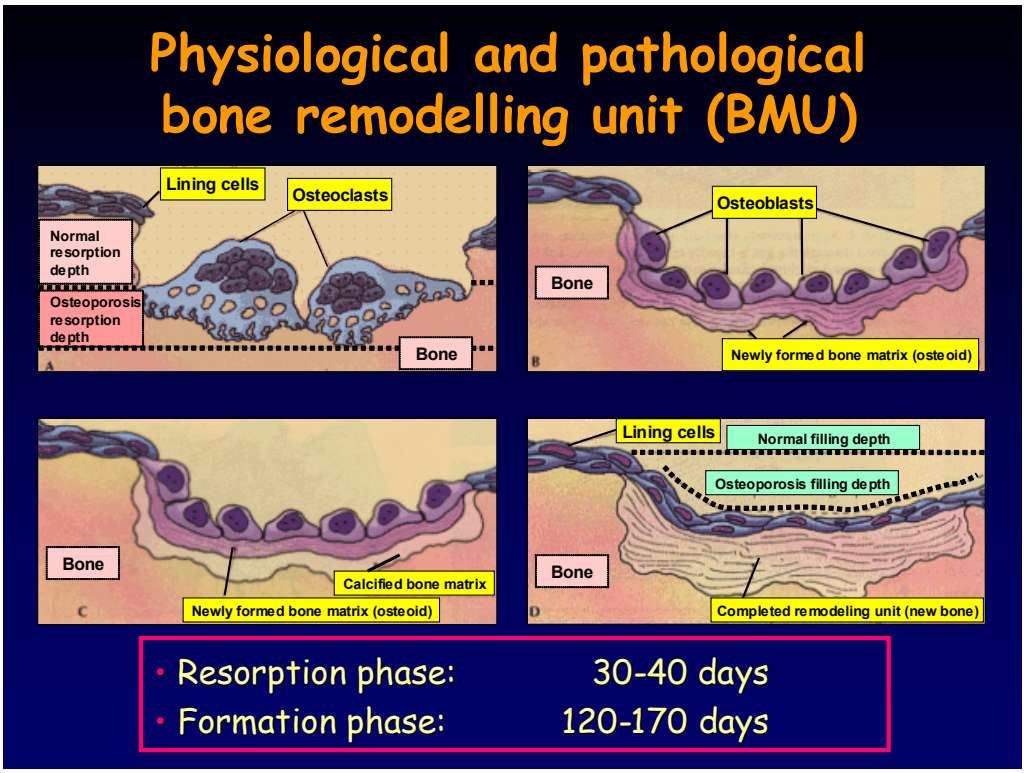
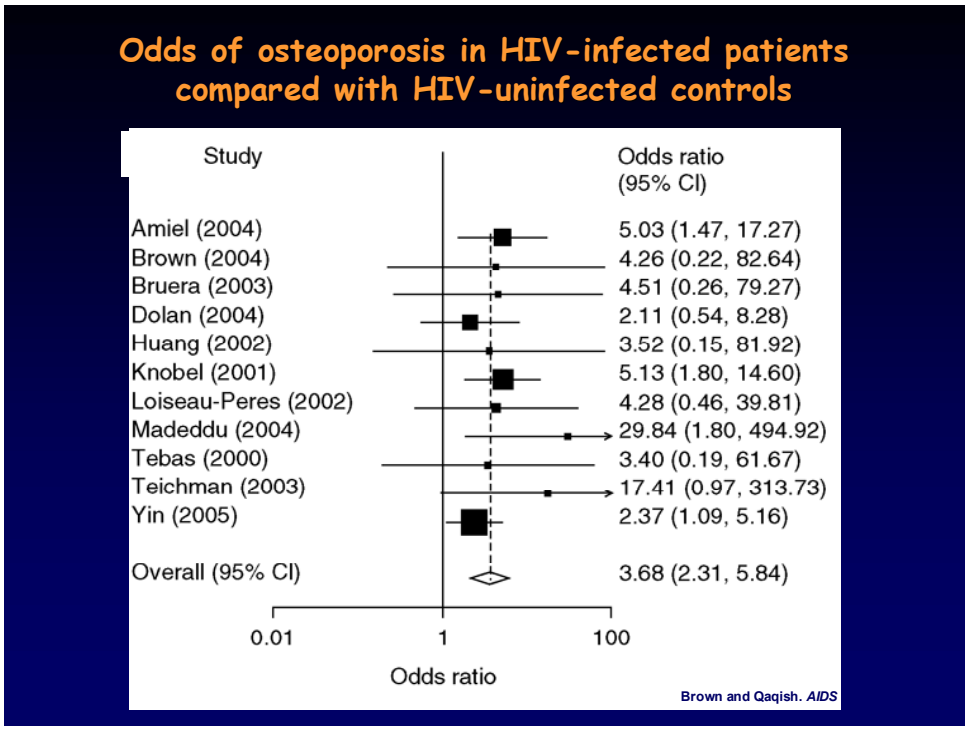
Both osteoblasts and osteoclasts act on bone homeostasis through a continuous remodelling process, necessary both to maintain calcium and phosphates homeostasis and to promote body adaptation to external tensional forces. The bone remodelling process begins with the proliferation and activation of osteoclasts on the bone surface and is controlled by systemic hormones like calcitonin, parathormone or estrogens, and local factors, most of them involved in inflammatory responses such as IL-1, IL-6, TNF-α and prostaglandins. Osteoporosis represents severe derangement of bone tissue and is considered a skeletal disease characterized by low bone mass and bone microarchitectural deterioration with a major increase in bone fragility and fracture susceptibility.

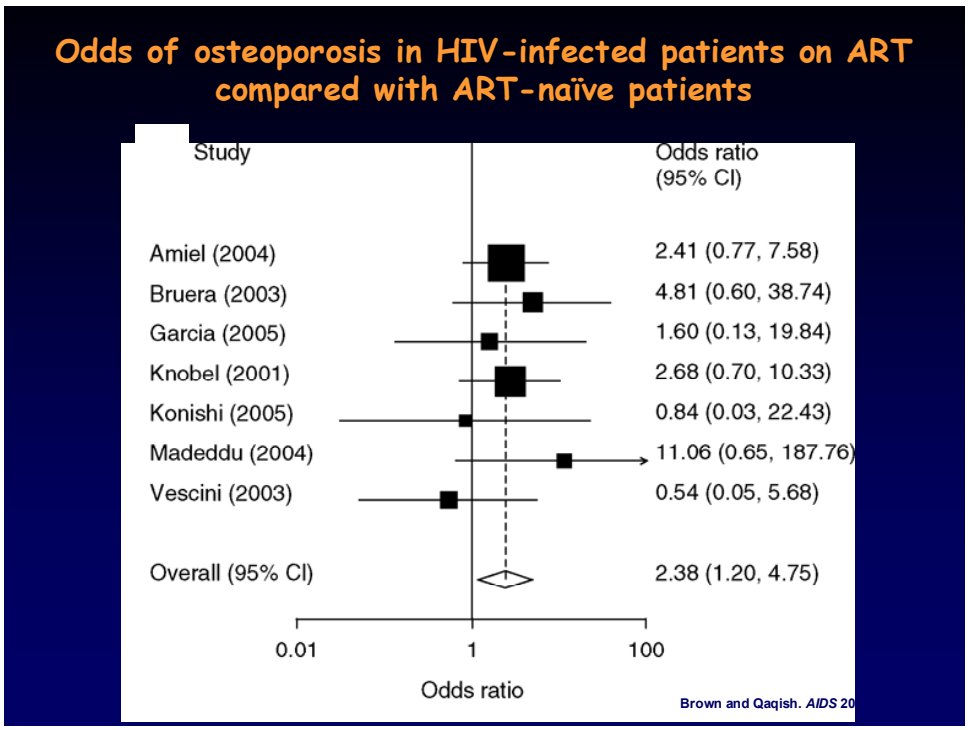


Since the 1990s many papers have reported on bone metabolism changes even in the pre-HAART era and there has always been a suspicion that the virus was the underlying problem. After the advent of HAART the issue became more complicated because on the one hand HIV-infected patients can live longer but on the other they present the side effects of treatment and older age. In addition, the changes in bone metabolism in this context appear to be a side effect of drugs.
The classical review by Brown and Qaqish (Brown

and Qaqish, 2006) shows a metanalysis study of more significant reports published from 1994 to 2005 about HIV/bone interaction where it is clearly demonstrated that the HIV infected naive patients have increased odds of osteopenia (6.4 fold) and osteoporosis (3.2 fold) in comparison with HIV uninfected subjects.



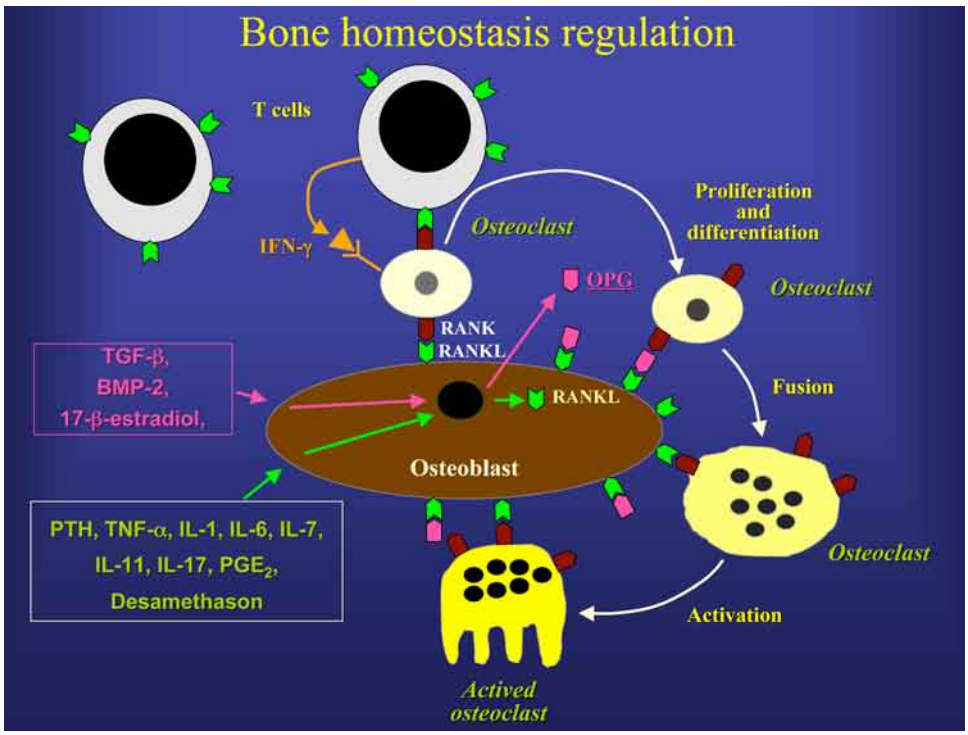
HIV-1, heat-inactivated HIV-1 and recombinant gp120 trigger apoptosis in primary osteoblasts and HOBIT cells, suggesting that HIV-1 does not infect osteoblasts, and that apoptosis induction is related to gp120/cell membrane interaction, resembling a mechanism similar to that already demonstrated in the derangement of haematopoietic CD34+ progenitor cells In addition to the direct role of HIV on osteoblast and osteoclast interaction, HIV has been associated with some risk factors for osteoporosis (Tomazic et al., 2007) such as undernutrition and maladsorption pathologies which can influence levels of vitamin D and calcium (Cashman, 2007), or endocrine complications, such as androgen and estrogen deficiency.



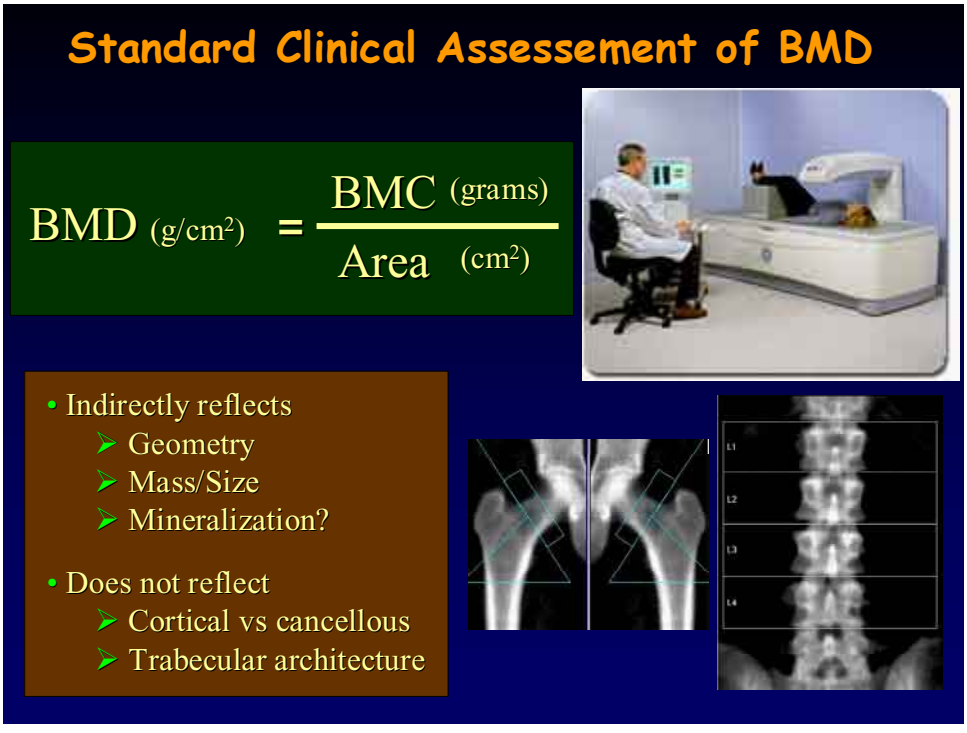
The association between osteopenia and PI emerged in several in vitro models and seems to have a different etiology depending on specific molecule.

A statistical meta-analysis (Brown and Qaqish 2006) demonstrated that the HIV positive HAART treated patients have increased odds (2.4 folds) of osteoporosis in respect to HIV positive naive individuals, and the PI treatment increases the osteoporosis odds 1.6 fold in comparison with patients treated without PIs.

The biological pathway represented by RANKL/RANK/OPG system plays an essential role in bone metabolism control. RANKL is a protein yielded by osteoblasts and T lymphocytes stimulating the differentiation and activity of osteoclasts through the binding with RANK a receptor detectable on osteoclast cell membrane. Its activity is modulated negatively by soluble molecule OPG, which inhibits the RANKL/RANK binding.

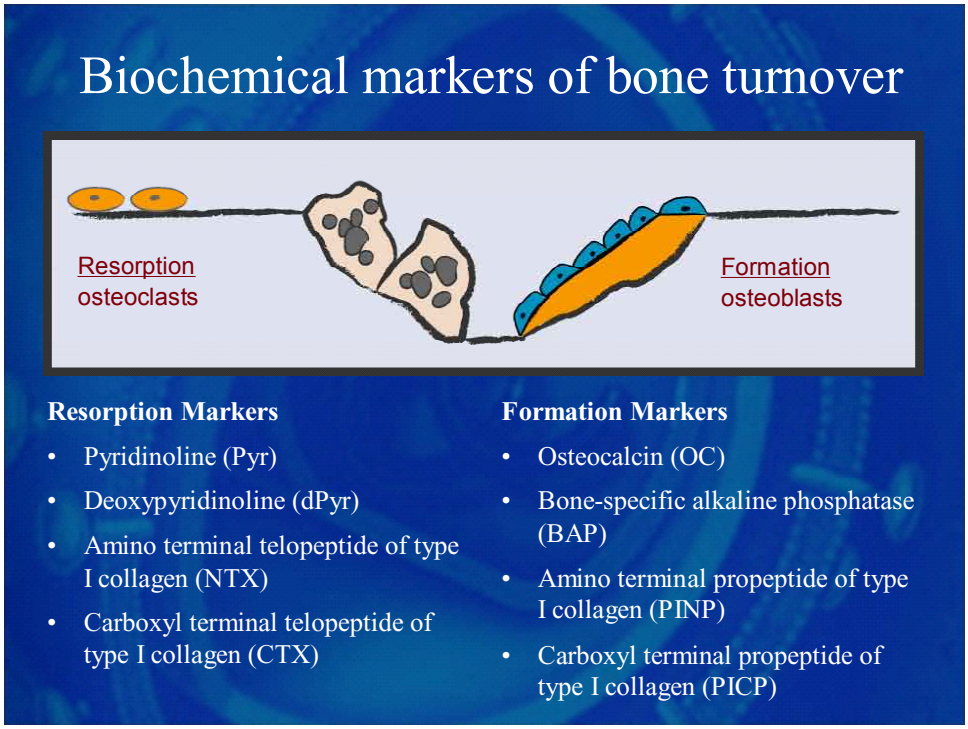


In order to estimate the possible extent of bone changes in patients with HIV infection, five factors need to be considered: a) the phases of bone remodelling (activation>reabsorption>formation) take at least 100 days; b) 10% of the skeleton is continuously being renewed; c) it takes a year for bones to be completely mineralised; d) the skeleton needs a total of eight to ten years for complete renewal; e) from the age of 40 years osteoblast activity is no longer sufficient to replace the bone consumed by osteoclasts, so there is a deficit in the skeletal budget with a loss of bone mass. To disclose the true mechanisms underlying the bone metabolism changes in HIV means analysing all the metabolic problems present in HIV positive patients and understanding the different action and interaction between each drug, and between the drugs and the virus. In addition, we have to consider the cumulative effect of the drugs, the infection and all the additional treatments patients have received during recent years for opportunistic infections or other diseases and coinfections, without disregarding the well known risk factors for osteoporosis in the general population.



The quantitative component of bone strength can easily be evaluated by dual X-ray absorptiometry (DXA) that can measure bone mineral density (BMD), a parameter widely demonstrated to predict fracture risk.

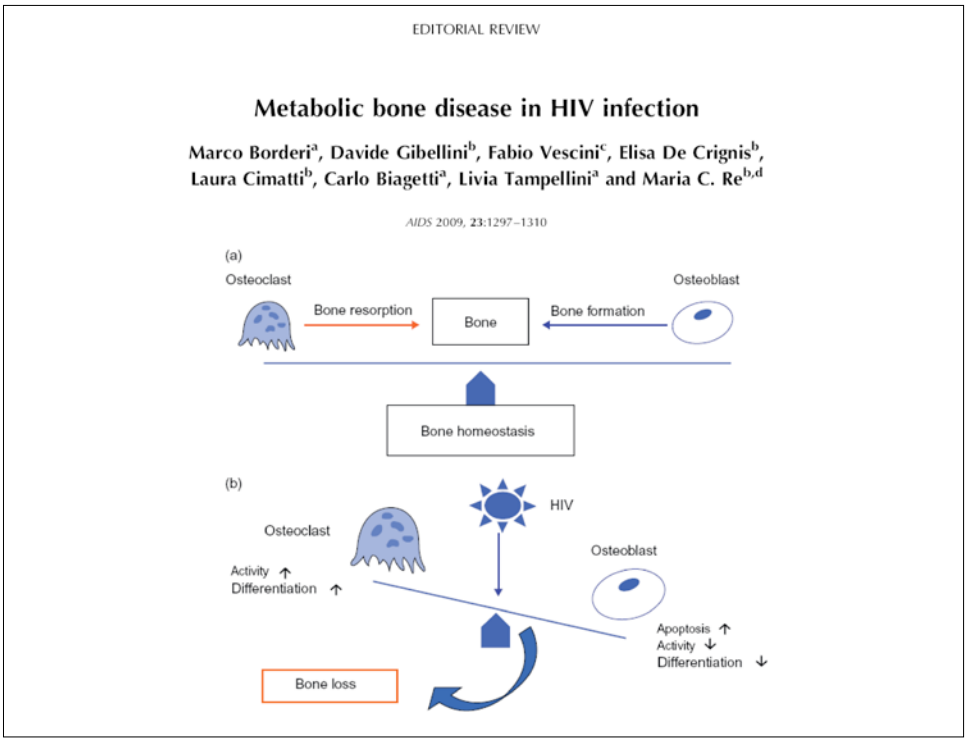
Bone mineral density is a static parameter useful for evaluating the risk of fracture but it does not provide any information on bone turnover, or the pathogenesis and short-term efficacy of drugs. The human skeleton is composed of two different types of bone tissues: cancellous bone comprising around 20% of the total, and cortical bone making up the remainder. Cortical bone is responsible for most support functions, whereas cancellous bone is mainly involved in the maintenance of mineral homeostasis. The recent guidelines devised by the "International Society for Clinical Densitometry" (ISCD) recommend using the T-score with the diagnostic cut-off value specified by the WHO only for women in menopause. Although definitive data are lacking, it is generally accepted that the same method be applied to men over the age of fifty.
For these subjects aged under fifty years, diagnosis is recommended using the Z-score that compares the patient's BMD to that of a healthy age- and sex-matched population. However, the Z-score has no clear cutoff value for osteopenia and osteoporosis and the following scores are recommended: patients with values lower than – 1 are classified as having low bone mass, while a severe bone mass reduction is identified by Z-score values lower than – 2.
Bone turnover is the main bone quality parameter, currently measured by biochemical markers, possibly flanked by traditional x-ray investigation. Bone turnover markers include markers of both bone formation and resorption offering indirect measurements of osteoblastic and osteoclastic activity respectively. Biochemical markers provide a dynamic view of the remodelling process, which covers rate of turnover and pathogenesis, and should improve fracture risk prediction. They can also direct the clinician to alternative diagnoses, since the values deviate excessively from reference levels. Furthermore, they can be used to monitor the short-term effects of therapy, and indicate if an excessive slowing of the remodelling process is occurring. Some studies have demonstrated that bone turnover markers, namely those of bone resorption, serve as a useful tool for fracture risk assessment it is impossible to ignore the utility of bone turnover markers. Considering that they are both easy to obtain and inexpensive, particularly when compared with other not always mandatory examinations, we conclude that the use of bone turnover markers in our clinical practice is justified.



Traditional x-ray examination, by means of lateral views, will disclose any spinal deformities that represent an important predictive factor for the risk of subsequent fractures.
The conclusions reached by the cited studies may appear discordant at a first sight, but some fundamental parameters should be addressed carefully. Some studies were confined to young homosexual men, whereas others involved only women or mixed patients. Results in yet other studies are related to BMI, smoking, calcium intake and other risk factors for osteopenia, but this is not always the case, preventing a comparison among studies. In addition not all studied investigated bone turnover. We can therefore conclude as follows:

- The prevalence of osteopenia is increased in the HIV positive population (32%-54%).
- BMD changes are more pronounced in HIV-infected men than in the HIV-negative population (Fernandez-Rivera, Overton, Cazanave).

- Osteoporosis in men preferentially affects cortical bone.
- Osteopenia in HIV-infected people is probably multifactorial resulting from diffferent aetiopathogenetic events.


EDITORIAL REVIEW

Metabolic bone disease in HIV infection

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Some open questions remain:

- Multifactorial pathogenesis: not only HIV or HAART are implicated in the increased bone mineral loss, but also many non HIV-related factors like: BMI, race, smoking, alcoholism, hypogonadism. Many studies have looked for a relation between these factors and the prevalence of BMD changes, but with different outcomes: Dolan, Arnsten and Overton found that they are related to low BMD, but a recent study by Calmy et al. failed to find this relation. A multifactorial origin is certain but it is difficult to establish the role of each factor.
- Many studies have shown a link between the HIV virus and BMD but it is hard to explain the role played by HIV in the pathogenesis and whether the action of antiretroviral drugs can in some way help to prevent osteporosis by combating the virus.
- Many studies show an effect of the drugs on bone metabolism (Vescini, Yin) but the role of PIs and whether TDF can also have a secondary effect on bone metabolism through kidney impairment (Calmy) remain unsettled issues.

One further issue remains: the bone effects of the new class of antiretroviral drugs such as integrase inhibitors and entry inhibitors: no study has yet analyzed the effects of these new drugs on bone metabolism, so ongoing attention is required to project the management of our patients in the right direction.

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