AIDS Rev. 2011;13:240-50

Bone Turnover Markers in HIV Disease

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Abstract

Biomarkers are being increasingly used in basic and clinical research of HIV disease as well as clinical management of infected individuals. Bone metabolism can be assessed by measurement of bone turnover markers, molecules released during bone formation and removal of old bone (resorption). In HIV-infected adults, there is a higher prevalence of low bone mineral density and fractures compared to the general population. This review discusses the findings regarding bone turnover markers in HIV-uninfected and -infected populations and their potential role in assessing fracture risk and predicting bone loss. Studies in postmenopausal women and elderly men show that increased bone turnover markers levels are associated with bone loss, and high levels of resorption markers may predict fractures independently of bone mineral density. Several HIV-related factors, including HIV infection and inflammation, have been found to affect the balance between bone formation and resorption. Some clinical studies found increased levels of bone turnover markers in HIV-infected adults compared to uninfected controls. Furthermore, bone turnover marker levels increased following initiation or switch to different antiretroviral agents in recent randomized trials. The clinical value of bone turnover markers is currently limited due to different sources of variability and limited data from studies in HIV-infected populations. Further research is needed to explore the potential value of bone turnover markers as additional measurements to bone mineral density in fracture risk assessment and monitoring treatment-induced bone effects in HIV-infected patients. **(AIDS Rev. 2011;13:240-50)**

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Key words

Antiretroviral therapy. Biomarkers. Bone loss. Bone turnover markers. Fracture risk. HIV.

Introduction

Biomarkers are increasingly common measures of interest in biomedical research. Very few of those studied ever translate into evidence-based clinical care. In 2010, an Institute of Medicine (IOM) Committee recommended that evaluation of biochemical markers should include analytical validation (assay performance), qualification (association to disease state and intervention effects), and utilization (contextual analysis of proposed use and whether it is supported by the first two steps)[1]. Biomarkers play a clear role in the routine care of people with HIV infection. In addition there is increasing interest in the use of biomarkers to examine aspects of disease pathogenesis and also treatment-related side effects in end organ-specific situations[2].

Current guidelines for clinical management recommend that skeletal status be assessed using dual energy X-ray absorptiometry (DXA) to determine bone mineral density (BMD). The BMD measurements are used to define osteoporosis[3]. Strategies for osteoporosis management are aimed at preventing fractures, starting with identification of individuals at high risk. It has been shown that the risk of fractures approximately doubles for each standard deviation (SD) reduction in BMD[4]. Nevertheless there is an overlap in the BMD of individuals with or without fractures, as BMD is only one of a number of risk factors for fracture[5,6].

The decision to initiate osteoporosis treatment (and to monitor its efficacy) is informed by using DXA. The current recommendation is to repeat BMD measurement

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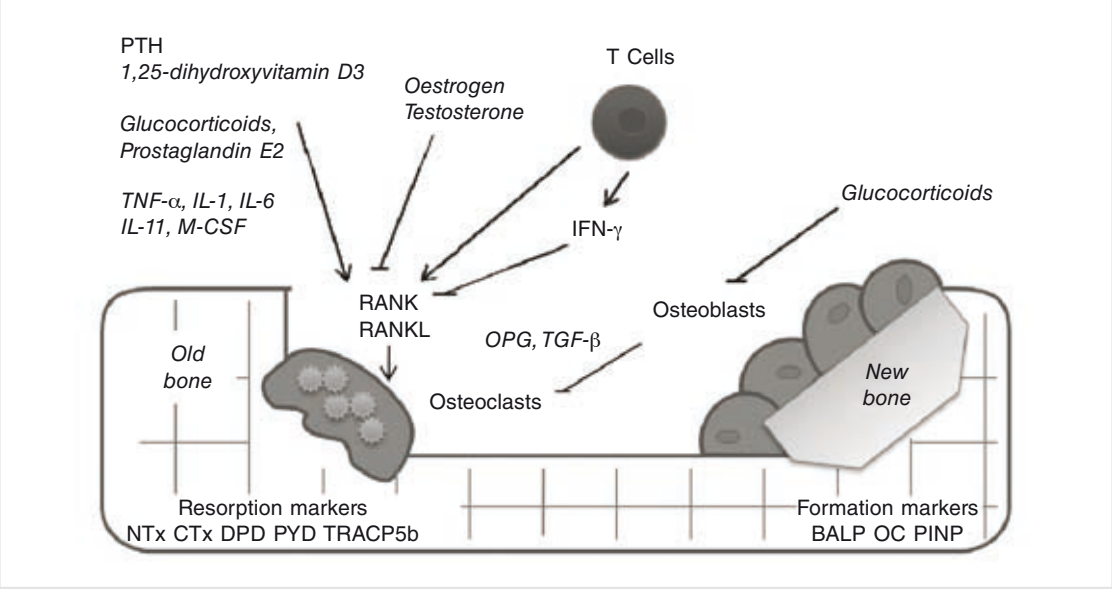

Figure 1. *Systemic and local regulators of normal bone formation and resorption.*
Arrows indicate stimulation and blocked arrow signals inhibition. BALP: bone-specific alkaline phosphatase; CTx: C-terminal telopeptide; DPD: deoxypyridinoline; IFN-γ: interferon-gamma; IL: interleukin; M-CSF: macrophage colony-stimulating factor; NTx: N-terminal telopeptide; OC: osteocalcin; OPG: osteoprotegerin; PINP: procollagen type I N-terminal propeptide; PTH: parathyroid hormone; PYD: pyridinoline; RANKL: receptor activator of nuclear factor kappa ligand; TGF-β: transforming growth factor-beta; TNF-α: tumor necrosis factor-alpha.

after 1-2 years of treatment[3,7]. However, BMD alone does not accurately detect an individual's early responses to treatment, as changes in bone mass are small compared to the precision error of DXA. Bone metabolism can be assessed indirectly by measuring bone turnover markers (BTM) in serum and urine. As BTM are able to provide an estimate of bone metabolism in shorter timescales than BMD with DXA, BTM measurement has been suggested as an additional tool for clinical management of osteoporosis[8,9].

Low bone mineral density, osteoporosis, and fractures appear more common in HIV-infected adults than in healthy adults[10-15]. The mechanisms underlying the possible relationship between BMD, fractures, and HIV are yet to be elucidated. Furthermore, there are no data on predicting fractures in HIV.

This review will explore the possible use of BTM in bone disease in HIV-infected adults. We first discuss BTM and their possible predictive role in bone loss and fractures. Recent findings on the possible links between HIV, its treatment, and BTM are summarized. Further considerations are raised for using BTM as effective biomarkers in the clinical management of HIV-infected patients as well as potential research directions.

Bone turnover markers

Bone is a metabolically active organ that continues to renew after skeletal growth has been completed. The main process in adult bone is remodeling (reconstruction), which maintains bone strength by continuous adaptation to mechanical loadings and constant microfracture repair[16]. In remodeling, new bone formation follows the removal of old bone (resorption) in distinct locations[17]. Bone resorption is mediated by osteoclasts and bone formation by osteoblasts[18]. These processes are well balanced in a healthy individual and highly regulated by complex mechanisms that are not completely understood. The various systemic hormones and local factors that are known to affect bone remodeling (Fig. 1) probably converge to a common mechanism that involves three specific cytokines: receptor activator of nuclear factor kappa ligand (RANKL), RANK, and osteoprotegerin (OPG)[19,20].

Histomorphometry in bone biopsy is the gold standard for assessing bone turnover. However, due to its invasive nature, biochemical markers of bone turnover are of interest. The BTM are enzymes and proteins synthesized during bone formation and the degradation

Table 1. Biochemical markers of bone turnover

	Description	Sample	Comments
Bone resorption			
N-terminal telopeptide (NTx)	Peptide fragment of collagen released during bone resorption	Serum/urine	
C-terminal telopeptide (CTx)	Peptide fragment of collagen released during bone resorption	Serum/urine	
Deoxypyridinoline (DPD)	Cross-linking amino acids between collagen molecules released during bone resorption	Serum/urine	Specific for mature collagen degradation in bone[22]
Pyridinoline (PYD)	Cross-linking amino acids between collagen molecules released during bone resorption	Serum/urine	Found in other connective tissues[23]
Tartate-resistant acid phosphatise 5b (TRACP5b)	Osteoclast-specific lytic enzyme	Serum	Reflects the number of osteoclasts[24]
Bone formation			
Bone-specific alkaline phosphatase (BALP)	Isoform of ALP on osteoblasts membrane involved in skeletal calcification	Serum	Assay shows cross-reactivity with liver isoform (15-20%) – problem for patients with liver disease[25]
Osteocalcin (OC)	Non-collagenous protein synthesised by osteoblasts for deposit in bone matrix	Serum	Rapid degradation results in various fragment sizes[26]. Excreted via kidneys thus affected by renal dysfunction[27]
Procollagen type I N-terminal propeptide (PINP)	Extension peptides cleaved when collagen deposited into matrix	Serum	

products released during bone resorption. They are classified according to the metabolic process they are considered to reflect. Markers for bone resorption include C-terminal cross-linking telopeptide of type 1 collagen (βCTx) and N-terminal telopeptide (NTx). Markers for bone formation include bone-specific alkaline phosphatase (BALP), procollagen type 1 N-terminal propeptide (P1NP) and osteocalcin (OC). The more commonly tested molecules are summarized in table 1, although novel biochemical markers are being developed continuously[21].

One factor limiting the use of BTM in clinical practice is their variability. There are several sources contributing to this variability, including pre-analytical (i.e. mostly subject-related) and analytical factors (i.e. mostly assay-related). The latter relate to the sample type (serum versus urine), sample collection mode, patient preparation, correct handling, processes, and sample storage[23,28], and while these technical aspects can be controlled, biological sources of variability (Table 2) are harder to control, if at all, in clinical practice.

Bone turnover markers, low bone mineral density and fractures in HIV-uninfected adults

A change in bone turnover implies a disturbance in a normally tightly controlled process. A perturbation in this homeostatic process can reflect excessive bone resorption, inadequate formation, and/or increased activation frequency of the bone turnover[46,47]. Each and all of these changes can affect bone quality and reduce bone strength.

The major advances in BTM research are in the field of osteoporosis. Increased bone turnover is associated with subsequent decreased BMD at the forearm in postmenopausal women[48,49], but with conflicting findings at the hip[50-52] and lumbar spine[50,53] (reviewed[54]); this is possibly because the DXA precision error is smaller for the distal forearm than the hip and therefore the correlations with BTM changes are better at the distal radius[32]. Averaging serial measurements over time improved BTM performance in predicting bone loss[52]. However, the mechanisms underlying the

Table 2. Subject-related factors affecting bone turnover markers

Factor	Effect
Age and sex	*In men:* BTM levels stabilize during the 3rd decade of life then decrease (0.4-2.7%/year). From the age of 60, bone resorption generally increases (1.2-2.4%/year)[29-30]. *In women:* Menopause is associated with an increase in bone resorption (79-97%) and bone formation levels (37-52%)[31,32]
Sex hormones	Oestrogen and testosterone levels inversely correlate with bone resorption in women and men, respectively[33]
Ethnicity	Lower BTM levels in black men compared to white and Hispanic men[34]
Diurnal variation	BTM are highest in the early morning and lowest in the late afternoon. Bone formation markers show lower variability than resorption[35-37]
Seasonal variation	BTM higher in winter compared to summer, may be attributed to reduced vitamin D[38]
Physical activity	Conflicting findings regarding the effects of exercise in both sexes[38-40]
Immobility	Reduced mobility associated with increased BTM in both sexes[41]
Smoking	Smoking did not affect BTM in men; associated with increased BTM in premenopausal women[39,42]
Alcohol consumption	Regular alcohol consumption was associated with reduced levels of bone formation markers in both sexes[38]
Food intake	Bone formation and resorption markers were lower with feeding compared to fasting, with greater effects on CTx[43]
Bone-related drugs	Anti-osteoporotic drugs affect all BTM within weeks of initiation and depend on the mechanism of the agent, dose and route of administration[32]
Corticosteroid therapy	Corticosteroids inhibit bone formation while resorption generally increases[44]
Recent fractures	Higher BTM levels following a fracture, can remain elevated for 12 months[45]

BTM: bone turnover markers; CTx: C-terminal telopeptide.

relationship between BTM and BMD are not yet fully elucidated. Abnormal levels of BTM can also be found in several other bone diseases (e.g. Paget's disease[55], metastatic bone disease[56]).

While the results for bone formation markers seem to be conflicting[57,58], the data regarding the association between elevated bone resorption and fractures are more consistent. A study of 1,040 elderly women found that high levels of resorption markers (TRACP5b and CTx) were associated with increased risk of any fracture during nine years follow-up with hazard ratios of 1.16 (95% CI: 1.04-1.29) and 1.13 (95% CI: 1.01-1.27) per SD increase, respectively[59]. Furthermore, bone resorption rate predicted fractures independently of BMD, and combining these two measurements detected women with very high risk of fracture[60]. Only a few studies have investigated the predictive value of BTM in men; the Dubbo cohort study of elderly (> 60 years) men similarly showed that men within the highest quartile of bone resorption marker levels had a 2.8-fold (95% CI: 1.4-5.4) increased risk of fracture compared with those in the lowest quartile, independent of BMD[61].

Bone turnover markers in HIV-infected individuals

Several HIV-related factors have been shown to affect the balance between osteoclast and osteoblast functions and consequently alter bone turnover in HIV-infected individuals.

HIV infection and bone turnover

A direct infection of osteoblasts has been suggested as a possible mechanism for the effects of HIV on bone formation. One study showed HIV infection in human osteogenic cells *in vitro*[62], but a more recent one did not observe this infection in osteoblast cultures from HIV-infected patients[63]. Other studies have demonstrated a possible role of HIV proteins on bone cells. *In vitro* studies showed that HIV-1 gp120 promoted apoptosis of osteoblasts[64] and that both HIV-1 p55-gag and gp120 reduced the functionality of these cells[65], and promoted resorption via induction of RANKL expression by T-cells *in vitro*[66]. Cross-sectional studies of

treatment-naive patients found increased levels RANKL and OPG[67] and reduced bone formation[68] when compared to HIV-uninfected controls.

Inflammation and bone turnover

The skeletal and immune systems share several regulatory molecules including cytokines, receptors, signaling molecules, and transcription factors[69]. In conditions where chronic immune activation is prominent, such as rheumatoid arthritis[70] and inflammatory bowel disease[71], tumor necrosis factor-alpha (TNF-α)[72], interleukin (IL)-1[73], IL-6[74,75], and IL-11 can all stimulate bone resorption[76]. High levels of proinflammatory cytokines are found in HIV-infected patients[77,78]. Furthermore, TNF-α was positively correlated with resorption markers in HIV-infected adults and negatively correlated in HIV-uninfected adults[79]. Therefore, it is possible that altered expression of cytokines in these settings may disturb the balance between bone resorption and formation, and consequently lead to bone loss. Brown, et al.[80], however, did not find an association between TNF-α and bone loss in HIV-infected patients, although the use of total body BMD is a potential limitation of this study.

The immune system can regulate bone remodeling via activated T lymphocytes that produce RANKL, which may lead to an increase in osteoclastogenesis and bone loss[81,82]. T-cells ($CD4^+$ and $CD8^+$) stimulated human osteoclast formation *in vitro* via RANKL-dependent and independent mechanisms[83]. Therefore, the systemic T-cell activation reported in HIV-infected patients[84] may lead to increased bone resorption. The hypothesis that increased bone resorption may occur through a mechanism involving T-cell repopulation and reconstitution was tested in a T-cell null knockout mice model; the transfer of T-cells into the mouse led to elevated bone resorption, increase in RANKL and TNF-α, and decreased BMD[85].

HIV treatment and bone turnover

In vitro studies found that the HIV protease inhibitors (PI) ritonavir and saquinavir increased osteoclast activity[66]. Similarly, the nucleoside reverse transcriptase inhibitors (NRTI) zidovudine (AZT), didanosine (ddI) and lamivudine (3TC) can stimulate osteoclastogenesis[86,87]. Tenofovir (TDF) treatment of osteoblasts *in vitro* altered gene expression that implicates loss of osteoblast function[88].

The clinical studies assessing BTM in HIV-infected individuals are summarized in table 3. Most of these are cross-sectional[79,89-95], with some contradictory findings about the effects of antiretroviral drugs on BTM[96,97]. Ten studies prospectively assessed BTM in HIV-infected individuals initiating or on antiretroviral treatment[85,98-104], and of these four were randomized[103-106]. In the ASSERT study, patients were randomized to initiate either abacavir (ABC)-3TC or TDF-emtricitabine (FTC). The BTM increased in both groups over 24 weeks, although increases were greater in the TDF-FTC group. Only formation markers remained significantly different at week 48[103]. In the STEAL study, participants were randomized to switch their current NRTI to either TDF-FTC or ABC-3TC[107]; bone formation and resorption were significantly increased from week 12 to 96 in the TDF-FTC group compared to ABC-3TC[105]. An additional randomized study showed increased BTM in patients initiating either AZT/3TC/lopinavir/ritonavir or nevirapine/lopinavir/ritonavir, with greater resorption levels found with AZT/3TC/lopinavir/ritonavir[104]. The SMART study showed that intermittent antiretroviral therapy (ART) was associated with decreases in bone formation and resorption compared to continuous ART[106]. Determining the impact of individual antiretroviral drugs on BTM levels in clinical studies is complex because these drugs are being used in combinations of three or more to form an effective regimen. This is further complicated when taking into account the patients' duration of exposure for each of the drugs.

Uncoupling of bone resorption and formation was observed in several studies. In a cross-sectional study of HIV-infected women versus healthy controls, Yin, et al.[79] found that formation and resorption markers were correlated in all groups except HIV-infected women who were not receiving ART. Similarly, no significant correlation was seen in patients with advanced disease initiating treatment, but a shift to a correlation ($r = 0.72$; $p < 0.01$) was shown following treatment initiation[109]. In the ASSERT study, BTM changes from baseline to week 48 were positively correlated with each other ($r = 0.265$-0.564; $p < 0.001$) except for CTx and BSAP[108]. These findings possibly indicate that an uncoupling of bone resorption and formation occurs in HIV infection and these processes are resynchronized after ART commencement, supporting the hypotheses that viral replication and inflammation alter bone turnover.

Notably, some studies found that $CD4^+$ T-cell count positively correlated with bone formation, while resorption markers were negatively correlated[90,110]. This correlation suggests that patients with advanced disease may be at higher risk of imbalanced bone turnover and low BMD than those with early disease.

Table 3 A. Cross-sectional studies assessing bone turnover markers in HIV-infected patients

Reference	(n)	Age (yrs)	Male (%)	ART	HIV– Control	BTM measured			BTM findings	Comments
						Formation	Resorption	Regulation		
Serrano, et al. 1995[68]	22	28	59	None	Yes (n = 17)	ALP, OC	Hydroxy-proline	None	Reduced bone formation in HIV+	Bone biopsies CD4+ and disease severity negatively correlated with OC. No BMD correlation
Nolan, et al. 2001[89]	17	NA	NA	Initiating IDV or NFV regimen	No	OC	None	None	Increased formation in the IDV group	
Teichmann, et al. 2003[90]	50	37	0	AZT, ddI, ddC	Yes (n = 50)	OC	PYD	None	Increased resorption and reduced formation in HIV+	CD4+ negatively correlated with resorption, positively with formation
Konishi, et al. 2005[91]	37	41	100	20% not on ART, 38% on HAART	No	None	DPD	RANKL	RANKL correlated with DPD. RANKL higher with HAART	Spine BMD negatively correlated with RANKL
Seminari, et al. 2005[92]	68	41	80	100% on ART	No	ALP, BALP, OC	DPD	OPG, RANKL	High levels of bone turnover in reduced BMD group compared to normal	BMD negatively correlated with OC, ALP and DPD
Fausto, et al. 2006[96]	161	39	64	Not detailed (all)	No	ALP, OC	NTx	None	No difference between naive to HAART recipients	No BMD correlation
Gibellini, et al. 2007[67]	31	37	100	None	Yes (n = 30)	None	None	OPG, RANKL, RANK	BTM significantly increased in HIV+ compared to HIV–	Viral load correlated with RANK and RANKL. BMD positively correlated with OPG/RANKL ratio and negatively with RANKL
Calmy, et al. 2009[93]	153	48	98	100% on HAART	No	ALP, BALP, OC	Hydroxy-proline	None	BTM higher with TDF compared to TDF-sparing regimen	No BMD correlation
Grijsen, et al. 2010[94]	33	38	100	None	No	ALP, OC, PINP	ICTP, CTx,	None	No difference in BTM between normal to reduced BMD groups.	Primary infection. No BMD correlation
Yin, et al. 2010[79]	92	56	0	79% on HAART	Yes (n = 95)	OC, BALP	NTx, CTx	None	Resorption higher in HIV+. Formation and resorption correlated in all groups except HIV+ ART–	TNF-α higher in ART. NTx positively correlated with TNF-α in HIV+ and negatively in HIV–. BMD negatively correlated with BTM
Welz, et al. 2010[95]	1,077	41	59	78% on HAART	No	ALP	None	None	EFV and TDF associated with increased formation	No association between vitamin D and ALP
Piso, et al. 2011[97]	113	43	56	76% on HAART	No	BALP	PYD, DPD	None	BTM higher in ART+ vs. ART–. No difference between TDF vs. other NRTI or between PI vs. NNRTI	

Table 3 B. Summary of longitudinal prospective studies assessing bone turnover markers in HIV-infected patients

Reference	Duration	(n)	Age (yrs)	Male (%)	ART	HIV–Control	BTM measured			BTM findings	Comments
							Formation	Resorption	Regulation		
Mora, et al. 2007[98]	24 wks	27	13	48	3TC, TDF and EFV	Yes (n = 336)	BALP	NTx	RANKL, OPG	BTM and RANKL/OPG ratio higher in HIV+. Levels decreased following ART	Adolescents
Ofotokun, et al. 2011[85]	24 wks	20	40	Not reported	Initiating LPV/r/ TDF/FTC	No	OC	CTx	RANKL	Resorption and RANKL increased followed by formation increase	
Fux, et al. 2008[99]	48 wks	1,091	39	68	Initiating or reinitiating TDF-based or -sparing regimen	No	ALP	None	None	TDF associated with increased ALP. Decrease following TDF discontinuation	
Mondy, et al. 2003[100]	72 wks	93	42	86	PI-based regimen (68%)	No	OC, BALP	PYD, DPD	None	BTM increased and stabilized over 72 wks. No association with ART	Bone biopsies (n = 7). No BMD correlation
Aukrust, et al. 1999[101]	96 wks	16	NA	NA	Initiating IDV+AZT+3TC	No	OC	CTx	None	Advanced disease associated with decreased formation and increased resorption. Following initiation, TNF-α decreased and OC levels increased over 96 wks	TNF-α negatively correlated with OC and positively with CTx. OC and CTx not correlated at baseline, correlated on HAART
Dolan, et al. 2006[102]	96 wks	25	41	0	88% on HAART	Yes (n = 25)	OC	NTx	None	BTM increased in HIV+; remained increased over 96 wks	NTx predictor of change in hip BMD

Table 3 C. Summary of randomized studies assessing bone turnover markers in HIV-infected patients

Reference	Duration	(n)	Age (yrs)	Male (%)	ART	HIV–Control	BTM measured			BTM findings	Comments
							Formation	Resorption	Regulation		
Stellbrink, et al. 2010[108]	48 wks	385	37	81	Initiating ABC/3TC or TDF/FTC	No	OC, BALP, PINP	CTx	None	BTM increased over 24 wks, then stabilized or decreased. Greater increase with TDF	BTM changes correlated. Renal tubular proteinuria markers not correlated with BTM. BTM negatively correlated with BMD
van Vonderen, et al. 2011[104]	48 wks	48	42	100	Initiating ZDV/3TC/ LPV/r or NVP/ LPV/r	No	BALP, P1NP	TRACP5b, CTx	None	BTM increased following ART. Greater resorption found in AZT/3TC/LPV/r	Greatest increases for resorption was by week 12 and formation by week 48. Bone remodeling correlated with spine bone loss
SMART Body Composition sub-study[106]	48 wks	202	44	83	Intermittent vs. continuous ART	No	BALP, P1NP	CTx, NTx	OPG, RANKL	BTM decreased and RANKL increased in the intermittent group	Early changes in BALP, NTX, βCTX and OPG predicted BMD change
STEAL Bone sub-study[105]	96 wks	301	45	99	Switching to ABC/3TC or TDF/FTC	No	BALP, P1NP	CTx	OPG, RANKL	BTM increased from week 12 onwards. Greater increase with TDF	Early changes in BTM did not predict BMD change at week 96

ABC: abacavir; ART: antiretroviral therapy; AZT: zidovudine; BALP: bone-specific alkaline phosphatase; BMD: bone mineral density; BTM: bone turnover markers; CTx: C-terminal telopeptide; d4T: stavudine; ddC: zalcitabine; ddI: didanosine; DPD: deoxypyridinoline; EFV: efavirenz; FTC: emtricitabine; HAART: highly active antiretroviral therapy; IDV: indinavir; NFV: nelfinavir; NTx: N-terminal telopeptide; OC: osteocalcin; PI: protease inhibitor; PINP: procollagen type I N-terminal propeptide; PTH: parathyroid hormone; PYD: pyridinoline; TDF: tenofovir; TNF-α: tumor necrosis factor-alpha; 3TC: lamivudine.

Bone turnover markers and low bone mineral density in HIV-infected adults

While no correlation was found between BTM and BMD in several cross-sectional studies[68,93,94,96], others showed a negative correlation[67,79,91,92]. In a prospective study, Dolan, et al.[102] found that a marker of bone resorption (NTx) was a predictor of change in hip BMD over 96 weeks of follow-up of 25 patients on HAART. Two randomized studies, ASSERT and MEDICALS, found that BTM negatively correlated with BMD[104,108], although these studies did not explore whether early changes in BTM predicted subsequent bone loss. Both STEAL and SMART studies explored whether early changes in BTM can predict subsequent bone loss. While the SMART study found that changes to week 12 predicted bone loss at week 48[106], the STEAL study did not show this association to bone loss at week 96[105]. A majority of the studies assessing BTM had relatively small sample size, and over short follow-up periods could not examine the relationship between BTM and fractures.

The effects of anti-osteoporotic treatment on bone turnover in HIV-infected patients were investigated in a double-blinded, randomized, placebo-controlled study of intravenous zoledronate (bone resorption inhibitor) in 30 HIV-infected patients. The study showed bone resorption markers (NTx and CTx) were decreased over 12 months in the zoledronate arm compared with placebo controls. No changes were observed in bone formation[111].

Should bone turnover markers be measured in HIV-infected patients?

Bone mineral density is measured to both define and diagnose osteoporosis. However, what is clinically more important than measuring BMD is measurement of fracture risk and identifying those HIV-infected patients at higher risk, both before and after fracture and in response to antiresorptive therapy. While measuring BMD and estimating fracture risk with the FRAX algorithm is the current standard, it does not appear to capture all risk factors for fracture in these individuals[93]. Assessment of fracture risk by combining BMD and BTM data has been shown to improve the identification of osteoporotic women at higher fracture risk in two large prospective studies[57,58]. However the combination of these tests has not yet been validated or explored in other populations such as men, different ethnic groups, or HIV-infected

patients. Similarly, the assessment of changes in BTM in response to ART initiation, switch of ART, or antiresorptive therapy to predict subsequent BMD has a potential clinical value as well. Further studies investigating BTM changes and the association to subsequent BMD changes and fracture risk in HIV-infected individuals are needed.

In HIV-uninfected individuals, early decrease in BTM levels following anti-osteoporotic treatment has been associated with reduced fractures incidence[112]. Monitoring BTM has also improved compliance with antiresorptive therapy in a randomized study[113]. Therefore, monitoring the efficacy of anti-osteoporotic treatment, or the effects of other agents with potentially detrimental effects on bone, is a potential clinical application for BTM. Several national societies and guideline development groups have issued recommendations for the clinical use of BTM in the general population (reviewed[114]). While none of these groups recommended the routine use of BTM for fracture prediction, several organizations such as the National Osteoporosis Foundation[7], the Belgian Bone Club[115], and the Japan Osteoporosis Society[116] suggest measuring BTM after 3-6 months of antiresorptive therapy to assess its efficacy; failure to see a change in BTM might suggest reevaluation of the treatment[117].

However, there is still a need for stronger evidence to apply BTM to routine clinical practice. Consequently, the International Osteoporosis Foundation and the International Federation of Clinical Chemistry and Laboratory Medicine recommend that a marker of bone formation (s-PINP) and a marker of bone resorption (s-CTX) are used as reference analytes for BTM in clinical studies to assist with adopting international reference standards[114].

Taken together, BTM cannot be used in routine clinical management of HIV-infected patients. Assessing BTM changes may be an option in the future, primarily for individuals in high risk of fractures, (i.e. an HIV-infected person with several independent risk factors such as prior fracture or low BMD), that initiates treatment with potential effect on bone (such as antiretroviral drugs or other medications), or commences anti-osteoporotic treatment.

Potential future research directions for bone turnover markers

Alterations in bone metabolism are found in HIV-infected patients, yet the relationship between HIV disease, BTM levels, reduced BMD, and fractures is still unknown. The questions are: What are the cellular mechanisms of bone loss in HIV-infected patient? Which markers reflect best the metabolic status of the skeleton in this population? Do BTM levels have a predictive value in bone loss and fractures in HIV-infected adults? Defining which soluble biomarkers offer the greatest precision and utility for diagnosis and clinical management requires further research. Furthermore, randomized studies exploring the effects of different antiretroviral drugs on bone turnover are needed. It is essential to establish reference ranges in different populations, including HIV-infected patients.

Conclusion

Bone turnover markers play an important role in improving our understanding of the cellular mechanisms underlying the links found between HIV and bone disease. Research findings from general population cohorts imply a potential role for BTM as additional tools to DXA in clinical management of low BMD. However, substantial variability and limited data in HIV-infected populations remain a challenge for the use of BTM in practice. Further research of BTM may assist with understanding the pathogenesis of bone loss in HIV and if there is a clinical utility for these markers in the management of HIV-infected patients.

Funding

The Kirby Institute (formerly the National Centre in HIV Epidemiology and Clinical Research) is funded by the Australian Government Department of Health and Ageing, The views expressed in this publication do not necessarily represent the position of the Australian Government. The Kirby Institute is affiliated with the Faculty of Medicine, University of New South Wales.

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